Association between bone and vascular calcification: evidence from clinical studies

Souvislost mezi kostní a cévní kalcifikací: důkazy z klinických studií

Pawel Szulc

INSERM UMR 1033, University of Lyon, France

✉ **Pawel Szulc, MD PhD** | pawel.szulc@inserm.fr | www.lyos.fr

Received | Doručeno do redakce | Doručené do redakcie 10. 2. 2020
Accepted | Přijato po recenzi | Prijaté po recenzii 19. 2. 2020

Abstract
Prior major fragility fracture and, to a smaller extent, lower bone mineral density (BMD), are associated with higher cardiovascular risk. Cardiovascular diseases are associated with higher risk of major osteoporotic fracture. Abdominal aortic calcification (AAC) may be assessed using Kauppila's semiquantitative score. Severe AAC is associated with higher risk of hip and vertebral fracture and, less consistently, with higher risk of other fractures and lower BMD. Greater carotid artery intima-media thickness was associated with lower areal BMD in some, not all, studies. Calcified carotid plaques tended to be associated with lower BMD and higher fracture risk. Severe coronary artery calcification is associated mainly with lower volumetric trabecular BMD (not cortical) in postmenopausal women (not in men). Thus, patients with severe osteoporosis may have high cardiovascular risk and *vice versa*, however, there are no official guidelines for the clinical management of these patients.

Key words: abdominal aortic calcification – cardiovascular disease – carotid artery calcification – coronary artery calcification – fragility fracture – osteoporosis

Abstrakt
Předchozí významná osteoporotická zlomenina a v menší míře nižší hustota kostního minerálu (BMD – bone mineral density) souvisí s vyšším kardiovaskulárním rizikem. Kardiovaskulární choroby jsou spojeny s vyšším rizikem závažných osteoporotických zlomenin. Kalcifikaci břišní aorty (AAC – abdominal aortic calcification) lze vyhodnotit pomocí tzv. Kauppilova semikvantitativního skóre. Závažná AAC je spojena s vyšším rizikem zlomeniny kyčle a obratle, méně pak s vyšším rizikem jiných zlomenin a nižší BMD. Větší poměr intima-media karotid byl v některých, ne však ve všech studiích spojován s nižší plošnou hodnotou BMD. Kalcifikované karotické pláty byly často spojovány s nižší BMD a vyšším rizikem fraktury. Závažná kalcifikace koronárních arterií souvisí převážně s nižší objemovou BMD trabekulární kosti (nikoliv kortikální) u žen v menopauze (netýká se mužů). U pacientů/pacientek s těžkou osteoporózou tedy může existovat vyšší riziko kardiovaskulárního onemocnění a naopak, pro klinické léčení těchto pacientů však nejsou k dispozici žádné oficiální pokyny.

Klíčová slova: kalcifikace břišní aorty – kalcifikace karotidy – kalcifikace koronárních arterií – kardiovaskulární onemocnění – osteoporotická zlomenina – osteoporóza

Osteoporosis and cardiovascular risk

The association between cardiovascular diseases and fracture risk has been shown in a large number of studies published over the last 15 years. History of fragility fracture (mainly hip fracture and clinical vertebral fracture) was associated with higher cardiovascular risk in both sexes [1–2]. This trend was found mainly for major cardiovascular events (stroke, myocardial infarction, death

for cardiovascular reasons), but also for ischemic heart disease, incident heart failure, transient ischemic attack (TIA) and other pathologies. One of the first studies on this subject carried out in a large group of postmenopausal women followed in the placebo arm of a large pharmaceutical trial showed that the risk of major cardiovascular event was 3.5-fold higher in the women with osteoporosis compared to women with osteopenia [3]. In the same study, women with severe or multiple vertebral fractures had higher risk of major cardiovascular event. Similarly, hip fracture was associated with higher risk of myocardial infarction and stroke [4–5]. Overall, the prior hip fracture was associated with a 30% higher risk of myocardial infarction and a 50 % higher risk of stroke [1,5]. Such trends were found in both sexes and in different ethnic groups.

