


# Calcification of Cardiac Valves in Metabolic Bone Disease: An Updated Review of Clinical Studies

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**Abstract:** Epidemiological and clinical data have suggested the existence of a relationship between cardiovascular diseases and metabolic bone disease. Several studies have demonstrated that heart valve calcification presents substantial similarities with that of bone. Literature data indicate that there are many active processes which promote osteogenesis and loss of mineralization inhibitors that lead to the deposition of extracellular matrix and proteins of bone tissue in cardiac valves. This review aimed to synthesize the available data in order to allow a better understanding of the relationship between osteoporosis or other metabolic bone diseases, such as primary hyperparathyroidism, and valvular calcification in humans. Electronic databases of Pubmed-Medline, Cochrane Library, and SCOPUS from inception to March 31, 2019 were searched. The full set of the articles potentially eligible were carefully assessed and reviewed. Finally, 23 studies were eligible and included in the systematic review. The majority of studies reported that osteoporosis and/or osteopenia were independent risk factors for valvular calcifications, even after adjusting for common cardiovascular risk factors. This suggests that this relationship is not only due to the presence of common cardiovascular risk factors but rather to underlying biological factors that connect them. Instead, regarding the association between primary hyperparathyroidism and valve calcification, conflicting data were found in the literature. To sum up, most of the literature data confirm that cardiac valve calcification processes are strongly influenced by alterations in bone metabolism. In particular, the patients with osteoporosis or primary hyperparathyroidism have an acceleration in the process of valvular calcification. Additional studies are needed to specifically address the mechanisms by which metabolic bone diseases could influence cardiac valve calcification.

**Keywords:** valvular calcification, osteoporosis, primary hyperparathyroidism, bone mineral density

## Introduction

Over the years there has been growing interest in studying the relationship between metabolic bone disease and cardiovascular diseases. Nevertheless, at present, literature data on relationships between metabolic bone diseases and valvular calcifications are scarce and inconclusive. Heart valve calcification is common in the elderly, and is associated with increased cardiovascular morbidity and mortality.<sup>1</sup> Among valve calcifications, the most studied is aortic valve calcification (AVC), which represents the most frequent cardiovascular disease after coronary artery disease and arterial hypertension, with a prevalence of 0.4% in the general population and 1.7% in the population over 65 years.<sup>2</sup> Moreover, if severe aortic stenosis remains untreated, life expectancy is reduced to less than 5 years. As regards mitral

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valve calcification (MVC), literature data indicate that these mainly affect the posterior part of the annulus and are influenced by advancing age, chronic kidney disease (CKD), and cardiovascular risk factors.<sup>3</sup>

As demonstrated by several studies, heart valve calcification presents substantial similarities with that of bone, sharing many regulatory pathways and subpopulation cells with osteoblastic phenotype.<sup>4</sup> Moreover, literature data indicate that there are many active processes which promote osteogenesis and loss of mineralization inhibitors that lead to the deposition of an extracellular matrix and proteins of bone tissue in cardiac valves. Among these, the endothelial damage induced by mechanical stress is also important.<sup>5</sup> The result is an “active and chronic” process, and not “passive or degenerative”, as hypothesized some time ago. Therefore, at present cardiac valve calcification should be considered the final consequence of a complex and gradual filling process of calcium and mineral phosphate on valves.

Although similar to the atherosclerosis and vascular calcification process, there are some important differences in valvular calcification, both from a physiopathological and pharmacological point of view.<sup>6,7</sup> Literature data, although often being controversial, allow us to better define the major regulatory pathways influencing the valve calcification process. The source of osteoblast-like cells within the cardiac valves remains one of the most controversial and crucial points. Transforming growth factor beta1 (TGF- $\beta$ 1) has been reported to be the most important factor in the differentiation of valve interstitial cells (VIC) into an osteoblast phenotype, which may represent the first step in the valvular calcification process. Transforming growth factor- $\beta$ 1 also promotes the increase of some important bone morphogenetic proteins (BMP).<sup>8,9</sup> In fact, bone formation in heart valves was associated with the expression of BMP-2 and BMP-4 which increase the activity of alkaline phosphatase and osteocalcin in VIC.<sup>11</sup> Other studies have reported that in the early stages of aortic valve calcification the differentiation of valve interstitial cells into an osteoblastic phenotype is influenced by the action of proinflammatory cytokines.<sup>7,12</sup> On the other hand, pathways able to modulate the process of valvular calcification have been identified. In particular, a recent study reported that Matrix Gla Protein (MGP), a known calcification inhibitor which antagonizes BMP-2, negatively regulates calcification of human aortic valve interstitial cells isolated from calcified aortic valves, so highlighting its role as an anti-calcification protein.<sup>13</sup>

