# Review Article

# Association of bone mineral density and trabecular bone score with cardiovascular disease

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## ABSTRACT

Traditionally, osteoporosis and cardiovascular disease (CVD) are considered as separate chronic diseases. Increasing evidence now links osteoporosis with hypertension, abnormal lipid metabolism, atherosclerosis, vascular calcification (VC), and congestive heart failure. VC coexists with bone loss, and aortic calcification is a strong predictor of low bone mineral density (BMD) and fragility fractures. The same holds true for coronary artery calcification (CAC): the lower the BMD, the higher the CAC. Trabecular bone score (TBS) iNsight software can analyze the existing BMD database to obtain the bony microstructure score (TBS). Many TBS-related studies include fracture risk, normal aging, diabetes, potential genes, obesity, and asthma severity prediction. The inverse relationship of TBS to VC may provide insight into bone–vascular interactions in chronic kidney disease. A higher TBS has been associated with moderate, but not high, CAC. One explanation is that bone microstructural remodeling becomes more active during early coronary calcification. Increased risk of 10-year likelihood of hip fracture and major osteoporotic fracture as estimated by the fracture risk assessment tool FRAX® is significantly and independently associated with more severe CAC scores. Dual-energy X-ray absorptiometry and FRAX® can be used to predict fracture risk and CAC scores, identifying patients who may benefit from early intervention. This review will discuss the relationship and possible mechanism of BMD, TBS, and FRAX® with CVD and VC or CAC.

**KEYWORDS:** *Bone mineral density, Cardiovascular disease, Coronary artery calcification, Trabecular bone score*

## INTRODUCTION

Osteoporosis and atherosclerosis frequently occur concomitantly, may share similar pathogenic mechanisms, and could be biologically linked [1-3]. However, their independent association is still unclear [4]. Vascular calcification (VC) is a major contributor to cardiovascular disease (CVD), which in turn contributes to VC [5]. Coronary artery calcification (CAC), a type of VC which occurs in the coronary artery, plays a role in the pathogenesis of coronary atherosclerosis [6]. The degree of VC or CAC is also a predictor of cardiovascular risk and mortality and is inversely correlated with bone mineral density (BMD) [7-9].

While some studies have investigated the relationship of BMD with CVD, VC, or CAC, the mechanism remains unclear. This review will explore the differences in trabecular BMD and cortical BMD and their relationship to CVD, VC, or CAC. This article will also review the clinical application of trabecular bone score (TBS) and fracture risk assessment tool (FRAX®) in terms of their association with CVD, VC, or CAC.

## BONE MINERAL DENSITY AND TRABECULAR BONE SCORE

The diagnosis of osteoporosis typically depends on area BMD measurements using dual-energy X-ray absorptiometry (DXA) [10]. Practically, DXA studies present BMD by including both cortical and trabecular bone content. However, cancellous bone microarchitecture is the key determinant of bone strength, which is often measured by quantitative computed tomography (qCT). However, this procedure involves

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higher radiation exposure, is more expensive, and requires a larger instrument requirement than DXA [11]. For cases with DXA measurement of the lumbar spine, the BMD value may be overestimated relative to cases with abdominal aorta calcification [12].

The TBS is a texture parameter that can be computed from the two-dimensional lumbar spine DXA image [13]. Since the BMD T-score may not fully capture the risk of fragility fracture, the noninvasive analytic tool TBS was developed. The TBS is a texture parameter that evaluates pixel gray-level variations in DXA images of the lumbar spine [10]. TBS decreases with age and appears to reflect qualitative aspects of skeletal structure complementary to BMD [13]. TBS, a variogram, is related to bone microarchitecture (bones with few large spans, i.e., low TBS, are mechanically weaker than those with a myriad of fine spans, i.e. high TBS) and is complementary to predict fracture risk, as well as lumbar spine BMD measurements. Therapeutic strategies for osteoporosis differ in terms of TBS [13].

Unlike qCT, with its higher radiation exposure and increased expense, TBS measure the trabecular microarchitecture with a simple DXA machine [14], which is cheaper, involves less radiation exposure, and only needs an immediately "1 click – 3 s" additional software analysis when measuring the traditional lumbar spine BMD. No additional examinations or radiation doses are needed. The TBS can also be retrospectively analyzed in the same equipment from an existing DXA scan to quantify the bone microarchitectural texture.