The link between osteoporotic fractures and cardiovascular events is important because of its practical clinical consequences. For instance, the risk of myocardial infarction and stroke was particularly high (13- and 9-fold higher vs. the controls) during the first month after the hip fracture [4]. Such early myocardial infarction or stroke are associated with a four- to sevenfold higher 30-day mortality compared with women who had no fracture [6].

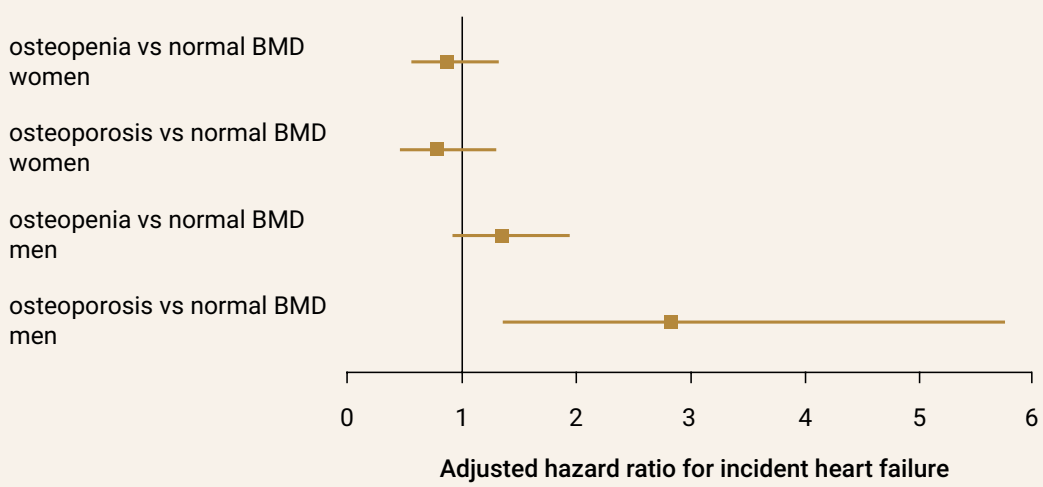
A substantial number of studies show a moderate but significant association between low bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) and higher risk of cardiovascular diseases (e.g. myocardial infarction or incident heart failure) and stroke [1,7–11]. In a large meta-analysis, a decrease in BMD by 1 standard deviation was associated with a 16 % higher risk of incident cardiovascular disease (HR = 1.16, 95% CI: 1.09–1.24, p < 0.001) [1]. This pattern was found mainly in older men and less consistently in older women [9–10]. For instance, in the Cardiovascular Health Study, higher risk of heart failure was found only in osteoporotic men, but not in osteoporotic women (figure 1).

Cardiovascular diseases and fracture risk

Cardiovascular diseases are associated with higher risk of major osteoporotic fracture, especially hip, vertebral and humerus fracture. Such association was found mainly for severe cardiovascular diseases, such as cerebrovascular diseases, myocardial infarction, heart failure, peripheral artery disease [12–17]. A recent meta-analysis shows that heart failure is associated with a threefold higher risk of hip fracture (RR = 3.45, 95%CI: 1.86–6.40, p < 0.001) and with a twofold higher risk of humerus fracture (RR = 1.91, 95%CI: 1.07–3.40, p = 0.03) [15]. Furthermore, prior stroke is associated with a twofold higher risk of hip fracture (RR = 2.06, 95%CI 1.68–2.52, P < 0.001) [14].

Some discordances between the studies may be related to the methodological factors. Various studies used different criteria and different methods for a given disease. In particular, in large studies using the healthcare registers, it is impossible to check which criteria were used for the diagnosis of a given cardiovascular diseases and, most probably, different criteria were used in different hospitals according to their diagnostic equipment. Studies are often poorly controlled for confounding factors (lifestyle, co-morbidities, treatments),

Figure 1 | Risk of incident heart failure in osteoporotic and osteopenic men and women in comparison with the sex-matched controls. The study was performed in 1 250 elderly men and women followed up prospectively for 10.5 years (Cardiovascular Health Study). Reproduced from [9]



which may also contribute to the fracture risk [18–19]. For instance, the use of thiazide diuretics or statins may be associated with a 20–40 % lower risk of fracture [18–19].