Fetuin-A is a circulating protein that can exist in isolation or as a complex with MGP. Fetuin-A, similarly to MGP, antagonizes BMP-2 and TGF- $\beta$ 1 and prevents calcification by binding to calcium crystals. Recently, significant correlations between low levels of fetuin-A and aortic valve stenosis or calcification have been reported.<sup>14,15</sup> Moreover, high levels of Asymmetric Dimethylarginine (ADMA), an inhibitor of Nitric Oxide (NO) synthase, were found in patients with aortic stenosis; therefore, NO appears to slow aortic valve calcification, probably via of a direct effect on valve interstitial cells.<sup>4,8</sup>

Wnt/ $\beta$ -catenin and a receptor activator of nuclear factor kappa  $\beta$  (RANK)/receptor activator of nuclear factor kappa  $\beta$  ligand (RANKL)/osteoprotegerin (OPG) pathways play a crucial role in the later stages of the valvular calcification process.<sup>7</sup> In vascular cells, TGF- $\beta$ 1 and BMP-2 are able to induce nuclear translocation of  $\beta$ -catenin and increase Wnt signaling expression, stimulating the osteogenic differentiation of mesenchymal progenitor cells.<sup>2</sup> The Wnt system is one of the most important regulators in bone formation, leading to expression of RUNX2 and promoting formation of bone tissue by osteoblasts.<sup>2,7,16</sup> In heart valves, stimulation of RANK by RANKL induces an osteoblastic phenotype in VIC (contrary to the bone tissue where the stimulation of RANK by RANKL promotes an osteoclastic phenotype). Moreover, while in bone OPG binds RANKL and prevents bone resorption, at a valvular level the inhibition of RANKL by OPG impedes valve calcification. Confirming this, whilst OPG-deficient mice develop osteoporosis, they simultaneously accelerate vascular calcification in association with increased expression of RANKL in both regions.<sup>7</sup> These data may explain the “calcification paradox” in osteoporosis which is associated with age-independent increases in vascular calcification and even cardiovascular mortality. Fibroblast Growth Factor-23 (FGF-23) works by inhibiting sodium-phosphate transporter in the kidneys, increasing the excretion of phosphate and inhibiting the enzyme 1- $\alpha$ -hydroxylase, so decreasing the production of active Vitamin D (calcitriol). A loss of its function leads to an increase in serum phosphates, with a potential risk of renal calcinosis. However, the Multi-Ethnic Study of Atherosclerosis (MESA) reported a significant correlation between elevated FGF-23 levels and the annual progression of mitral valve calcification but not that of the aortic valve.<sup>17</sup> PTH is a key factor in the regulation of bone metabolism and essential for bone tissue formation; nevertheless, the role of PTH in the valvular calcification process remains unclear. However, the

increase in PTH values is correlated with the progression of aortic valve calcification and with an increase of valve calcification area.<sup>18,19</sup> Finally, human VIC cells, cultured with high concentrations of extracellular adenosine triphosphate (ATP), enhance the expression of osteoblast cell markers such as alkaline phosphatase, and demonstrates the inhibitory effects of adenosine on this process.<sup>4,20</sup>

The major regulatory pathways influencing valve calcifications are listed in Table 1.

This review aimed to summarize the available data in order to allow a better understanding of the relationship between osteoporosis or other metabolic bone diseases, such as primary hyperparathyroidism, and valvular calcification in humans.

## Materials and Methods

A literature review was conducted from inception to May 31, 2019. Pubmed-Medline, Cochrane Library, ClinicalTrials.gov, and SCOPUS databases were searched using the following search terms (“Valvular Calcification” or “Aortic valve calcification” or “Mitral valve calcification”) and (“osteoporosis” or

“Bone Mineral Density” or “Primary Hyperparathyroidism” or “Paget’s disease”).

The process of selection of the studies for review was carried out according to the PRISMA checklist and a PRISMA flow diagram has been shown in Figure 1.