## CARDIOVASCULAR DISEASE/CORONARY ARTERY CALCIFICATION

The CAC score, measured by multidetector row computed tomography (MDCT), is a surrogate marker for total calcified plaque burden (subclinical and overt atherosclerosis) and may predict future coronary events independently of other risk factors [15,16]. The absence of CAC strongly excludes obstructive coronary artery disease (CAD), and CAC predicts the presence of coronary atherosclerotic plaque. However, its absence does not exclude the presence of coronary atherosclerotic plaque, especially in patients aged <55 years. Plaque composition shifts from noncalcified to calcified with increasing age, which may affect the vulnerability of these lesions over time [17]. CAC has a role in CAD development [18-20]. Indeed, CAC and CT angiography in asymptomatic elderly patients can predict CAD [21]. In one analysis using simple linear regression [22], similar to prior studies, hypertension, hyperlipidemia, blood pressure, and triglyceride levels were positively correlated with the CAC score and with the risk for coronary as well as other cardiovascular events [23,24]. CAC has also been associated with high serum concentrations of some biomarkers, including undercarboxylated osteocalcin and fibroblast growth factor 23 [25,26].

## BONE MINERAL DENSITY AND CARDIOVASCULAR DISEASE/CORONARY ARTERY CALCIFICATION

BMD has been inversely associated with subclinical and clinical CVD, even after adjusting for potential confounding factors [27]. Subjects who self-report a previous myocardial infarction had higher odds of having low BMD, when adjusting for CVD and osteoporosis risk factors; this risk was not significant in women but was significant in men [28]. Postmenopausal women with osteoporosis are at an increased risk for cardiovascular events, in proportion to the severity of osteoporosis at the time of diagnosis [29].

Some studies showed an inverse association between BMD or volumetric BMD (vBMD) and the score or presence of aortic calcification (AC) or CAC [3,30,31]. This relationship may be related to age [27], shared risk factors (smoking) or common pathophysiological mechanisms (hormones or inflammatory cytokines) [3]. Although many studies have found little or no association between BMD and CAC, several studies did [32]. This inconsistency in results may be due to sex-and/or ethnicity-specific differences [3,27]. An increased CAC score and subclinical atherosclerosis plaque burden as determined by MDCT has been associated with low BMD in all women, independent of cardiovascular risk factors and age [33]. BMD of the femur and lumbar spine were inversely associated with the CAC score after adjusting for age and metabolic parameters in women, but not in men [33]. In the study, their correlation between BMD and CAC score was more significant for the femur area than for the lumbar spine. In another study analyzing FRAX® and CAC, only the right femoral neck T-score and left total hip T-score showed a significantly inverse relationship with the CAC score [34].

One model was reported to show that hypertension, hyperlipidemia, triglyceride, and L spine T-score were predictors of CAC when CAC was >0 and could explain 73.2% of the variance in CAC [22]. Longitudinally, the Rotterdam Study showed no association between CAC and BMD or fracture risk, except for BMD loss with higher follow-up CAC in women, an association which may be related to low estrogen levels [35]. In patients on dialysis, high parathyroid hormone level and osteoporosis predict CAC progression [36]; and bone volume/total volume scores, assessed by high-resolution peripheral qCT, were significantly lower in patients with CAC scores ≥100 [37]. In a study measuring BMD with DXA, lower BMD (total body BMD and BMD of subregions, in particular the legs) was independently associated with higher CAC scores, but only in female patients with end-stage renal disease [38]. Another study on 5,590 consecutive individuals, which calculated thoracic BMD by MDCT, found that lower BMD levels were independently associated with CAC severity, and CAC could predict mortality in both genders across ethnicities [39]. A recent 2019 study, measuring volumetric thoracic BMD and CAC using MDCT, also found BMD and CAC were inversely related in both men and postmenopausal women, supporting the hypothesis of a direct relation between bone loss and the development of atherosclerosis, irrespective of sex [32].

It is estimated that about 30% of postmenopausal women in developed countries have osteoporosis and at least 40% of women and 15%–30% of men with osteoporosis will sustain a fracture [40,41]. Another study showed that 4.7% of their study cohort had osteoporosis, and 26.3% had low bone mass

in totally included 490 middle-aged women [3]. A study focus on the CAC in postmenopausal women showed that 17.7% of the patients had osteoporosis in the lumbar spine and 44.6% had osteopenia, whereas in the femoral neck, 14.0% had osteoporosis and 46.8% had osteopenia [42]. In this study, according to lumbar spine T-score, it showed 10.4% osteoporosis, 35.1% osteopenia in patients without CAC, and 22.9% osteoporosis, 51.4% osteopenia in patients with CAC. According to femoral neck T-score, data reported 7.8% osteoporosis, 41.6% osteopenia in group without CAC, and 18.3% osteoporosis, 50.5% osteopenia in group with CAC [42].

