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Beta-blocker use is associated with fragility fractures in postmenopausal women with coronary heart disease

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ABSTRACT. ***Background and aims:*** *An association between cardiovascular disease and osteoporosis is described. A number of drugs often used by patients with coronary heart disease, such as thiazides, statins and beta-blockers, have shown controversial effects on bone. 1) To study the possible association between coronary heart disease (CHD) and bone mass density (BMD), quantitative ultrasound measurements (QUS) and the prevalence of fragility and vertebral fractures. 2) To study the possible influence of a number of drugs, statins, thiazides and beta-blockers, on BMD and fractures.* ***Methods:*** *Case-control study performed on 74 postmenopausal women who had recently suffered from CHD, and 111 age-matched controls. BMD was measured by Dual X-Ray Absorptiometry (DXA) at the lumbar spine and proximal femur. Quantitative Ultrasound (QUS) was also measured at the heel. Vertebral fractures were diagnosed by lateral, thoracic and lumbar X-rays. The occurrence of non-vertebral fractures was determined by examination of medical records.* ***Results:*** *Patients with CHD had higher values of BMI. They had a higher prevalence of arterial hypertension and hyperlipidemia, and consequently higher consumption of beta-blockers and statins, but not of thiazides, and had lower alcohol consumption. Patients with CHD had higher BMD values, measured by DXA at the proximal femur, than controls, but there were no differences in DXA values at the lumbar spine or QUS at the heel between the two groups. The prevalence of all fragility factures was slightly higher in patients with CHD, but not to a significant extent. The prevalence of vertebral fractures was similar in the two groups. In a logistic analysis to identify factors associated with all fractures, beta-blockers were positively associated with fragility fractures, and DXA at the femoral neck was inversely associated with fragility fractures.* ***Conclusions:*** *Postmenopausal women with CHD have higher values of BMD at the proximal femur but, despite this, show a slight but non-significant increase in the prevalence of fragility fractures. Beta-blockers are independently associated with fragility fractures, but thiazides and statins are not.*
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INTRODUCTION

Osteoporosis and atherosclerosis are two multifactorial and degenerative entities, which have become major public health problems in Western countries. These diseases accompany the aging process, share common risk factors, and often coexist in both genders worldwide, particularly in the elderly (1).

Several studies have also indicated a causal relationship between atherosclerosis and osteoporosis (1-4), suggesting that the presence of one is a predictor of the other. Similar associations between osteoporosis, bone turnover, bone mineral density (BMD) or fractures, and mortality, coronary heart disease (CHD), arterial peripheral disease, stroke and arterial calcification (1, 5) have also been described.

Although Dual X-ray Absorptiometry (DXA) is considered the "gold standard" for measuring BMD (6), Quantitative Ultrasound (QUS) measurements have been proposed as an alternative method for non-invasive as-

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Key words: Atherosclerosis, beta-blockers, bone mineral density, coronary heart disease, fracture, osteoporosis, quantitative ultrasound.

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sessment of skeletal status, as they reflect not only BMD but also qualitative aspects of bone tissue, such as elasticity, structure and geometry (7). Indeed, QUS has been shown to predict the risk of fragility fractures (8).

Fewer studies have been published on atherosclerosis and QUS measured at the calcaneus (9-12). Because of this, we studied the possible association between QUS and DXA measurements and CHD in a population of postmenopausal women who had recently suffered an acute coronary event (angina or acute myocardial infarction).

MATERIAL AND METHODS

Study

This is a case-control study. Cases considered were postmenopausal women who had suffered a coronary event in the previous six months of the study: angina pectoris or acute myocardial infarction. All cases were studied in a cardiology/coronary unit and when patients were discharged from hospital, they were referred for the bone metabolic study. Controls were age-matched postmenopausal women of similar weight and height, who had never had coronary symptoms. Participants were recruited from nine centers in nine provinces of Spain.

Overall, 188 subjects agreed to participate: 77 cases and 111 controls. Of the 77 patients with CHD, 51 (66.2%) had suffered acute myocardial infarction and 26 (33.8%) angor pectoris. They were all informed about the aims of the study and gave their written consent. The study was approved by the Ethics Committee of the Hospital University Insular, Gran Canaria.