## Results

### Heart Valve Calcifications and Osteoporosis

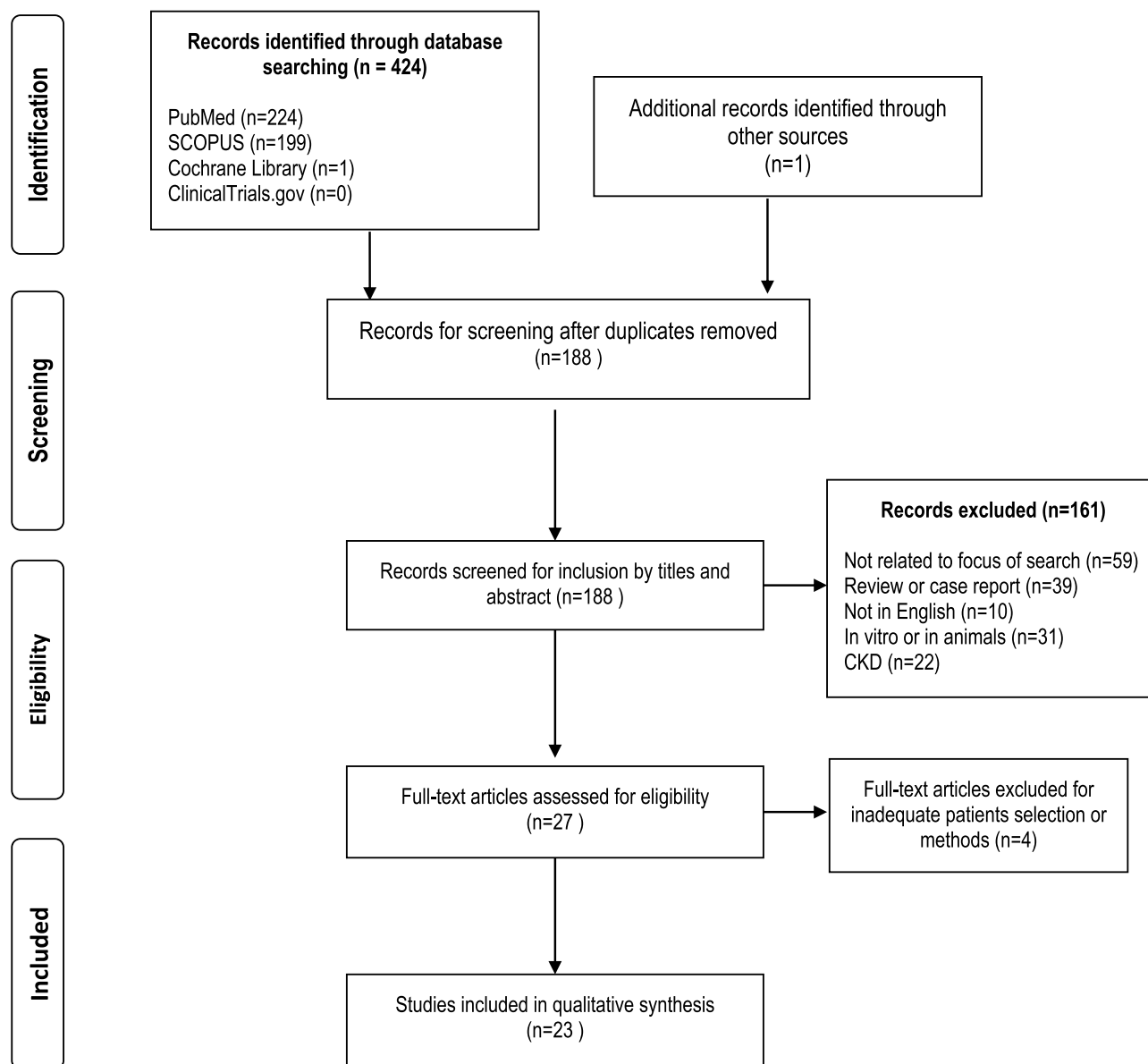
Studies on valvular calcification, both in vitro and in animal models, have shown evidence of regulatory pathways and cell types similar to those of bone tissue. Over the years, although the interest in the association between bone metabolism and cardiovascular disease has been the subject of increasing attention, only a few clinical studies correlated valvular calcification and osteoporosis (or decreased bone mineral density) obtaining non-univocal results. The studies reporting the correlations between these two conditions are listed in Table 2.

In 1990 Mori et al<sup>21</sup> first observed a statistically significant correlation between the lower values of bone

**Table 1** Factors Influencing Valvular Calcification

TGFBI	Stimulates the differentiation of VIC into osteoblastic-like cells <sup>8,9</sup> and promotes the increase of BMP. <sup>10</sup>
BMP	Bone formation in heart valves was associated with the expression of BMP 2 and 4 <sup>11</sup> that increase activity of alkaline phosphatase and osteocalcin in VIC.
MGP	There is a correlation between low levels of MGP and aortic valve calcification, <sup>13</sup> highlighting its role as an “anti-calcification protein”.
WNT	WNT system is one of the most important regulators in bone formation, leading to expression of RUNX 2, and formation of bone tissue by osteoblasts. <sup>16</sup>
RANK/RANKL/OPG	The stimulation of RANK by RANKL induces an osteoblastic phenotype in VIC contrary to the bone tissue where promotes an osteoclastic phenotype. Inhibition of RANKL by OPG avoids valve calcification. Mice Knock-out for OPG gene present osteoporosis and valvular calcification. <sup>7</sup>
NO	NO appears to slow the aortic valve calcification process by a direct effect on VIC. <sup>4,8</sup>
ATP	Human VIC cells, cultured with high concentrations of extracellular ATP, enhance the activity and expression of bone markers. <sup>20</sup>
Fetuin A	The levels of fetuin A inversely correlate aortic valve stenosis, <sup>14</sup> especially when the calcium-phosphorus metabolism is altered. <sup>15</sup>
FGF-23	FGF-23 increases the excretion of phosphate and decreases the production of active Vitamin D (calcitriol). A loss of its function leads to an increase in serum phosphates, with a potential risk of calcinosis. However, the MESA study reported a significant correlation between elevated FGF-23 levels and the annual progression of mitral valve calcification. <sup>17</sup>
PTH	The role of PTH acts in the valvular calcification process remains unclear. However, the increase in PTH values is correlated with the progression of aortic valve calcification <sup>18</sup> and with the increase of valve calcification area. <sup>19</sup>