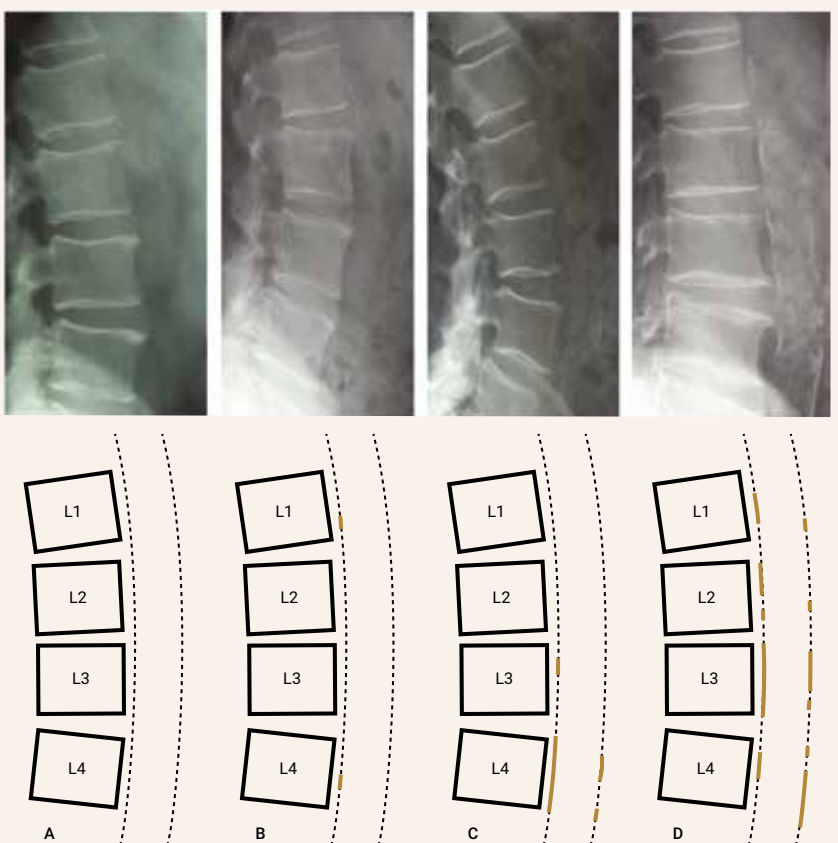
Abdominal aortic calcification and its assessment

Abdominal aortic calcification (AAC) may be easily assessed on lateral radiographies of lumbar spine and on lateral spine scans obtained by DXA [20–21]. Both are inexpensive, easily available, rapid and safe. AAC is assessed using a 24-point semiquantitative score (AAC-24) [20], which reflects the length of calcification at the posterior and anterior aortic walls adjacent to the first four lumbar vertebrae (figure 2). AAC is assessed in eight segments and lines drawn through the middle of intervertebral spaces are segment boundaries. In every segment AAC is scored from 0 to 3 on the basis of the length of AAC. The agreement of the AAC scores obtained using AAC-24 on the X-ray and on the DXA scan is very good [21–22].

The simplified 8-point semiquantitative score (AAC-8), based on the initial AAC-24 score, is rapid and less influenced by small calcification dispersed in different segments [22]. Specked calcification dispersed in different segments may result in a falsely elevated AAC-24 score. This limitation is avoided with AAC-8 score. However, for the AAC-8 score, the aggregate length of AAC in different parts of the aortic wall has to be calculated mentally and compared to the average length of the vertebral segment. Despite this limitation, the results from AAC-8 are strongly correlated with those from AAC-24 both on X-rays and on DXA scans [22].

The advantage of DXA compared with X-ray is that the scan is made during the same exam as BMD measurement. In addition, dose of irradiation is lower compared with an X-ray (5 μSv vs. 600 μSv). Adjustment of brightness and of contrast on the screen of the DXA device

Figure 2 | Semiquantitative score of Kauppila. Reproduced from [117]



A – no abdominal aortic calcification (AAC) – **B** – mild AAC (small calcification at the posterior wall at the level of L1 and L4) **C** – moderate AAC (calcification on the entire length of the posterior wall at the level of L4, smaller calcification in the anterior wall at the level of L4 and at the posterior wall at the level of L3) **D** – severe AAC (calcification on the entire length of the posterior segment of the aortic all at the level of L3, calcification at the posterior wall at the level of L1 and L2 and at the anterior wall at the level of L3 and L4, smaller calcification at the anterior wall at the level of L1 and L2 and at the posterior wall at the level of L4)