Questions regarding the occurrence of bone fractures since the age of 40, age at the time of each fracture, number of pregnancies, duration of breast-feeding, age at menopause, smoking habits and alcohol intake were also asked.

Physical examination

A complete physical examination was performed. Height and weight were measured to obtain the body mass index (BMI; calculated as weight [kg]/height [m]^2) of each subject. Height was measured without shoes and weight with light clothes on a balance scale. Postmenopausal women were defined as those who had had their last period at least one year before, in accordance with the clinical definition of the World Health Organization (13).

Measurements

Calcaneal QUS measurements of all subjects were made on a Sahara Clinical Sonometer (Hologic, Bedford, USA). Every center had its own device. An ultrasonic contact gel was used between two transducer pads and the patient's skin; this method avoids the water bath that was necessary in the past. The system consists of two unfocused transducers mounted coaxially on a motorized caliper. One transducer acts as transmitter and the other as a receiver. The transducers are acoustically coupled to the heel with soft rubber pads and an oil-based coupling gel. The lower part of the dominant leg was immobilized, and the correct leg angle set by a positioning aid with moldable foam.

The Sahara device measures both BUA and SOS at a fixed region of interest in the mid-calcaneus, and combines BUA and SOS into a single parameter, the quantitative ultrasound index (QUI):

QUI = 0.41 (SOS) + 0.41 (BUA) 7571

Instrumental quality control

Quality control checks were performed daily by scanning manufacturer-provided phantoms prior to scanning the subjects. Each ultrasonometer had its own phantom with previously known values for SOS and BUA. We have previously described short-term *in vivo* precision values (CV) of 4.88% for BUA, 0.36% for SOS and 3.45% for QUI; *in vitro* precision was 0.40% for SOS and 2.67% for BUA (14).

Dual X-ray Absorptiometry (DXA)

The BMD of the lumbar spine and proximal femur was calculated with several Hologic densitometers (Hologic Inc. Waltham, USA) at the lumbar spine (L2-L4) and femoral neck. All measurements were made by the same technician in each center. Z- and T-scores were calculated from previously reported data for the normal male Spanish population (15).

Fracture determinations

Non-vertebral fractures (NVF). Assessment of non-vertebral fractures was made from written reports from radiologists, emergency reports and X-rays provided by patients, and after examining their medical records. In both patients and controls, fractures were recorded only if properly documented and if they had occurred with minor trauma. Childhood fractures were excluded.

Vertebral fractures (VF) were identified from lateral X-ray of the spine in all patients. Assessment of VF was performed with the widely accepted criteria of Genant (16). Interpretation of X-rays was centralized at the University Hospital Insular in Gran Canaria. All X-rays were examined by two experts on bone and mineral metabolism.

Other measurements

Physical activity: Participants were asked to report the average amount of time spent per week during the previous year in each of 7 activities: walking or hiking outdoors, jogging, running, cycling, racquet sports, swimming and other aerobic activities (e.g., dancing). Actual calcium intake was assessed with a food frequency questionnaire (17).

Statistical analysis

Data from the two groups are presented as means and standard deviations (SD) for continuous variables, and cat-

Table 1 - *Basal characteristics of study population.*

	Coronary heart disease		
	Yes (n=77)	**No (n=111)**	***p*-value**
Age (yrs)	65.3±11.1	64.6±10.3	0.817
Weight (Kg)	70.1±11.8	68.0±14.4	0.298
Height (cm)	154±7.8	156±7.1	0.051
BMI (Kg/m^2)	29.7±5.2	27.9±5.7	0.034
Age at menarchy (yrs)	12.8±1.6	12.7±1.6	0.763
Age at menopause (yrs)	49.3±3.9	48.1±5.4	0.082
Surgical menopause (%)	11.1	22.0	0.060
Low physical activity (%)	37.0	31.1	0.415
Alcohol consumption (%)	5.5	16.2	0.028
Coffee consumption (%)	49.3	56.8	0.322
Tobacco consumption (%)	14.9	10.8	0.413
Arterial hypertension (%)	73.0	34.2	<0.001
Hyperlipidemia (%)	56.9	40.0	0.025
Actual calcium intake (mg/day)	643±520	659±580	0.117

