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Letters

Bone Mineral Density and Progression Rate of Calcific Aortic Valve Stenosis

Calcific aortic valve stenosis (AS) is the most prevalent heart valve disease in high-income countries (1). There is currently no effective pharmacotherapy to prevent or reduce its progression. The pathobiology of AS is complex and involves several mineralizing processes, similar to skeletal bone formation (1). Previous studies reported an association between altered bone metabolism and risk of AS (1,2). Some studies also suggested that osteoporosis (i.e., osseous demineralization) may be associated with aortic valve/vascular calcification (i.e., ectopic mineralization), which is referred as to the *calcification paradox* phenomenon (1). Nevertheless, it remains unknown whether low bone mineral density (BMD), a marker of altered bone turnover, predicts faster AS progression rate in patients with established disease. In this prospective study, we tested the pre-specified hypothesis that lower BMD and/or osteoporosis, as assessed by dual-energy x-ray absorptiometry (DEXA), is associated with faster hemodynamic progression rate of AS.

The purpose and design of the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis) study were previously described (3). Briefly, patients with AS were prospectively recruited and underwent comprehensive Doppler-echocardiography annually. Furthermore, a subset of patients underwent a DEXA examination within 3 months of their baseline echocardiography. The areal BMD measurement was performed by an experienced technician, blinded to the demographic data of patients, with the use of central DEXA. Moreover, for this study, the femoral neck BMD was used because it is less prone to measurement variability (4). Of the 334 patients recruited through November 2017, 162 patients were included in this sub-analysis.

The primary endpoint was the AS progression rate measured as the annualized increase in peak aortic jet velocity (V_{peak}).

Among the 162 patients (mean age: 65 ± 13 years; 29% women), comorbidities, including hypertension, metabolic syndrome, diabetes, and smoking, were similar across the tertiles of femoral neck BMD, defined by sex-specific thresholds (women: bottom tertile: ≤0.80 g/m^2; middle tertile: 0.81 to 0.88 g/m^2; top tertile: >0.88 g/m^2; men: bottom tertile: ≤0.88 g/m^2; middle tertile: 0.88 to 1.01 g/m^2; top tertile: >1.01 g/m^2) (all $p \geq 0.18$). Moreover, there were no significant differences between groups regarding the calcium ($p = 0.54$) and vitamin D ($p = 0.29$) supplement use or bisphosphonate use ($p = 0.61$). However, patients in the lowest tertiles of femoral neck BMD were older (mean age: 69 ± 10 years vs. 65 ± 10 years vs. 60 ± 17 years, respectively; $p = 0.002$). As expected, there were significant differences between groups for the femoral neck T-score (-2.0 ± 0.4 vs. -1.0 ± 0.3 vs. 0.1 ± 0.5, respectively; $p < 0.0001$) and for diagnosis of osteoporosis defined by a T-score of ≤-2.5 (9% vs. 0% vs. 0%, respectively; $p = 0.003$). Of note, although this did not reach statistical significance, patients who had osteoporosis ($n = 5$; 3%) were older (mean age: 76 ± 7 years vs. 64 ± 13 years; $p = 0.05$) but were less likely to be women (0% vs. 30%; $p = 0.32$), to use calcium (0% vs. 18%; $p = 0.59$) or vitamin D supplements (0% vs. 28%; $p = 0.32$), or to use bisphosphonates (0% vs. 4%; $p = 1.00$) compared with those without osteoporosis. With regard to Doppler echocardiography data, there was no significant difference in baseline AS severity (i.e., V_{peak}) across tertiles of femoral neck BMD (276 ± 54 cm/s vs. 273 ± 50 cm/s vs. 277 ± 50 cm/s, respectively; $p = 0.76$).