**Abbreviations:** TGFBI, transforming growth factor beta 1; VIC, valvular interstitial cells; BMP, bone morphogenetic proteins; MGP, matrix Gla protein; WNT, Wnt signaling pathways; RUNX2, runt-related transcription factor 2; RANK, receptor activator of nuclear factor; RANKL, receptor activator of nuclear factor ligand; OPG, osteoprotegerin; NO: nitric oxide; ATP, adenosine triphosphate; FGF-23, fibroblast growth factor-23; PTH, parathormone.



**Figure 1** Flow chart of the studies identified and included in the review.

mineral density (BMD) and mitral annular calcification in elderly Japanese women. Similarly, some years later, Ouchi et al<sup>22</sup> showed that BMD values were significantly lower in elderly women with aortic valve calcification (AVC). Interestingly, another study carried out on 239 elderly subjects (62 males and 177 females) reported that BMD at lumbar spine (as assessed by Computed Tomography CT) was inversely associated with MVC but not with AVC, in postmenopausal women only.<sup>23</sup>

In 2004, Davutoglu et al<sup>24</sup> in a study of 340 women (mean age 56±10 years), observed that the incidence of MVC was higher in women with osteoporosis and that there was a positive correlation between severity of

mitral calcification and severity of osteoporotic disease. Instead, the study by Aksoy et al<sup>25</sup> conducted on 114 patients (49 with AVC and 65 without), found that age and hypertension but not gender were independent risk factors for the development of valve calcification; in this study BMD was inversely correlated with the presence of AVC, and this correlation remained significant after adjusting for age. Similarly, a study carried out on a subset of the EPIC population (Norfolk, UK), found an inverse correlation between BMD at calcaneus, as measured by ultrasound, and risk of AVC independently of known risk factors and potential confounders.<sup>26</sup>

**Table 2** Main Characteristics of the Nine Studies Included in the Review on Valvular Calcifications in Osteoporosis

Study/Year	Study Population	Primary Measures	Bone Evaluation	Valve Calcification Evaluation	Results: Changes in Outcomes
Ouchi Y. 1993 <sup>22</sup>	16♀ (69.6±1.3 years) AVC+ 32♀ (67.3±0.8 years) AVC-	AVC LS-BMD WB-BMD	DXA	Echocardiography	↓ WB-BMD and LS-BMD in AVC+
Sugihara N. 1993 <sup>23</sup>	62♂ and 177♀ (80.2±4.4 years) Group-C: MAC-AVC- Group-M: MAC+AVC-/+ Group-A: AVC+ MAC-	AVC MAC LS-BMC	CT	Echocardiography	↑ osteoporosis in ♀ MAC+AVC-/+ ↓ LS-BMC in MAC+AVC-/+
Davutoglu V. 2004 <sup>24</sup>	340 PM♀ (56±10 years) 217♀ (58.7±9.8 years) MAC+ 123♀ (52.3±9.2 years) MAC-	MAC LS-BMD Hip-BMD	DXA	Echocardiography	↑ osteoporosis in ♀ MAC+ T-score was independent predictor of MAC+ (OR=2.66; 95% CI 1.85–3.83)
Aksoy Y. 2005 <sup>25</sup>	23♂ and 26♀ (68±8 years) AVC+ 43♂ and 29♀ (63±8 years) AVC-	AVC LS-BMD Hip-BMD	DXA	Echocardiography	↓ BMD T-score in AVC+ (-2.15±1.10 Vs -1.2±1.3; P<0.001) T-score inversely associated with AVC+ (OR=0.59; 95% CI=0.41–0.87)
Choi H.S. 2009 <sup>27</sup>	50♂ (62.3± 6.9 years) AVC+ 161♂ (52.4± 7.5 years) AVC- 18♀ (62.3± 6.9 years) AVC+ 99♀ (52.4± 7.5 years) AVC-	AVC LS-BMD Hip-BMD	DXA	Echocardiography	↓ BMD T-score in ♀ AVC+ T-score was independent predictor of AVC+ in ♀ (OR=0.38; 95% CI 0.14–1), but not in ♂
Celik A. 2010 <sup>29</sup>	59 RSF subjects (41.5 years) 11 MAC+; 48 MAC- 40 healthy subjects (44.2 years): 1 MAC+ 39 MAC-	MAC LS-BMD Hip-BMD	DXA	Echocardiography	↓ BMD T-score in ♀ MAC+ (1.6±1.0 Vs -0.5±1.2; P<0,01) BMD T-score predictive of MAC+ (P=0.04)
Pfister R. 2014 <sup>26</sup>	15,651 (62.1±9.1 years) of the EPIC Norfolk population study since Jan 1998 to Oct 2000	AS BUA at heel	QUS by CUBA device	AS defined by ICD-10 code 135	Inverse association between BUA and AS ↑ SD in BUA is associated with ↓ 20% in AS (HR=0.80)
Chan J.J. 2015 <sup>37</sup>	619♀ and 628♂ (60 years) of the Framingham Offspring Study since 2002 to 2005	AVC MVC AAC CAC vBMD of L3	CT	Agastone Score by CT	No association between vBMD and AVC+ or MAC+ vBMD inversely associated with CAC+ and AAC+ in ♀ but not in ♂
Messera D. 2017 <sup>38</sup>	868♀ and 629♂ (76.2 ± 4.8 years) of the Cardiovascular Health Study	AVC MAC Hip-BMD	DXA	Echocardiography	No association between BMD and AVC+ or MAC+ in ♀ or in ♂ Inverse association between Hip-BMD and AVC+ (RR=1.24; 95% CI 1.01–1.56) in ♂ Borderline association Hip-BMD and MAC+ in ♀