Table 2 - *Consumption of some drugs affecting bone.*

	Coronary heart disease		
	Yes (n=77)	**No (n=111)**	***p*-value**
Hormonal contraception (%)	21.6	19.1	0.675
Beta-blockers (%)	52.7	12.6	<0.001
Statins (%)	56.8	29.7	<0.001
Oral steroids (%)	4.1	6.4	0.511
Thiazides (%)	8.3	13.5	0.283

egorical variables were summarized as percentages. Percentages were compared with the chi-square test and means by the *t*-test. DXA and QUS values were compared after adjusting the mean by age, BMI and use of beta-blockers. To identify factors independently associated with coronary heart disease and the presence of fractures, logistic regression models were developed. For each model, a selection of variables based on the likelihood ratio test was carried out. For the resulting models, the adjusted odd-ratios of the selected factors were estimated by means of 95% confidence intervals (CI). A test was considered significant if its *p*-value was less than 0.05. Analyses were carried out with the statistical package SPSS (SPSS Inc, Chicago, IL, USA), version 15.0.

RESULTS

The characteristics of participants with and without CHD are listed in Table 1. Women with CHD had similar weight and height, but higher values of BMI. There were no statistical differences between CHP and controls in age at menarchy, age at menopause, prevalence of surgical menopause, prevalence of low physical activity, and coffee and tobacco consumption.

Levels of physical activity was similar and low in both groups. Patients with CHD had a higher prevalence of arterial hypertension and hyperlipidemia. Actual calcium intake was also similar in patients and controls. As a result of the higher prevalence of arterial hypertension and coronary disease alone, women with CHD showed a higher prevalence of consumption of beta-blockers and, because of the higher prevalence of hyperlipidemia, they also showed a higher prevalence of consumption of statins. The use of thiazides was similar in both groups (Table 2).

Postmenopausal women with CHD had higher BMD values than controls, measured by DXA at every anatomical location at the hip: femoral neck, trochanter and total hip (Table 3). These differences were statistically significant but, when the DXA values were compared after adjusting for age, BMI and beta-blocker use, there was no statistically significant difference between any DXA mea-

Table 3 - *Bone mineral density estimated by DXA at lumbar spine and hip, and QUS parameters measured at heel.*

	Coronary heart disease		
	Yes (n=77)	**No (n=111)**	***p*-value**
L2-L4 (g/cm^2)			
Observed mean±SD	0.922±0.171	0.887±0.178	0.194
T-Score	-1.134±1.646	-1.474±1.712	
Adjusted mean*±SD	0.907±0.020	0.923±0.020	0.598
Femoral neck (g/cm^2)			
Observed mean±SD	0.754±0.156	0.698±0.138	0.013
T-Score	-0.786±1.432	-1.300±1.264	
Adjusted mean*±SD	0.750±0.015	0.728±0.015	0.336
Trochanter (g/cm^2)			
Observed mean±SD	0.662±0.135	0.628±0.124	0.087
T-Score	-0.071±1.594	-0.475±1.460	
Adjusted mean*±SD	0.654±0.014	0.652±0.014	0.930
Intertrochanter (g/cm^2)			
Observed mean±SD	1.051±0.173	0.966±0.167	0.002
T-Score	-0.092±1.492	-0.824±1.442	
Adjusted mean*±SD	1.025±0.018	1.003±0.017	0.401
Total hip (g/cm^2)			
Observed mean±SD	0.893±0.143	0.820±0.135	0.001
T-Score	-0.271±1.472	-1.024±1.393	
Adjusted mean±SD	0.875±0.014	0.851±0.021	0.237
BUA (db/MgHz)			
Observed mean±SD	63.7±17.5	62.9±16.9	0.756
T-Score	-0.890±1.101	-0.940±1.065	
SOS (m/s)			
Observed mean±SD	1531±29.5	1529±26.4	0.649
T-Score	-1.124±0.962	-1.185±0.860	
QUI-Stiffness			
Observed mean±SD	82.8±18.3	81.8±16.9	0.692
T-Score	-1.096±0.995	-1.152±0.921	

*Adjusted for age, BMI and beta-blocker use.

