Association between cardiac calcification, sarcopenia, bone fragility: a clinical study

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ABSTRACT

Background: Cardiovascular disease, osteoporosis and sarcopenia are very common conditions. In recent years, interest in the association between bone, muscle and cardiovascular disease has grown. This study aimed to investigate the relationships between cardiac calcification, assessed using the Global Cardiac Calcium Score (GCCS), and bone mineral density (BMD), fragility fractures and sarcopenia.

Methods: In a cohort of 106 subjects (70.4±5.8 yrs) we measured lumbar BMD (BMD-LS), femoral BMD (femoral neck: BMD-FN, total femur: BMD-FT), and body composition using dual-energy X-ray absorptiometry. We also evaluated the presence of sarcopenia. All subjects underwent transthoracic color Doppler echocardiography to assess, by means of the GCCS, the presence of valvular calcification.

Results: After dividing the population, on the basis of their T-scores, into osteoporosis, osteopenia and normality, the degree of valve calcification as assessed using the GCCS was found to be significantly higher in the patients with osteoporosis ($p<0.001$). An inverse correlation emerged between the BMD and GCCS values which reached statistical significance at the level of the lumbar spine and femoral sub-regions in the female population ($p<0.01$). After dividing the population by the presence of fragility fractures, we observed that GCCS values were significantly higher in subjects with fractures versus non-fractured ones ($p<0.05$). Multiple regression models showed that BMD-LS and BMD-FT were independently associated with cardiac calcification. GCCS values were significantly associated with BMI and appendicular skeletal muscle mass in women ($p<0.01$ and $p<0.05$, respectively) and with handgrip strength in men ($p<0.05$).

Conclusion: Our data confirm the presence of a relationship between valvular calcification and decreased BMD values. This is also the first study which relates sarcopenia with valvular calcification.

KEYWORDS

Osteoporosis, cardiac calcification, sarcopenia, GCCS, bone mineral density, cardiovascular risk, echocardiography.

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and the leading cause of mortality in developed countries. Since its prevalence increases with older age, the coming years will clearly see CVD having major economic consequences that could undermine the sustainability of health systems. Non-modifiable risk factors for CVD are: family history, male sex, and advanced age. The major modifiable ones, on the other hand, are hypertension, cholesterol levels (high levels of LDL and low levels of HDL), alcohol consumption, diabetes, overweight/obesity, and smoking [1].

Most cardiovascular events are due to the effects of atherosclerosis in which endothelial dysfunction plays an important role [2]. Also, vascular calcification, previously considered a passive consequence of atherosclerosis, is now recognized as an important and independent risk factor for cardiovascular events. In particular, cardiac calcification and coronary artery calcium (CAC) have been proposed as early markers of atherosclerosis and therefore of CVD [3-5].

Cardiac calcification and CAC are commonly found during computed tomography (CT) or echocardiography examinations. Many studies have demonstrated that CAC detected by CT can be a measure of coronary atherosclerosis [6]. A CAC score was proposed, based on the calcium present in the coronary arteries; this was initially quantified using electron beam tomography [7], although CT has since become the method most frequently used to assess the extent and severity of CAC [8,9]. However, due to its characteristics, CAC as detected by CT is not an easy measure to use in clinical practice.

Subsequently, a semiquantitative echocardiographic score, the global cardiac alcium score (GCCS), was proposed [10]. The GCCS is easily calculated during routine echocardiographic interpretation by assigning points for calcium deposits found at

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the level of the aortic valve, aortic root, mitral annulus, mitral valve, and sub-mitral valve apparatus [10]. Moreover, the GCCS has been reported to be highly correlated with CAC detected by CT and independently associated with stroke, myocardial infarction, and all causes of cardiac mortality [10-12]. Compared with CT, the GCCS is reproducible, readily available, and, being an echocardiographic score, does not involve the use of ionizing radiation. For all these reasons it could constitute an easier and quicker method for predicting cardiovascular risk, to be added to commonly used scores and clinical risk factors.