**Abbreviations:** ♀, female; ♂, male; AVC, aortic valve calcification; BMD, bone mineral density; LS-BMD, BMD at lumbar spine; WB-BMD, BMD at whole body; Hip-BMD, BMD at femoral; DXA, dual-energy X-ray absorptiometry; MAC, mitral annular calcification; LS-BMC, bone mineral content at lumbar spine; CT, computed tomography; PM, postmenopausal; RSF, renal stone formation; MVC, mitral valve calcification; AS, aortic stenosis; ICD-10, "International Classification of Disease" (ICD)-10 hospital discharge code 135; QTC, quantitative computed tomography; AAC, abdominal aortic calcification; CAC, coronary artery calcification.

Also Choi et al,<sup>27</sup> in a study conducted on 328 Korean patients (211 men and 117 women), reported that the presence of AVC, assessed by echocardiography, was inversely

correlated with BMD; however, in this latter study, after adjusting for various comorbidities (age, BMI, cigarette smoking, arterial hypertension, hypercholesterolemia, and

diabetes mellitus), the BMD remained independently and inversely related with AVC only in women.<sup>27</sup>

As previously reported, MVC is correlated not only with common cardiovascular risk factors, but also with the presence of CKD and, consequently, altered phospho-calcic metabolism.<sup>28</sup> In fact, the study by Celick<sup>29</sup> reported that the prevalence of MVC was higher in patients with renal stones compared to healthy controls, whereas the BMD of patients with MVC was significantly lower with respect to those without.

The incidental finding of vertebral fractures during routine radiographic examinations, such as the CT, is common and has been demonstrated to be correlated with an increase in mortality from all causes.<sup>30</sup> Low BMD and vertebral fractures are also associated with cardiovascular diseases and cardiovascular mortality, especially in diabetic patients or those who have suffered coronary events.<sup>31,33</sup> On the other hand, the finding of calcifications in the cardiovascular system has been reported to be correlated with the presence of osteoporosis and bone fractures.<sup>33,35</sup>

In order to clarify if vertebral fractures found during routine radiographic examinations were independent predictors of future cardiovascular events, Gondrie et al<sup>36</sup> conducted research in the multi-center PROVIDI study (Prognostic Value of unrequested Information on Diagnostic Imaging). The results showed that having at least one fracture was a predictive element of future cardiovascular events, and this finding remained statistically significant after adjusting for age and sex. However, statistical significance became borderline when adjusted for valvular, aortic, and coronary calcifications.<sup>36</sup> However, this study provided further evidence of an association between valvular (mitral and aorta) and coronary calcifications with vertebral fractures that resulted independent of age and gender.

Another two recent studies evaluated the correlation between osteoporosis and valve calcification. Chan et al,<sup>37</sup> in a study carried out on 1317 elderly subjects (689 women and 628 men with a mean age of 60±9 years), found no significant correlation between AVC and BMD; however, in both men and women, there was a significant inverse correlation between reduction of BMD and severity of vascular calcification, especially at the level of the abdominal aorta.