Table 4 - *Logistic analysis to identify factors associated with coronary heart disease.*

Factor	*p*-value	OR (95% CI)
Alcohol consumption	0.016	0.19 (0.05-0.73)
Arterial hypertension	0.001	3.40 (1.65-6.98)
Use of beta-blockers	<0.001	6.19 (2.76-13.89)

Table 5 - *Logistic analysis to identify factors associated with all fractures.*

Factor	*p*-value	OR (95% CI)
Beta-blockers	0.005	3.27 (1.42-7.51)
DXA femoral neck (per 0.1 units)	<0.001	0.563 (0.411-0.770)

surement. QUS measurements (BUA, SOS and QUI) were similar in both groups, and no statistically significant differences were found.

Table 4 lists the results of logistic analysis performed to identify factors associated with CHD. Patients with CHD had a higher prevalence of arterial hypertension (OR 4.05, 95% CI 1.82-9.01), p=0.001, and use of beta-blockers (OR 6.51, 95% CI 2.82-14.98), p<0.001. Conversely, moderate alcohol consumption was associated with a lower prevalence of CHD (OR 0.17, 95% CI 0.042-0.66; p=0.011).

We also performed a logistic analysis to identify factors associated with all fragility fractures (Table 5). We found a statistical association only with the use of beta-blockers: OR 3.27, 95% CI 1.42-7.51, p=0.005) and DXA measured at the femoral neck: OR 0.563, 95% CI 0.411-0.770, p<0.001.

Table 6 shows the prevalence of fragility fractures in both groups. CHD patients had a slightly higher prevalence of fragility fractures: 27.1% *vs* 18.3%, although it did not reach statistical significance (p=0.164).

DISCUSSION

Osteoporosis and atherosclerosis are major causes of morbidity and mortality in both women and men in the Western world, and the incidence is expected to rise, in view of population demographics and increased life expectancy (18). As both disease processes are common, both conditions are often seen in the same individual, and progress silently until a fracture or myocardial infarction occurs (19, 20).

For years, osteoporosis and cardiovascular disease were thought to be independent chronic diseases which increased markedly with advancing age. However, increasing evidence now supports a direct association between the two.

Our patients with CHD had a higher prevalence of arterial hypertension and hyperlipidemia than controls, which were obviously etiopathogenic factors in the development of CHD. They also had a greater BMI than controls, but this was not due to higher prevalence of low physical activity, which was similar in both groups. Moderate alcohol consumption was found to be more prevalent in the control group, which suggest the protective effect of alcohol on CHD, as previously suggested (21). As a result of the presence of underlying diseases, patients with CHD had a greater consumption of beta-blockers and statins but, curiously. they did not have a higher consumption of thiazides.

Women suffering from CHD had higher BMD values at different anatomical sites in the hip (femoral neck, trochanter, intertrochanter, total hip) than controls, but these differences were observed only with crude DXA values. The CHD patients in our study had a higher BMI than controls, and the effect of weight on BMD is well-known. When DXA values were compared after adjusting for age, BMI and beta-blocker use, the DXA values were similar and there were no statistically significant differences (Table 3).

A relationship between BMD and CHD has been reported in some publications. For instance, studies of postmenopausal women have noted the increased risk of cardiovascular-related and stroke mortality for each decrease in standard deviation in bone mass (2, 3, 22), Another study (3) revealed that, for each standard deviation decrease in bone mass, there was a 1.2- to 1.3-fold increased risk of dying from coronary artery disease or other forms of atherosclerosis. Von der Recke et al. (2) reported that the lowest quartile of bone mass was associated with a 2-fold increase in the risk of CVD-related death (*vs* highest quartile). Tanko et al. (23) found that, after adjustment for potential confounders, women with osteoporosis had a 3.9-fold (95% CI 2.0-7.7; p<0.001) increased risk of cardiovascular events compared with women with low bone mass. This increased risk could not be explained by common risk factors alone. In our study, we found controversial results, because patients suffering from CHD showed greater values of BMD than controls at every anatomical site of the proximal femur, but this finding was not

Table 6 - *Prevalence of fragility fractures (all fractures and vertebral fractures).*

	Coronary heart disease		
	Yes (n=77)	No (n=111)	*p*-value
Fractures (%)			
All (vertebral and non-vertebral) fractures	27.1	18.3	0.164
Vertebral fractures	8.6	10.1	0.735

observed either with DXA at the lumbar spine (L2-L4) or in QUS at the calcaneus.