For years, osteoporosis and CVD were thought to be independent chronic diseases showing a similar increasing prevalence with aging. Several epidemiological and clinical studies have reported that individuals with osteoporosis have an increased risk of developing severe atherosclerosis, vascular calcification, and cardiovascular events [13].

There is also evidence of a correlation between decreased bone mineral density (BMD) and cardiac calcification: one of the first papers on this topic was published back in 1990 [14]. Furthermore, the literature contains several studies (conducted both *in vitro* and in animal models) showing that the process of calcification of cardiac valves seems to be similar to that of bone tissue [15-17].

Sarcopenia is a skeletal muscle disorder characterized by loss of muscle mass and function and associated with physical disability, falls, and fractures. There is emerging evidence that people with sarcopenia have an increased risk of CVD and stroke [18]. To date, however, there are few studies in which the GCCS was used to assess cardiac calcification in osteoporosis. The aim of the present study was twofold:

1) to evaluate the prevalence of valvular calcification, osteoporosis, and sarcopenia in a healthy outpatient population;
2) to evaluate possible correlations between the GCCS, BMD values, and sarcopenia.

Methods

Study population

A cohort of 106 Caucasian subjects aged 55 years or more and living in the area of Siena (Italy) was recruited from a subgroup of men and women who had been participating in a longitudinal assessment as part of a previous larger epidemiological study [19]. The subjects who agreed to participate in the prospective study were consecutively referred to the Center of Prevention, Diagnosis and Therapy of Metabolic Bone Diseases at the University of Siena (Italy) between June 2021 and June 2022.

Individuals with significantly impaired hepatic function, kidney failure, hyperthyroidism, pituitary disease, intestinal malabsorption due to Crohn's disease, celiac disease, or chronic diarrhea in the previous 12 months were excluded. Other exclusion criteria were prolonged intake of drugs known to affect bone metabolism, such as systemic glucocorticoids, gonadic hormones, anticonvulsants, anabolic steroids, teriparatide, vitamin D analogues, denosumab or bisphosphonates, and a history of alcohol abuse.

Written consent was obtained from all participants, and the study was approved by the Institutional Review Board of Siena University Hospital. For all subjects, a detailed medical history was obtained. In addition, height and weight were measured in a standardized manner. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. According to the World Health Organization (WHO) categorization of BMI, the subjects were classified into four groups: underweight (BMI <18.5 kg/m^2), normal weight (BMI ≥18.5 but <25 kg/m^2), overweight (BMI ≥ 25 kg/m^2 but <30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Densitometric and body composition assessment

Using a dual-energy X-ray absorptiometry device (Lunar Prodigy; GE Healthcare, Waukesah, WI), we measured, in all the subjects, BMD at the lumbar spine (LS-BMD) and at femoral subregions, namely the femoral neck (FN-BMD) and total hip (TH-BMD), as well as whole-body BMD (WB-BMD). Osteoporosis and osteopenia were diagnosed according to the WHO definitions: Sex-matched Italian reference data were used for the calculation of T-score Body composition parameters, (fat mass, lean mass, etc.) were determined using the same DXA device (Lunar Prodigy) in conjunction with Encore 2002 software. All scans were performed by the same operator while the subjects were wearing light indoor clothing and no removable metal objects.

Appendicular skeletal muscle mass (ASMM) was determined by combining the lean tissue mass of the regions of the arms and legs, excluding all other regions from the analyses. It was then normalized for the person's height (expressed in squared meters), obtaining the ASMM index (ASMMI) [20]. The definition of sarcopenia was based on the ASMMI, applying the cutoffs proposed by Baumgartner et al.: 5.45 kg/m^2 for women and 7.26 kg/m^2 for men, corresponding to 2 SD below the mean ASMMI for a young reference population of non-Hispanic white men and women [20].