Moreover, the study by Messera et al,<sup>38</sup> carried out on 1497 elderly patients from the CHS (Cardiovascular Health Study), showed that there were no significant associations between BMD and the presence of any valvular calcification (aortic and/or mitral valve). However, aortic calcification was greater

in male patients with osteoporosis at total femur after adjusting for various confounding factors. This result has not been demonstrated for women. Conversely, in women there was a correlation (although not statistically significant) between calcification of the mitral valve and the decrease in BMD at the femur.<sup>38</sup>

## Valvular Calcifications in Primary Hyperparathyroidism

It has long been known that patients with primary hyperparathyroidism (PHP) have structural and functional changes to the heart, with a consequent increasing of cardiovascular events. The principal studies which have evaluated the relationship between valve calcification and primary hyperparathyroidism are reported in Table 3.

Already in 1981, Roberts and Waller,<sup>39</sup> by evaluating morphological aspects in the heart during the autopsies of 18 patients with chronic hypercalcemia, reported that chronic hypercalcemia was associated with an accelerated deposition of calcium in heart valves, in media and intima of coronary arteries and in the myocardium.

More recently, Nierdle et al,<sup>40</sup> in a study carried out on 21 PHP patients and compared with 21 age- and sex-matched controls, observed a significant increase in the incidence of aortic valve and mitral annulus calcifications in subjects with PHP compared to controls.

In a prospective study, Stefenelli<sup>41</sup> evaluated the effects of PHP on heart valves, myocardium, and myocardial function in 54 PHP patients, who underwent echocardiography examination before and 12±2 months after parathyroidectomy. A control group of 49 people was used for comparison; also in this case, the results highlighted a close correlation between the presence of primary hyperparathyroidism and cardiac valve calcifications. In fact, AVC was found in 63% of subjects with PHP and MVC in 49% (vs controls: 12% and 15%, respectively). Interestingly, while left ventricular hypertrophy presented a regression after parathyroidectomy, valve calcifications remained unchanged and without progression over time.

Some years later, a prospective study by the same authors carried out on 123 PHP patients undergoing parathyroidectomy and controlled up to 41 months later, confirmed regression of left ventricular hypertrophy and no progression of valvular calcifications.<sup>42</sup> Also, in the study by Langle et al<sup>43</sup> a significant increase of cardiac calcifications in patients with PHP compared to controls was reported, but in this study no significant correlations

**Table 3** Main Characteristics of the Nine Studies Included in the Review on Valvular Calcification in Primary Hyperparathyroidism

Study/ Year	Study Population	Primary Measures	PHP Evaluation	Valve Calcification Evaluation	Results: Changes in Outcomes
Nierdle B. 1990 <sup>40</sup>	20 ♀ and 1 ♂ (58±12 years) PHP+ 21 Controls (59±10 years)	AVC MVC	Ca, P, CaxP, Cr, PTH serum level	Echocardiography	AVC 57% in PHP+ and in 1 controls. MVC 33% in PHP and 13% in controls
Stefenelli T. 1993 <sup>41</sup>	47 ♀ and 7 ♂ (61.4±10.7 years) PHP+ 50 Control (60.1±10.6 years)	AVC MVC	Ca, P, CaxP, Cr, PTH serum level	Echocardiography	AVC in 63% of PHP Vs 12% controls MVC in 49% PHP Vs 15% controls
Langle F. 1994 <sup>43</sup>	94♀ and 38♂ (57±16 years) PHP+: Asymptomatic (5♀and 2♂) (49±20 years) Minimal symptoms (39♀and 9♂) (65±13 years) Classic symptoms (50♀and 27♂) (58.14 years)	AVC MVC MC	Ca, P, CaxP, Cr, PTH serum level	Echocardiography	103 (78%) PHP+ had ≥1 cardiac abnormalities PHP+ with classic symptoms: AVC 40% Severe AVC 5% MVC 42% Severe MVC 3% PHP+ with asymptomatic and minimal: AVC 64% Severe AVC 7% MVC 38% Severe MVC 5%
Dalberg K. 1996 <sup>44</sup>	32♀ and 12♂ (52–70 years) PHP+ 3♂ and 20♀ (51–67 years) Controls	VC MC	Ca, PTH serum level	Echocardiography	19 PHP+ (43%) had C.C. Vs 14 Controls (61%)
Stefenelli T. 1997 <sup>42</sup>	90♀ and 33♂ PHP+ (61.2±13.9 years)	AVC AS MVC	Ca, P, CaxP, Cr, PTH serum level	Echocardiography	Prior PTX: AVC 46%; grade 2–3 AVC: 10.6% MVC 29%; grade 2–3 MVC: 7.3% After PTX (41 month): AVC 39%; grade 2–3 AVC 5.5% MVC 31%; grade 2–3 MVC 7.3%
Walker MD. 2010 <sup>45</sup>	54 mild PHP+ (62±7 years) 19% ♂ 76 Controls (63±9 years) 20% ♂	MAC	Ca >10.2 but <12 mg/dL, PTH serum level	Echocardiography	PHP+ no association between Ca <sup>2+</sup> or PTH and VC MAC in mild PHP: 13%; MAC in Controls 21%
Iwata S. 2011 <sup>19</sup>	51 PHP+ (61.4±1 years) 20% ♂ 49 Controls (63.4±0.8 years) 24% ♂	AVCa	Ca >10.2 but <12 mg/dL, PTH serum level	Echocardiography	AVCa ↑ in PHP+ (0,24±0,02 cm <sup>2</sup> vs 0.17 ±0.02; P<0.01) AVCa associated with PTH (P<0.05)
Walker MD. 2012 <sup>62</sup>	44 PHP+(62±8 years) 80%♀	MVC AVCa	Ca > 10.2 but <12 mg/dL, P, PTH serum level	Echocardiography	MC and VC not decline after PTX. AVCa increased by 5% at 1 year post PTX and remained above baseline at 2 years. MVC: 16% before and 14% 2 years after PTX
Mishra A. K. 2017 <sup>46</sup>	8♂ and 10♀ (38.61±12.54 years) PHP+ 18 controls (age- and sex-matched)	VC	Ca, P, Cr, PTH serum level	Echocardiography	No patients with severe PHP had VC