## Trabecular volumetric bone mineral density, trabecular bone score, and cardiovascular disease/coronary artery calcification

Cortical and trabecular bone is known to have different turnover rates and age-related patterns [43]. Previous studies of the relationship between trabecular vBMD and AC or CAC have yielded inconclusive results [3,27,35,44]. Cortical, but not trabecular, vBMD was associated with significantly decreased odds of the prevalence of abdominal AC (AAC) independent of other traditional risk factors (age, body mass index [BMI], lifestyle factors, diabetes, and hypertension) [27]. Other studies showed an association of trabecular vBMD with AC or CAC [3]. In a study of vBMD and VC measured by CT in middle-aged women, the population of AC and CAC was divided into three levels and lower trabecular BMD of the spine was found significantly associated with both high AC levels and high CAC levels; the latter was not significant after adjusting for age [3]. No association of vBMD with moderate AC or CAC was observed [3].

TBS, obtained from lumbar spine DXA images, measures the trabecular microarchitecture of the bone and provides a surrogate measure of microarchitectural integrity not captured by BMD. An Australian study found no significant correlation of AAC scores to any BMD parameter. However, TBS values were inversely correlated to AAC scores ($\beta = -0.206$, $P = 0.013$), a relationship that remained significant in multivariable linear regression after adjusting for age, BMI, and time on dialysis ($\beta = -0.160$, $P = 0.031$) [45]. Similarly, a Taiwan study suggested that TBS value (per 1 standard deviation increase) could predict moderate CAC (odds ratio [OR] =2.39, $P = 0.011$) but not high CAC (OR = 1.03, $P = 0.928$). This relationship still existed even after adjusting for covariates [11]. This result is significantly different from those of previous studies with qCT and CAC [4,37]. The difference may be due to the diverse methodologies used. Since VCs have complex mechanisms, another possible explanation may be that early CAC is associated with a more complex variogram of bone microarchitecture during bone remodeling. However, when CAC is far advanced, the higher TBS has no significance in predictive value. This would mean that the molecular cascades and procalcific microenvironment are dynamic during VC, changing as the bone microarchitecture forms. During early CAC, both are similar. In severe CAC, the direction of the kinetic equilibrium is stable and therefore the relationship between CAC and TBS is not further developed [11].

## FRAX® and cardiovascular disease/ coronary artery calcification

Fragility fractures are associated with a high risk of cardiovascular events, and patients with CVD have a higher fracture risk [46-48]. Hip fractures are associated with higher risk of myocardial infarction [49]. Patients with recent coronary events have a higher prevalence of vertebral fractures, a risk independent of BMD [50]. In a recent meta-analysis including 28 longitudinal studies and 1,107,885 participants, low BMD and fractures were associated with a small but significantly increased risk of CVD and possibly death. The presence of fractures at baseline was associated with an increased risk of developing CVD (hazard ratio = 1.20; 95% confidence interval, 1.06–1.37; $I^2 = 91\%$), independent of other known conditions [40].

Severe AAC is associated with higher cardiovascular morbidity and mortality, lower BMD, and higher bone fragility and risk of fracture [30,51-53]. The link was significant for major fracture types, but data were less consistent when various fractures were analyzed jointly [1,54].

FRAX®, which combines BMD and clinical risk factors to provide a comprehensive osteoporotic fracture risk assessment, may serve as a general guideline for the clinical management of osteoporosis [55]. Clinical risk factors used in FRAX® include age, sex, weight, height, a prior history of fracture, use of oral glucocorticoids, current smoking, alcohol intake of three or more units daily, rheumatoid arthritis, a parental history of a hip fracture, and other secondary causes of osteoporosis. FRAX® effectually estimates the 10-year likelihood of hip and major osteoporotic fracture. Fracture risk, rather than mere BMD, was significantly positively correlated with CAC scores. This correlation is probably because, in addition to the BMD value, the calculation of major osteoporotic fracture and hip fracture risk takes into account other fracture risk factors [34].

## Mechanism

Adiponectin, leptin, and vaspin are related to markers of bone and vascular health and may contribute to the observed association between osteoporosis and CVD [56]. Although osteoporosis, VC and CVD share common risk factors; direct pathophysiological pathways also link these entities [57]. Recently, VC promoters and inhibitors have been identified [2]. Cell-culture study has demonstrated that oxidized low-density lipoprotein-cholesterol can inhibit the differentiation of osteoblasts in bone, as in osteoporosis, and promote calcification of smooth muscle vascular cells, as in atherosclerosis [58]. Calcification of arteries involves many factors, including genetic factors, hormones, cytokines, abnormal mineral metabolism, transport of calcium and phosphate, and transdifferentiation of vascular smooth muscle cells towards an "osteoblast-like" phenotype [59].