Muscle strength and performance

At the assessment visit, maximal isometric contraction handgrip strength (HGS) in both hands was measured using a digital hand dynamometer (DynEx; Akern/MD Systems, Florence, Italy). While being tested using this device, patients were seated with their shoulder adducted, elbow flexed at 90°, and forearm and wrist in a neutral position; the mean value of three tests was taken into account. HGS values <16 kg in women and < 27 kg in men indicate a condition of low muscle strength (dynapenia) [21].

In all the subjects we evaluated muscle performance using the Short Physical Performance Battery (SPPB). The SPPB consists of a chair stand test (CST), a gait speed test (GST), and a balance test (BT) [22]. In more detail, the CST was performed by instructing the subjects to stand up from a seated position and then sit down quickly, repeating the actions five times. For the GST, subjects were asked to walk forward for a distance of 3 m after standing up from a seated position, and the time taken was counted. For the BT, there are four standing positions that get progressively harder to maintain for patient:

1. Stand with feet side-by-side;
2. Place the instep of one foot so it is touching the big toe of the other foot;
3. Tandem stance Place one foot in front of the other, heel touching toes;
4. Stand on one foot. Not being able to hold the tandem stance (task number 3) for 10 seconds is an indication of increased risk of fall.

The CST, GST, and BT scores each range from 0 to 4, and the SPPB total score, which is the sum of the three scores, thus range from 0 (worst performance) to 12 (best performance). The presence of sarcopenia was established on the basis of EWGSOP2 (European Working Group on Sarcopenia in Older People) guidelines, considering appendicular lean mass (ALM) relative to height (women: ALM and ALM/height^2 <16 kg and < 5.45 kg/m^2, respectively; men: ALM and ALM/h^2 < 27 kg and < 7.26 kg/m^2, respectively) [20,21].

Fracture assessment

Fracture history was collected during the assessment visit. In particular, details of previous fracture sites, including the spine, hip, wrist, clavicle, upper arm/shoulder, rib, pelvis, ankle, upper leg, and lower leg, were taken. In addition, we checked all the reports in the Carestream database of Our Hospital for fracture diagnoses.

Laboratory examination

In all the subjects, fasting blood samples were drawn between 08.00 and 09.00 a.m. to evaluate serum levels of calcium (Ca), phosphate (P), creatinine (Cr), parathyroid hormone (PTH), and 25-hydroxyvitamin D (25OHD). Serum 25OHD was determined by a radioimmunometric method (DiaSorin, Saluggia, Italy) and the intra- and inter-assay coefficients of variation were 6.8% and 9.2%, respectively.

Serum PTH was assessed by means of an immunoradiometric assay using two goat polyclonal antibodies against the human PTH molecule (DiaSorin, Saluggia [VC], Italy). The results were expressed in picograms per milliliter, and the intra- and inter-assay coefficients of variation were 3.6% and 4.9%, respectively.

Global cardiac calcium score (GCCS) measurement

In all the patients, transthoracic echocardiography was performed using a high-resolution ultrasonography device (MyLab™60, Esaote, Italy) with a linear probe of 7.5 MHz. Standard measurements of various echocardiographic and Doppler parameters were performed by the same operator (P.C.) in accordance with American Society of Echocardiography guidelines.

Moreover, we evaluated the GCCS, a semiquantitative echocardiographic calcium score used in previous studies [10,11]. The GCCS is calculated by assigning points for calcium deposits in the aortic root and valve, the mitral annulus and valve, and the submitral apparatus. Points are also added for restriction of leaflet mobility. The score is weighted toward the calcium deposits found at the level of the aortic valve, aortic root, mitral annulus, mitral valve and submitral valve apparatus. The maximum GCCS is 12 points [10,11].