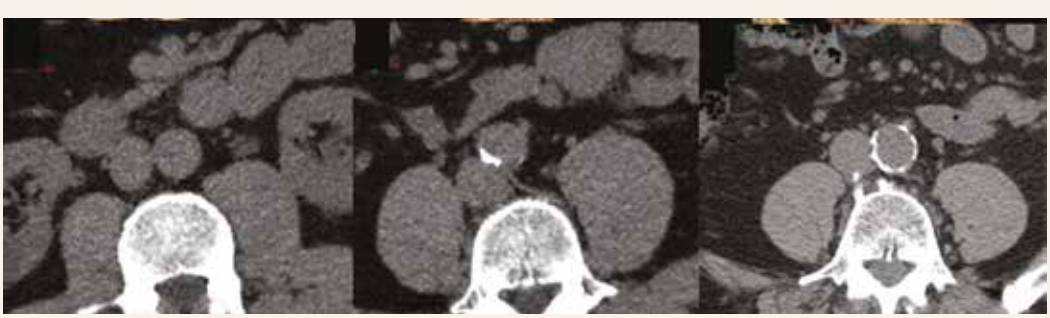
permit to improve visibility of AAC. However, DXA has lower resolution compared to X-rays and small calcification may be overlooked on the DXA scan. Hence average AAC score is slightly lower on a DXA scan compared to an X-ray [23]. Consequently, the agreement of AAC score on the X-ray vs the DXA scans was only moderate, when the agreement of the AAC scores on the X-ray vs the DXA scan was analyzed as dichotomized variables (using the same threshold for X-ray and for DXA) [21].

Both methods share some limitations. Poor image quality is the major limitation (insufficient space in front of the lumbar spine, "soft" X-rays with blurred barely visible lines, movement, and rotation). Severe obesity may impair the visibility of calcified aortic walls. The assessment of linear calcification in the anterior or posterior aortic wall is straightforward, whereas the assessment of marble-like calcification present in lateral walls is more subjective. In patients with severe scoliosis and/or lumbar osteoarthritis, abdominal aorta may be tortuous, partly covered by vertebral bodies and/or long osteophytes. Severe fractures of the first four lumbar vertebrae may change the trajectories of intervertebral spaces (which define the segment boundaries) and consequently, the lengths of the segments. Thus, it may be difficult to imagine the reference length of the segment. The posterior height of vertebral body may be used as a reference in case of the wedge vertebral fractures [24]. By contrast, it is impossible to recommend the reference in case of severe crush vertebral fractures. Aortic bifurcation may be situated above the lower boundary of the L4 segment (in front of the fourth lumbar vertebra). In such case, calcification present in the proximal parts of the common iliac arteries is "assigned" to the AAC score using subjective mental operations [24]. AAC cannot be assessed in case of aortic aneurysm. Bones (e.g. ribs) and other ectopic calcification (e.g. in the renal artery wall, in the initial segments of the superior and inferior mesenteric arteries, kidney stones, calcified non-vascular tissues) should also be assessed and excluded.

AAC may be also assessed using quantitative computed tomography (QCT) [25]. Calcification burden is calculated in the entire investigated vascular bed (e.g. a given part of the aorta) as Agatston score which is a product of calcified lesion area and calcium score reflecting average density expressed in Hounsfeld units (HU) or as the volume of calcification in the investigated segment of the aorta (figure 3) [25–26]. AAC severity assessed on DXA scans was significantly correlated with AAC quantified by QCT [27]. Nonetheless, the results provided by these methods (QCT vs X-ray, QCT vs DXA) are not directly comparable. QCT quantifies AAC more accurately than semiquantitative scores on radiograph or DXA scan. However, QCT is not appropriate for the AAC assessment in clinical or epidemiological studies, because it is less available, more expensive and more irradiating than DXA or radiography. As various QCT studies assessed different segments of aorta using different approaches, these studies are not really comparable (although all used QCT). QCT combined with magnetic resonance imaging (MRI) of the aorta permits to evaluate jointly the spatial relationships between calcification and the presence of atherosclerotic plaque areas [28].