The processes of atherosclerosis and bone loss – and subsequently increased fracture risk and then fractures – are linked.
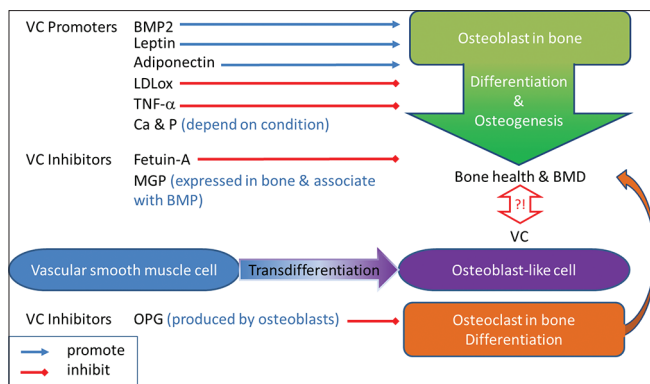
**Figure 1:** Flow diagram of the potential interaction in biological aspect of mechanism. VC: Vascular calcification, BMP2: Bone morphogenetic protein 2, LDLox: Oxidized low-density lipoprotein-cholesterol, TNF-α: Tumor necrosis factor-alpha, Ca: Calcium, P: Phosphorus, MGP: Matrix-gla protein, OPG: Osteoprotegerin, BMD: Bone mineral density

| Relationships in the literatures | |
|---|---|
| VC/CAC ↑ | CVD ↑ |
| VC/CAC ↑ | BMD ↓ |
| VC/CAC ↑ | Fracture ↑ |
| BMD ↓ | CVD ↑ |
| Fracture ↑ | CVD ↑ |
| **Relationships in our previous studies** | |
| MOF (FRAX) ↑ | CAC ↑ |
| HF (FRAX) ↑ | CAC ↑ |
| TBS ↑ | Moderate CAC odds ↑ |
| TBS ↑ | High CAC odds (no effect) |

**Figure 2:** The relationships among CVD risk, BMD, TBS, fracture, VC and CAC. VC: Vascular calcification, CAC: Coronary artery calcification, CVD: Cardiovascular disease, BMD: Bone mineral density, MOF: 10-year probability of major osteoporotic fracture, HF: 10-year probability of hip fracture, FRAX: Fracture risk assessment tool, TBS: Trabecular bone score

VC has been linked to dysregulated bone and mineral metabolism, reduced BMD and increased fracture rates [51,53,60]. If fragility fractures of the bone and VC have reciprocal causation and are mutually related, their involved, dynamic, highly regulated processes in the physiologic microenvironment of the bone and vessels may provide a more reasonable explanation for this linkage. FRAX® can help identify individuals at high risk of osteoporotic fractures, an increased CAC score, and cardiovascular events [34]. The relationship between fractures and CVD may be explained by the mechanisms that explain low BMD [40]. In addition, reduced physical activity after a fracture (particularly at the hip) is common and is a key risk factor for CVD [61,62].

VCs have a composition similar to bone minerals. Currently, intima-related VCs are commonly associated with atherosclerotic plaques (in the vicinity of lipid or cholesterol deposits) and recently-calcified lesions, whereas media-related VCs are associated with lesions calcified early (in the absence of lipid or cholesterol deposits) [63]. Even if medial and intimal calcifications share some common pathomechanisms and can occur together in patients, it is reasonable to maintain a distinction between the two [64]. VCs represent a complex biological process of calcium phosphate deposition and are related to regulation of osteogene expression, bone morphogenetic protein, calcification inhibitors (osteoprotegerin, matrix-Gla protein, fetuin-A) and inflammatory cytokines (tumor necrosis factor-alpha, C-reactive protein, and cluster of differentiation [CD] 40–CD154) [63,64]. Unfortunately, it is impossible, or at least extremely difficult, to distinguish between intimal and medial calcification in the coronary arteries [64]. Molecular cascades and the procalcific microenvironment during VC change as the bone microarchitecture forms [11]. Exposure to high calcium concentrations may also influence the development of low-turnover bone disease and CAC in patients on hemodialysis [65]. The flow diagram of the potential interaction in biological aspect of mechanism is drawn in Figure 1.

## CONCLUSION

We list the relationships among CVD risk, BMD, TBS, fracture, VC, and CAC in Figure 2. Atherosclerosis and VC are dynamic processes; together with bone microarchitecture, they reach a dynamic equilibrium in bone remodeling. Furthermore, increased risks of hip and major osteoporotic fracture as estimated by FRAX® are significantly and independently associated with more severe CAC scores. DXA and FRAX® can be used to predict fracture risk and CAC scores and identify patients who may benefit from early intervention. Alterations in signaling pathways that are common to normal bone remodeling and arterial calcifications, such as BMP2, osteocalcin, and matrix Gla proteins, may play a role. Due to the complex regulatory networks of VCs, many interesting findings between bone health and CVD/CAC have been reported and understanding the mediators of these changes will provide valuable insight into the interaction of bone, VC and CVD risk.

## Conflicts of interest

There are no conflicts of interest.

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