Statistical analysis

All values were expressed as mean ± SD. The Kolmogorov-Smirnov test was used to verify the normality of the distribution of the outcome variables. Clinical data and initial values of the variables measured in the study groups were compared using Student's t-test and the Mann-Whitney U-test as appropriate. Categorical variables were compared by χ^2 test or Fisher's exact test, as appropriate. Analysis of variance (ANOVA) was used to analyze the presence of osteoporosis/osteopenia, fragility fracture, and sarcopenia in men and women. Correlation coefficients between the GCCS and other variables were calculated by partial correlation analysis. Multivariate linear regression models were used to estimate the determinants of GCCS in all subjects. All tests were two-sided, and $p<0.05$ was considered statistically significant. All tests were performed using the SPSS statistical package for Windows version 16.0 (SPSS Inc., Chicago).

Results

Table I shows the clinical characteristics of the study population. The males had slightly higher serum levels of creatine than the females. As expected, the densitometric values were higher in the men than in the women, as were ASMM, ASMMI, and the handgrip strength measurements. Our data showed reduced serum levels of vitamin D in both the men and the women, but without any significant difference between the two groups. Moreover, the GCCS was slightly higher in the women than the men ($p<0.05$).

Table II shows the burden of osteoporosis/osteopenia, fragility fractures and sarcopenia in the population grouped by gender. The percentage of the sample affected by osteoporosis was significantly higher in the women ($p>0.001$), while there were no significant differences in the prevalence of fragility fractures and sarcopenia between the two groups.

Figure 1 shows the GCCS values in subjects with osteoporosis, osteopenia or normal BMD (A), in subjects with and in those without fracture(s) (B), and in those with and without sarcopenia (C). The subjects with osteoporosis had higher GCCS values than those with osteopenia or normal BMD ($p<0.001$). The subjects with previous fragility fractures and those with sarcopenia showed higher GCCS values compared with the participants without fractures and without sarcopenia; however, the difference was significant only for the presence of fragility fracture ($p<0.05$).

Table III shows the age-adjusted partial correlations of the GCCS with variables measuring sarcopenia in the men and in the women. BMI and ASMM were significantly inversely correlated with GCCS in the women ($p<0.01$ and $p<0.05$, respectively) and with HGS in the men ($p<0.05$).

Figure 2 shows Spearman's correlations of BMD-LS and BMD-FT with GCCS in the men and in the women. GCCS was negatively associated with BMD-LS and BMD-TH, but these associations reached statistical significance only in the female population ($r=-0.31$; $p<0.01$; and $r=-0.29$; $p<0.01$, respectively).

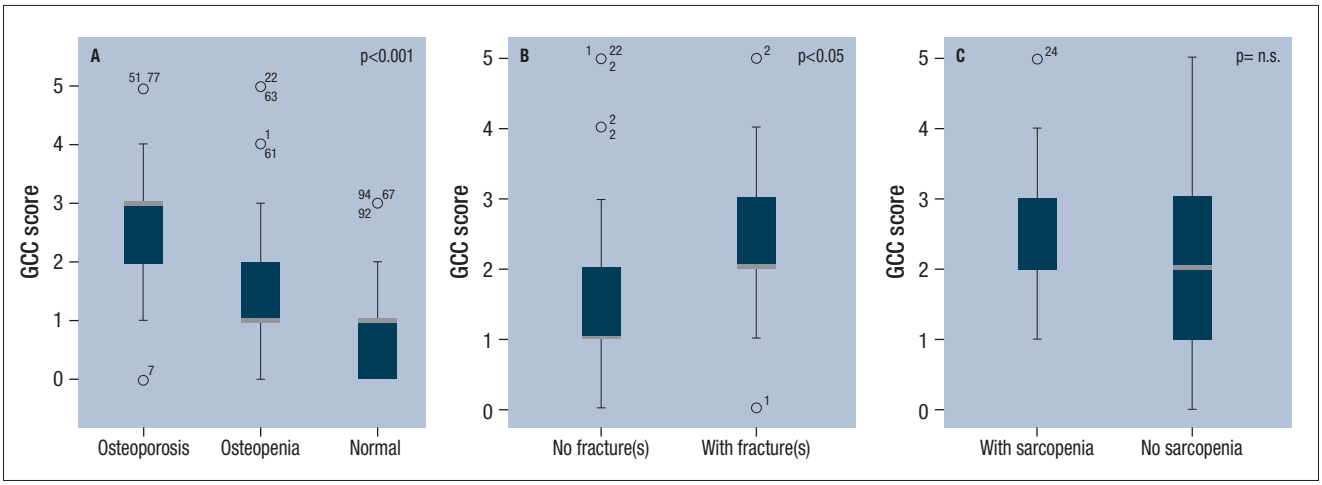
Table I Clinical characteristics of the study population.