The semiquantitative approach of Kauppila's score limits its use in longitudinal studies. AAC is a dynamic process; however, its progression is slow and a long-term follow-up is necessary for a reliable detection of AAC progression in clinical studies in the general population [29]. Follow-up of less than 5 years is insufficient. In particular, a short-term follow-up may be also insufficient to detect or to exclude the change in AAC score in pharmaceutical studies aimed at preventing AAC progression [30–31]. However, age, smoking, hypertension, obesity, and vitamin D deficit are associated with

Figure 3 | Axial slices presenting abdominal QCT scans: no abdominal aortic calcification (left panel), mild calcification limited to right posterior quandrant (middle panel), and severe calcification nearly on the entire circumference (right panel). Reproduced with senior author´s permission [26]



more rapid AAC progression in prospective studies [32–33]. Consquently, minimum duration of a follow-up may vary according to the characteristics of the cohort.

Therefore, more accurate, precise and quantitative methods are needed for the assessment of AAC progression. Multidetector computed tomography (MDCT) and electron beam computed tomography (EBCT) improve the sensitivity of the quantification of vascular calcium burden [34–35]. These methods express calcium deposits in Agatston units. They do not necessitate contrast injection. Most studies show good reproducibility of the calcium burden assessment. However, high radiation dose, elevated cost and poor availability limit their use. MDCT has higher reproducibility and increased signal-to-noise ratio, whereas EBCT has lower radiation dose and faster acquisition time. Data on their use for the assessment of AAC are limited [34–36]. The correlation between aortic calcium deposits obtained by MDCT or by EBCTwith AAC severity assessed by semiquantitative approach has not been thoroughly studied. Interestingly, they seem to be useful for the assessment of the effect of therapeutic prevention of AAC progression, at least in hemodialysis patients [37–38].

Abdominal aortic calcification and bone mineral density

Data on the association between AAC and areal bone mineral density (BMD) measured by DXA are inconsistent. On the one hand, several studies assessed groups with mild/moderate AAC or groups with mixed, but maily mild AAC. The analyses adjusted for age show that BMD was similar in individuals with AAC and those without AAC regardless of skeletal site [39–42]. Other studies presented bivariable analyses not adjusted for potential confounders [43–49]. In these studies, BMD was significantly lower in subjects with mild or moderate AAC vs those without AAC. However, the subjects with AAC were significantly older than those without AAC and the differences became non-significant after adjustment for age [43,49]. On the other hand, individuals with severe AAC had lower BMD compared to those without AAC [50–52]. The differences remained significant after adjustment for age and other confounders, at least for some skeletal sites. For instance, in a cohort of older men, BMD was 3–4 % lower at whole body and distal forearm in men with severe AAC (AAC score >6) vs men who had lower AAC score (AAC score 0 to 6). [51]. In a large cohort of Australian older women, total hip BMD was 3 % lower in those with severe AAC (AAC score > 5) vs those without AAC [52].

After adjustment for confounders, more severe AAC is associated with lower trabecular vBMD at the lumbar spine and the hip (total hip, femoral neck) in peri-, postmenopausal and elderly women in some [25,35,53–56], not all [57–58], studies. For instance, perimenopausal women with severe AAC had 11 % lower trabecular volumetric BMD at the lumbar spine vs women who had no AAC [25]. In another group of older women, severe AAC was associated with a 40 % lower trabecular volumetric BMD at the spine vs women who had no AAC and the difference remained significant after adjustment for age [53]. Similarly, data in men show inconsistent trends in both compartments. Men with more extended AAC had slightly lower trabecular vBMD at the lumbar spine [55–58] or, conversely, lower cortical (but not trabecular) vBMD at the distal radius and distal tibia [59]. By contrast, Chow et al found no association between AAC severity and vBMD in men [58].