During a median follow-up of 3.0 years (interquartile range [IQR]: 2.0 to 4.0 years), the median and mean ± SD annualized increase in V_{peak} were 8 cm/s/year (IQR: 2 to 19 cm/s/year) and 11 ± 18 cm/s/year, respectively. The median and mean annualized increase in V_{peak} was similar between bottom versus middle versus top tertile of femoral neck BMD (median: 11 cm/s/year [IQR: 3 to 19 cm/s/year] vs. 6 cm/s/year [IQR: 2 to 19 cm/s/year] vs. 7 cm/s/year [IQR: 1 to 19 cm/s/year], respectively; $p = 0.66$) (mean: 14 ± 23 cm/s/year vs. 11 ± 14 cm/s/year vs. 10 ± 17 cm/s/year, respectively; $p = 0.55$). Moreover,

TABLE 1 Association of Bone Mineral Density and Osteoporosis With Hemodynamic Progression Rate of Calcific Aortic Valve Stenosis

	Univariable Analysis			Multivariable Analysis*		
	Coeff ± SE	β†	p Value	Coeff ± SE	β†	p Value
Annualized progression rate of V_{peak} according to tertiles of femoral BMD						
Middle vs. bottom tertile of femoral BMD (V_{peak} progression: 11 ± 14 vs. 14 ± 23 cm/s/yr)	-2.8 ± 3.5	-0.07	0.42	-2.7 ± 3.3	-0.07	0.41
Top vs. bottom tertile of femoral BMD (V_{peak} progression: 10 ± 17 vs. 14 ± 23 cm/s/yr)	-3.6 ± 3.5	-0.10	0.30	-3.3 ± 3.3	-0.09	0.32
Annualized progression rate of V_{peak} according to femoral BMD in continuous format						
Femoral BMD, g/m^2	-0.1 ± 11.3	-0.0008	0.99	-13.2 ± 11.5	-0.09	0.25
Annualized progression rate of V_{peak} according to osteoporosis						
Osteoporosis (yes vs. no) (V_{peak} progression: 34 ± 49 vs. 11 ± 16 cm/s/yr)	**23.8 ± 8.0**	**0.23**	**0.003**	**22.6 ± 8.0**	**0.22**	**0.005**

Bold indicates statistical significance. *Multivariable analysis adjusted for age, sex, hypertension, metabolic syndrome, diabetes, lipid-lowering agents, anticoagulants, calcium, and vitamin D supplements, bisphosphonates, creatinine clearance, and baseline aortic valve stenosis severity (i.e., peak aortic jet velocity). †β is the standardized regression coefficient, which indicates the change in SD of the annualized increase in peak aortic jet velocity (V_{peak}) for each increase of 1 SD of each independent variable (i.e., tertiles of femoral BMD, femoral BMD in continuous format, and osteoporosis).

BMD = bone mineral density; Coeff = estimate coefficient; V_{peak} = peak aortic jet velocity.

when compared according to sex, there were no significant differences between tertiles (women: +8 cm/s/year [IQR: -5 to 11 cm/s/year] vs. +4 cm/s/year [IQR: -2 to 7 cm/s/year] vs. +2 cm/s/year [IQR: -10 to 6 cm/s/year], respectively; p = 0.33) (men: +14 cm/s/year [IQR: 4 to 22 cm/s/year] vs. +9 cm/s/year [IQR: 3 to 24 cm/s/year] vs. +12 cm/s/year [IQR: 5 to 22 cm/s/year], respectively; p = 0.72). However, the diagnosis of osteoporosis at baseline was significantly associated with faster AS progression rate (p = 0.003) (Table 1). After adjustment for several risk factors, presence of osteoporosis remained significantly associated with faster AS progression rate (p = 0.005), whereas femoral neck BMD was not associated with AS progression (both p ≥ 0.25) (Table 1).

The main limitation of this study is the small number of patients with low BMD and with diagnosis of osteoporosis.

In summary, this study suggests that osteoporosis may be associated with faster progression of AS. The vast majority of patients who presented osteoporosis were not treated with antiosteoporotic drugs. Whether the treatment of osteoporosis in patients with AS could be efficient to reduce AS progression needs to be further investigated. To this effect, an ongoing randomized clinical trial, SALTIRE II (Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis), is testing bisphosphonates and denosumab as novel treatments for AS.

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