	TOTAL	MEN	WOMEN
N (%)	106	21 (19.8)	85 (80.2)
Age (years)	70.4 ± 5.8	71.1 ± 8.4	70.2 ± 5.1
BMI (kg/m^2)	26.9 ± 4.9	28.2 ± 2.6	26.5 ± 5.3
Calcium (mg/dl)	9.5 ± 0.5	9.3 ± 0.4	9.5 ± 0.5
Phosphate (mg/dl)	3.5 ± 0.5	2.9 ± 0.4	3.6 ± 0.4*
Creatinine (mg/dl)	0.8 ± 0.2	1.1 ± 0.3	0.8 ± 0.1*
25OHD (ng/ml)	23.0 ± 10.2	18.6 ± 5.2	23.5 ± 10.5
PTH (pg/ml)	38.7±19.8	43.5±27.1	38±18.9
BMD-LS (g/cm^2)	1.022 ± 0.207	1.237 ± 0.206	0.968 ± 0.170**
BMD-FN (g/cm^2)	0.817 ± 0.162	0.953 ± 0.176	0.770 ± 0.126**
BMD-TH (g/cm^2)	0.806 ± 0.155	1.074 ± 0.171	0.846 ± 0.132**
ASMM (kg)	17.9 ± 4.0	23.1 ± 3.4	16.6 ± 2.9**
ASMMI (kg/m^2)	6.7 ± 1.2	8.0 ± 0.9	6.4 ± 1.1**
Right Handgrip strength (kg)	21.4 ± 6.8	31.7 ± 8.7	19.8 ± 4.8**
Left Handgrip strength (kg)	22.1 ± 7.3	32.8 ± 9.7	19.0 ± 5.3**
Short Physical Performance Battery (SPPB)	10.42 ± 2.0	10.6 ± 1.6	10.4 ± 2.1
Global cardiac calcium score (GCCS)	1.73 ±1.3	1.4 ±1.0	1.8 ± 1.3*
Left ventricular ejection fraction (%)	61 ± 4	58 ± 3	62 ± 3
* p<0.05, ** p<0.01 men vs women			

Table II Prevalence of osteoporosis/osteopenia, fragility fractures and sarcopenia by gender

CHARACTERISTICS	STUDY POPULATION	MEN (*n*=21)	WOMEN (*n*=85)	*p*-VALUE
Diagnosis osteoporosis	Osteoporosis	1/21 (4.8%)	29/85 (34.1%)	0.0001
	Osteopenia	7/21 (33.3%)	43/85 (50.6%)	
	Normal	13/21 (61.9%)	13/85 (15.3%)	
Presence of Fragility Fractures	Yes	4/21 (19.1%)	26/85 (30.6%)	0.293
	No	17/21(80.9%)	59/85 (69.4%)	
Presence of sarcopenia	Yes	2/21 (9.5%)	9/85 (10.6%)	0.886
	No	19/21 (90.5%)	76/85 (89.4%)	
Dichotomous variable, reference category = no (Chi-square test with Yates' correction).				