Several [50,53,60–62], but not all [63], prospective studies showed faster bone loss in subjets with rapid progression of AAC. In a cohort of 228 older women followed up prospectively for 2 years, women in the highest quartile of AAC gain had fourtfold greater bone loss (5.3 vs 1.3 %/year, $p < 0.001$) than women of similar age in the lowest quartile [53]. This association was found mainly in postmenopausal and elderly women, but less consistently in older men [60–61]. However, measurement errors of the changes in AAC and BMD are relatively high in comparison with the individual rates of bone loss and of AAC progression. Therefore, a long-term follow-up is necessary for such analyses, especially in individuals who have slower bone loss (e.g. in men compared to women) [42,60]. Therefore, these results should be interpreted with caution. Some positive results may be fortuitous. The publications bias reflecting the trend that researchers publish positive results, but restrain from publishing negative results, is possible. However, given the low number of studies and methodological differences, a meta-analysis permitting to detect such phenomenon would be difficult to perform.

Overall, these data show that the association between AAC and BMD is weak and strongly dependent on age and other confounders (presumably shared risk factors). In addition, even in the studies showing significantly lower BMD in individuals with severe AAC, the differences are relatively small and limited to some skeletal sites. This is probably one of the reasons the differences attain statistical significance in the multivariable models only in the groups including a sufficient number of individuals with severe AAC. In addition, the link between between AAC severity and volumetric BMD seems to be stronger in trabecular bone. Thus, it is plausible that the fraction of trabecular bone at a given skeletal site and the severity of its deterioration determine the strength of the association between

AAC severity and areal BMD. Finally, the presence of artifacts may influence the result. For instance, lumbar spine contains a large fraction of trabecular bone and its volumetric BMD is negatively correlated with severe AAC. However, in the elderly, areal BMD may be falsely elevated by osteophytes and severe AAC itself.

Abdominal aortic calcification and fractures

The association between severe AAC and fractures was assessed in cross-sectional and prospective studies. Cross-sectional studies were focused on vertebral fractures. They show that severe AAC is associated with significantly two- to fourfold higher odds of prevalent vertebral fractures after adjustment for age, weight and bone mineral density (BMD) measured by DXA [40,44,52–54,64–66]. This association was found in men and in women regardless of the ethnic group. The odds were higher for severe vertebral fractures (vs mild fractures) and for multiple fractures (vs simple fractures), table [40,61,64–65]. The results were similar regardless of the method used for the assessment of AAC (X-ray, DXA, QCT) or for vertebral fracture (X-ray, DXA).

However, some limitations should be signaled. Cross-sectional design does not permit to establish the temporal sequence. Vertebral fractures and AAC are assessed side by side on the same image, thus, the assessment of the two variables cannot be really double blind. Of note, in case of abnormality in the lumbar spine (crush fracture, scoliosis), the length of the aortic segment (denominator) is apparently smaller, thus, for the same length of AAC (numerator) the value of the AAC score may be spuriously high.

Prospective studies assessed the association between baseline AAC severity and the prospectively assessed risk of fracture (figure 4). Severe AAC is associated mainly with higher risk of hip fracture and of vertebral fracture [45,47–48,50,52]. The similar patterns were found for men and women regardless of the ethnicity. After adjustment for confounders, older Chinese women with severe AAC (AAC score > 6) had threefold higher risk of incident vertebral fracture compared with women who had no AAC [45]. In the MrOS cohort (5400 American men aged 65 and over), severe AAC was associated with higher risk of hip fracture (HR = 2.33, 95% CI: 1.41–3.87, p < 0.01), figure 5 [47]. By contrast, data on the association between severe AAC and other non-vertebral fractures are less consistent [41,45,47–48,51,61]. Of note, these associations tended to be significant in the studies, where the group "non-vertebral fractures" included hip fractures [45,51], but not in the analyses of the non-hip-non-vertebral fractures [47]. Mild AAC were not associated with the fracture risk [41–42].