**Abbreviations:** ♀, female; ♂, male; PHP, primary hyperparathyroidism; AVC, aortic valve calcification; MCV, mitral valve calcification; Ca, calcium; P, phosphate; Cr, creatinine; CaxP, calcium-phosphate-product; PTH, parathyroid hormone; MAC, mitral annular calcification; AS, aortic stenosis; AVCa, aortic valve calcification area; VC, valvular calcifications; MC, myocardial calcification; PTX, parathyroidectomy.

between cardiac calcification findings and severity of the clinical features were observed.

In contrast, Dalberg et al,<sup>44</sup> in a study published several years before, found a non-significant correlation between cardiac and valvular calcifications and PHP.

Also the study by Walker et al,<sup>45</sup> carried out on a group of 54 PHP subjects, reported that there was no correlation between PHP and valve calcification or cardiac hypertrophy. In 2011, in a study conducted in the same patients cohort, Iwata et al<sup>19</sup> compared the structure and function of the aortic

valve of PHP patients with a control population and found that aortic valve calcification area resulted greater in PHP subjects (even when adjusted for risk factors such as age, sex, BMI, cigarette smoking, hypertension, hypercholesterolemia, and GFR estimated). Note that aortic valve calcification area was positively and significantly correlated with parathyroid hormone values, but not with remaining parameters of phospho-calcium metabolism such as serum calcium, serum phosphate, and 25 hydroxy-Vitamin-D.<sup>19</sup> This demonstrates a significant role of PTH in the pathophysiology of cardiac valve calcification.

It should be noted, however, that the patients enrolled in the studies of Walker et al, Iwata et al, and Dalberg et al had serum calcium levels below 12 mg/dL, while in other studies the serum calcium levels were higher (>12 mg/dL), implying a possible dose dependent effect of calcemia in the valve calcification process.

Nevertheless, a recent study conducted on a small number of patients suffering from PHP (18 patients), with mean calcemia values higher than 12 mg/dL (12.5 ± 1.4 mg/dL) did not show the presence of valvular calcifications in affected patients.<sup>46</sup>

## Valvular Calcifications in Paget's Disease of Bone

Also Paget's disease has been associated with an increase in cardiac calcifications, including myocardium and valve apparatus.<sup>47-51</sup> The first studies date back to 1944, when Harrison and Lennox,<sup>47</sup> using data from autopsies, reported an increase in incidence of valvular calcifications in patients suffering from Paget's disease compared to unaffected subjects (17 of 43 cases, 39%, vs 8% in 223 controls of similar age distribution). Later, Strickberger et al,<sup>49</sup> in a study based on autopsy reports, found a higher incidence of aortic valve calcification with respect to mitral valve and that the severity of the calcifications was correlated with the severity of Paget's disease.