Figure 1 GCCS in subjects with osteoporosis/ostepenia (**A**), in subjects with fracture(s) (**B**) and in subjects with sarcopenia (**C**)



The results of the two models of multiple linear regression analysis, performed to estimate the determinants of GCCS, are shown in Table IV. Model 1 included age, sex, BMI, BMD-LS, BMD-FN, BMD-TH, history of fracture(s) and ASSMI in the analysis. The multiple regression analysis showed that GCCS was positively associated with age (b=0.102; p<0.001) and inversely associated with BMD-LS (b=-2.962; p=0.001). Model 2 included age, sex, BMI, BMD-LS, BMD-FN, BMD-TH, history of fracture(s), ASSMI, sarcopenia, PTH and 25 OH vitamin D in the analysis. Again, the multiple regression analysis showed that GCCS was positively associated with age (b=0.099; p<0.002) and inversely associated with BMD-TH (b=-1.421; p=0.018).

Discussion

The main finding of this study was that the degree of cardiac calcification, as assessed by the GCCS, is significantly inversely associated with BMD in an elderly population. Furthermore, the multiple regression analysis showed that BMD was independently and negatively associated with the GCCS. To the best of our knowledge, this is the first study to use the GCCS, a semi-quantitative echocardiographic score, to evaluate the degree of cardiac calcification in subjects with osteoporosis and fragility fractures. The existence of a relationship between CVD and osteoporosis has been confirmed in numerous epidemiological and clinical studies. In particular, some longitudinal studies conducted in large cohorts of postmenopausal women demonstrated that progression of aortic calcification was more marked in women who had a greater loss of bone mass and a

Table III Age-adjusted partial correlations of GCCS with variables measuring sarcopenia in men and women.

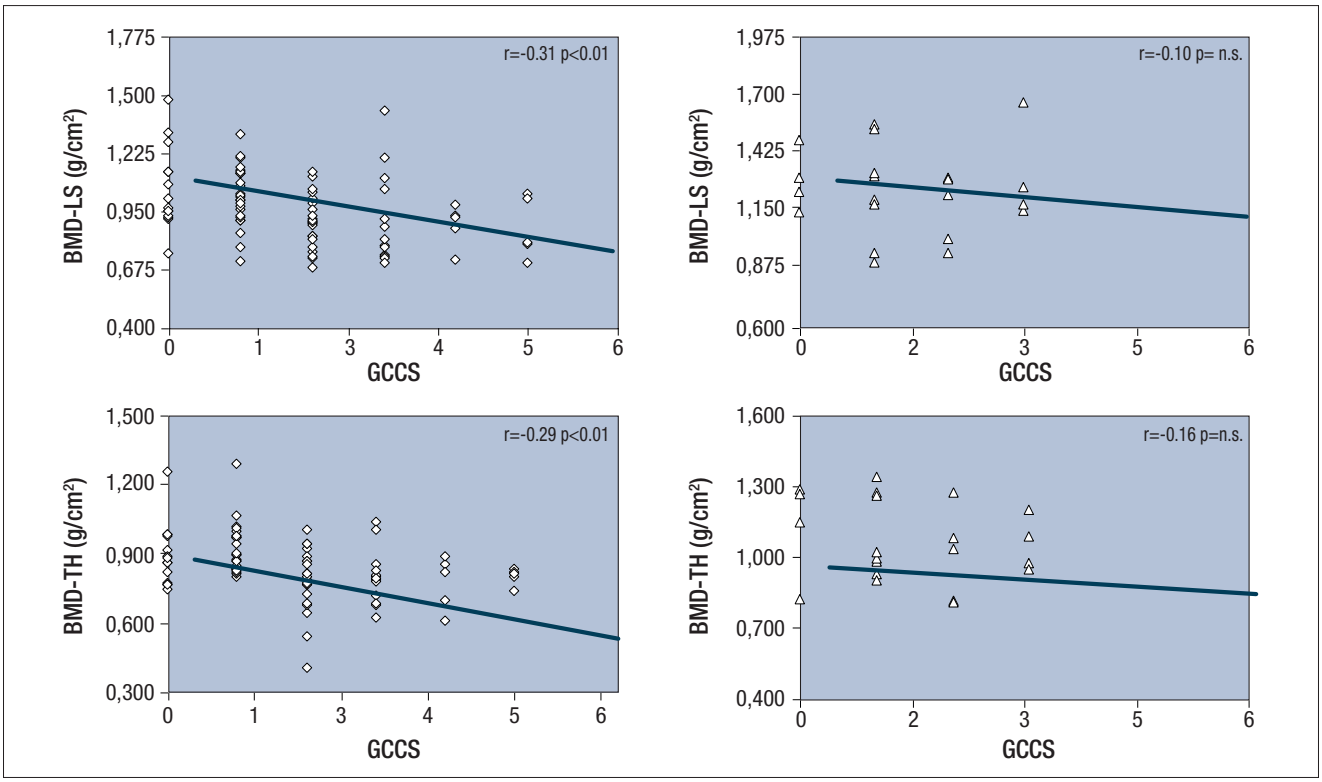
CHARACTERISTICS	MEN	WOMEN
BMI (kg/m^2)	r = -0.13 p = n.s.	r = -0.25 p < 0.01
ASMM (kg)	r = 0.06 p = n.s.	r = -0.18 p < 0.05
ASMMI (kg/m^2)	r = 0.18 p = n.s.	r = -0.10 p =n.s.
Right Handgrip strength (kg)	r = -0.33 p < 0.05	r = -0.05 p =n.s.
Left Handgrip strength (kg)	r = -0.28 p = n.s.	r = 0.06 p =n.s.
Short Physical Performance Battery (SPPB)	r = -0.09 p = n.s.	r = -0.02 p =n.s.