In this additive regression model, performed to identify which factors could be associated with BMD, we also found a statistical association between beta-blockers and BMD. Some studies have described an increase in BMD produced by the use of beta-blockers (24, 25), but the investigators of the *Epidémiologie de L'Ostéoporose Prospective Study* concluded that there is currently no convincing evidence supporting the hypothesis that pharmacological blockade of the beta-adrenergic system is beneficial to the human skeleton after menopause (26). Similar conclusions were reported in a review by Reid et al. (27).

When we performed another additive regression model to identify which factors could be associated with fragility fractures (Table 5), we found only two: BMD measured at the femoral neck was found to reduce the risk of fracture (OR 0.563, 95% CI 0.411-0.770, $p<0.001$), but the use of beta-blockers was associated with an increased risk of fragility fractures: OR 3.27, 95% CI 1.42-7.51, $p=0.005$. These results suggest an independent association between the use of beta-blockers and fragility fractures, which is the most surprising finding of our study.

There are conflicting observations regarding the use of beta-blockers and the risk of fractures. Some studies have reported that the use of beta-blockers is associated with a reduced risk of fractures in middle-aged and older subjects from the general population (28-30). In the MONICA/KORA Augsburg cohort study, the use of beta-blockers was associated with a lower risk of any fracture (HR 0.57; 95% CI 0.36-0.90) after adjustment for age, sex and survey. Further adjustment for BMI and years of education only slightly attenuated the relationship (HR 0.60; 95% CI 0.38-0.95), and additional adjustment for a variety of further risk factors did not attenuate the association (HR 0.60; 95% CI 0.37-0.96) (29). In other studies, the protective effect of beta-blockers was only found in patients with a history of use of other antihypertensive agents, but not in patients using beta-blockers only. Also, in patients with a history of use of other antihypertensive agents, no dose-response relationship with beta-blocker use was found (28). A meta-analysis concluded that beta-blocker use is associated with a significant decrease in fracture risk (31). However, more recent studies cast doubt on this finding (27, 32, 33), and the limited data regarding fractures in randomized controlled trials certainly do not support this conclusion (34).

In view of the conflicting results from published studies, no conclusions can be drawn on the potential bone effects of treatment with beta-blockers (35). It is difficult to explain how beta-blockers increase BMD and at the same time are associated with the presence of fragility fractures, as we found. We can only hypothesize that beta-blockers produce bone of poor quality, as occurs if sodium fluoride is used (36). In the last decade, there has been increasing concern about the importance of bone quality (37, 38). Similar findings – increase in BMD and an increase in the risk of fragility fractures – have also been reported in patients suffering from Type 2 diabetes mellitus (39).

There are several limitations to this study. First, the population studied is limited, because we focused on postmenopausal women who had suffered a CHD event recently, in the previous 6 months. Some results, such as age and age at menopause, are on the border of statistical significance in the logistic analysis performed to identify factors associated with coronary heart disease, and we believe that, with a higher number of patients, these findings would have achieved statistical significance. Second, we did not record either the amount of beta-blockers or the time that patients had been taking them. Third, we examined only women of Caucasian origin, and our results may therefore not apply to men or to other ethnic groups.

In conclusion, the knowledge that, in postmenopausal women suffering from CHD, treatment with beta-blockers is associated with an increased risk of fragility fractures should aid early identification of subjects at risk in order to indicate preventive or therapeutic actions. Cardiovascular diseases are common and occur mainly in the elderly, in whom osteoporotic fractures are also very common. Because of this, it is important to establish whether drugs used in the treatment of cardiovascular diseases affect bone, in order to minimize any adverse effects. Until there are definitive, randomized, controlled trials on beta-blockers which include fracture as an endpoint, it is unlikely that the current confusing situation can be resolved. Further studies are needed to clarify this interesting conflict.

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