Similarly, the study by Hultgren et al<sup>50</sup> showed a strong association between aortic valve calcification and Paget's severity (22% in severe disease vs 5.5% in moderate disease and 3.5% in controls). Moreover, in this latter study no differences in the severity of atherosclerosis between pagetic patients and controls were found, suggesting that in Paget's disease cardiac valve calcification may be independent from atherosclerosis.<sup>50</sup> Finally, a more recent study carried out on 220 pagetic patients the valvular calcifications were found to be present in 15% of pagetic patients.<sup>51</sup>

## Discussion

Although valvular calcification and osteoporosis share several cardiovascular risk factors such as age, hypertension, dyslipidemia, diabetes, and cigarette smoking,<sup>52</sup> the majority of studies of this review reported that osteoporosis and/or osteopenia were independent risk factors for valvular calcifications even after adjusting for common cardiovascular risk factors. This suggests that this relationship is not only due to the presence of common cardiovascular risk factors but most probably also to underlying biological factors that connect them.

Furthermore, it seems unlikely that valvular calcification could be secondary only to the catabolic processes in osteoporotic bone, also considering the lack of any significant impact of bisphosphonate therapy in the progression of aortic valve calcification, as confirmed in a recent retrospective observational study.<sup>53</sup> The existence of underlying bio-humoral mechanisms that connect the two pathological conditions would seem more probable. In support of this, it has been proposed that Vitamin D may also represent a common regulator of both bone metabolism and valve calcification.<sup>54-56</sup> In fact, in the study by Ortlepp et al<sup>54</sup> it was shown that the genetic polymorphism of vitamin D (VDR Bsm1 allele B with respect to b) associated with low bone mineral density is also associated with a higher risk of developing calcific aortic stenosis.

Interesting results were also noted in gender difference, in particular as reported in the study by Choi et al,<sup>27</sup> the association between low bone mineral density and aortic valve calcification seems to be stronger in women than in men. Estrogens could explain this relationship; in fact, estrogens play an important role in the pathophysiology of both osteoporosis and cardiovascular diseases in women. Moreover, an estrogen receptor-alpha gene polymorphism that is associated with BMD in many clinical studies,<sup>57,58</sup> has also been observed in post menopausal women with AVC.<sup>59</sup>

Moreover, in Messera et al's<sup>38</sup> study, BMD values at the femoral neck correlated with AVC in males, while in women they correlated with MVC. Similarly, in the study by Sugihara and Matsuzaki<sup>23</sup> a higher incidence of MVC was found in women with low bone mineral density than in men. A stronger association between MVC and low BMD in women than in men could be explained by the fact that mitral valve calcification is more common in women as they have a higher incidence of osteoporosis, also due to the effect of the estrogenic decline in the post menopausal



period. Furthermore, alteration in bone metabolism seems to have a greater impact on development of MVC.<sup>60</sup> These considerations support a higher risk of MVC in women suffering from bone metabolism disorders.

Also, with regard to the association between primary hyperparathyroidism and valve calcification, conflicting data has been found in the literature.

Normally, PTH plays a central role in the regulation of calcium homeostasis and its release is triggered by a reduction in serum calcium level.<sup>61</sup> Certainly, there is a positive correlation between the severity of the disease and valvular calcification. In PHP, the role of hypercalcaemia found in the advanced stages of the disease appears to be a fundamental element for the development of valvular calcifications. This could explain the poor association between these two conditions in the studies where the mean value of calcemia was lower than 12 mg/dL.<sup>19,45,62</sup>

In the study by Iwata et al,<sup>19</sup> the aortic valve calcification area was greater in PHP patients than in controls, implying a role of PTH not only in the beginning of calcification but also in its progression. Also, it is important to emphasize that in PHP patients who have undergone parathyroidectomy there is an absence of regression but also of progression in valve calcification.<sup>41,42,62</sup>

The fact that in patients without PHP affected by severe AVC there is a significant recurrence of the AA variant of *PTH* gene<sup>63</sup> and that patients with secondary hyperparathyroidism present a significant increase in valvular calcifications<sup>19</sup> supports the crucial role of PTH in the valve calcification process.

In pagetic patients the high AVC incidence can be explained by hemodynamic changes that occur in advanced stages of the disease rather than to alterations of serum calcium and phosphate which are usually normal in patients with Paget's disease.

In fact, due to the increased cardiac output, the aortic valve is affected by a greater stress which would lead to endothelial damage which would favor the triggering of calcification and thickening of leaflet; this hypothesis seems to confirm literature data reporting that the degree of aortic valve calcification was positively correlated with the severity of Paget's disease.<sup>49,50</sup>

To date, the fact that the prevalence of valvular calcifications is lower in more recent reports about Paget and PHP is probably due to the early stage of diagnosis in these diseases.

To sum up, most of literature data confirm that cardiac valve calcification processes are strongly influenced by

alterations in bone metabolism. In particular, the patients with osteoporosis or primary hyperparathyroidism have an acceleration in the process of valvular calcification. Additional studies are needed to specifically address the mechanisms by which metabolic bone diseases could influence cardiac valve calcification.

## Disclosure

The authors report no conflicts of interest in this work.

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