Table IV Multiple linear regression analysis of predictors of GCCS.

VARIABLE	UNSTANDARDIZED COEFFICIENT, B	95%CI	P
MODEL 1			
GCCS			
– Age	0,102	0,052 to 0,152	0,001
– BMD-LS	-2,962	-4,727 to -1,198	0,001
MODEL 2			
GCC score			
– Age	0,099	0,037 to 0,161	0,002
– BMD-TH	-1,421	-5,094 to -0,490	0,018

Whole set of variables included in model 1: age, sex, BMI, BMD-LS, BMD-FN, BMD-TH,history of fracture(s) , ASSMI.
Whole set of variables included in model 2: age, sex, BMI, BMD-LS, BMD-FN, BMD-TH, history of fracture(s), ASSMI, sarcopenia,25OHD, PTH.

Figure 2 Spearman's correlations of BMD-LS and BMD-TH with GCCS in men and women.



greater incidence of fragility fractures [23,24]. In other studies, conducted in both men and women, a reduction in BMD corresponded to an increase in coronary calcification evaluated with cardiac computed tomography angiography [25,26]. Moreover, Graumam et al., in a study conducted in patients with chronic obstructive pulmonary disease, found femoral neck BMD to be negatively associated with abdominal aortic calcification [27]. Instead, a previous study carried out in a large cohort of elderly Dutch subjects (the Rotterdam Study) had reported that the extent of coronary vessel calcification, as measured by electron-beam computed tomography, was significantly associated with loss of BMD in women but not in men [28].

Over 30 years ago, Mori et al. first observed, in a group of elderly women, the existence of a negative correlation between low BMD values and mitral valve calcification [14]. To date, despite growing interest in the relationship between bone metabolism and CVD, only a few clinical studies (recently the focus of a systematic review [16]) have investigated the relationship between valvular calcification and osteoporosis. Most of these studies found that BMD values were inversely associated with aortic valve or mitral valve calcification, especially in women. An important limitation of these studies is the fact that they mostly used transthoracic echocardiography for a mainly qualitative evaluation of aortic valve and mitral valve calcification [16].

In the past, calcification of the heart valve apparatus was believed to be a process of "passive deterioration" of the anatomical structures, rather like vascular calcification; now, however, it is regarded as an "active disease" [29]. It is well accepted that the valve calcification process involves a complex interaction between cells, the extracellular matrix, and biochemical and biomechanical signals. The main cardiovascular risk factors such as hypertension, diabetes, and especially hypercholesterolemia have been extensively studied in the process of vascular and valvular calcification, and all these factors can operate either alone or synergistically [29,30]. Albeit via mechanisms that are not yet fully understood, the mechanical forces exerted at valve level are also involved in the calcification process, both directly and indirectly, acting at the level of the valve cells. The most crucial and controversial aspect of the mechanism of cardiac calcification is the origin of osteoblast-like cells, found to be involved in the process [31]. Transforming growth factor beta1 seems to be the most important factor in the differentiation of valve interstitial cells (VICs) into an osteoblast phenotype, which may be the first step in the valvular calcification process [32-34]. Moreover, in the early stages of cardiac valve calcification, the differentiation of VICs into an osteoblastic phenotype is influenced by the action of proinflammatory cytokines [33]. The same mediators involved in bone tissue and vascular calcification have been found in cardiac calcification, but their role in the heart has not yet been defined [16,29,31].

Another interesting finding of this study is the observation of a relationship between sarcopenia and cardiac calcification. In recent years there has been a growing interest in studying the relationships between sarcopenia and CVD in elderly people. In fact, sarcopenia and CVD share some risk factors and pathogenetic mechanisms, such as physical inactivity, insulin resistance, malnutrition, and inflammation; moreover, when sarcopenia and CVD coexist, mortality increases and quality of life decreases [35]. To date, the few studies on this topic have focused on the relationship between sarcopenia and heart failure [35,36]. Even smaller is the number of studies that have examined the relationship between sarcopenia and vascular or cardiac calcification. A cross-sectional study, carried out in hemodialysis patients, found that sarcopenia parameters did not show any difference between patients with or without cardiac valvular calcification assessed using two-dimensional echocardiography [37].

Ramirez-Velez et al. reported that lower muscular strength, as measured by HGS, is associated with higher AAC (Abdominal Aortic Calcification) scores in the U.S. population ≥40 years of age [38]. Another recent study, from Korea, found insignificant correlations between sarcopenia and coronary artery calcification, whereas osteosarcopenia (i.e., the coexistence of osteoporosis and sarcopenia) was significantly associated with coronary artery calcification [18]. Our data demonstrate the existence of an inverse correlation between the GCCS and sarcopenia. Therefore, sarcopenia may represent a parameter of cardiometabolic risk; accordingly, new prevention strategies targeting muscle quality and quantity in the elderly population could improve prognosis and progression of CVD.

Our study has some limitations. First, its cross-sectional nature precluded the establishment of any relationships of causality between the parameters. A second limitation is the small number of male subjects. Nevertheless, our study has several strengths: first, it is the first study to correlate sarcopenia in a healthy population with cardiac calcification evaluated using the GCCS. In particular, the study population was well evaluated in terms of biochemical parameters and sarcopenia, the latter evaluation being based on assessment of muscle mass and muscle performance.

Conclusions

In short, this study showed that, in elderly subjects, reduced BMD and the presence of fragility fractures are significantly associated with an acceleration of cardiac calcification. The semi-quantitative echocardiographic GCCS was found to be a valid tool for assessing the degree of cardiac calcification and therefore presumably of cardiovascular risk. Furthermore, this study suggests the presence of a close correlation between the degree of sarcopenia and the extent of non-coronary cardiac calcification. Additional studies are needed to specifically address the mechanisms by which osteoporosis and sarcopenia may influence cardiac calcification.

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