The association between severe AAC and the risk of major fragility fracture remained significant after adjustment for age, BMD and other potential confounders, including shared risk factors, such as smoking, diabetes mellitus, poor renal function of vitamin D level. The association between AAC severity and fracture risk was significant in men and in women. Bone fragil-

Table | Odds of vertebral fracture associated with abdominal aortic calcification (AAC score > 6 versus ≤ 6) in 901 men aged 50 and older from the STRAMBO cohort assessed using age-adjusted and multivariable-adjusted logistic regression. Reproduced from [40]

fracture prevalence	age-adjusted OR (95% CI)	multivariable-adjusted*) OR (95% CI)
grade ≥ 1 (n = 98) vs grade 0	2.1 (1.2–3.6)	2.5 (1.4–4.5)
grade ≥ 2 (n = 80) vs grade ≤ 1	2.1 (1.2–3.9)	2.6 (1.4–5.1)
fracture severity**)		
grade 1 (n = 18)	1.6 (0.4–6.1)	1.8 (0.4–7.3)
grade 2 (n = 60)	2.0 (1.0–3.9)	2.4 (1.2–5.1)
grade 3 (n = 20)	2.8 (0.99–8.1)	4.4 (1.3–15.1)
number of fractures**)		
1 fracture	1.7 (0.9–3.4)	2.0 (0.98–4.2)
> 1 fracture	2.7 (1.2–6.0)	3.5 (1.4–8.6)
data are presented as odds ratios (OR) and 95% confidence interval (95%CI)		

*) adjusted for age (years), weight (kilograms), femoral neck BMD (grams per square centimeter), smoking (ever/never), ischemic heart disease (yes/no), and hypertension (yes/no) **) assessed by polytomous logistic regression using men without vertebral fracture (grade 0) as the reference group

ity measures (BMD, prevalent vertebral fracture) and severe AAC contributed jointly to the higher risk of incident fracture [51–52]. For instance, in the large Australian cohort, the risk of clinical fracture was more than twofold higher (HR=2.43, 95%CI: 1.54–3.85, p<0.001) in women who had severe AAC and prevalent vertebral fractures compared to the women who did not have these characteristics [52].

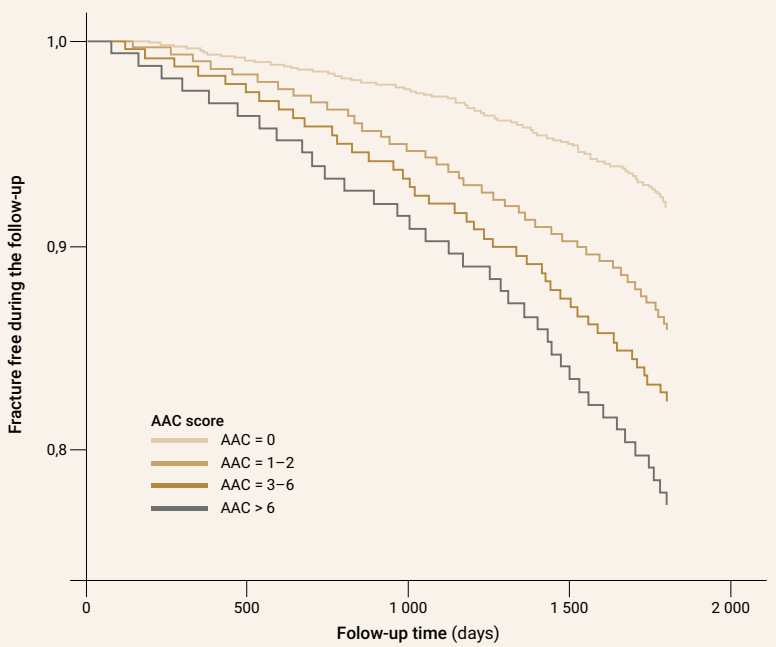
Some observations may explain the discordant results of different studies. Increased fracture risk was found mainly in individuals with severe AAC, but not in those with mild AAC. Therefore, a low threshold of AAC score may not be sufficiently specific and may provide inconsistent results according to the number of subjects with severe AAC among those with AAC. The association between AAC and fracture risk could not be detected in cohorts, in which few individuals had severe AAC, for instance in younger cohorts. Vascular calcification is a dynamic process and its current severity cannot predict its progression over a long period. Therefore, the association between AAC severity and fracture risk has been most often significant in the follow-up of 10 years or less [45,48,50–52]. By contrast, it was not significant in long-term follow-ups, especially when then median follow-up until fracture was long [48,67]. For instance, in the SOF cohort, severe AAC was associated with a significantly twofold higher risk of vertebral fracture during a 4-year follow-up, but not during the 15-year follow-up [48]. Importantly, severe AAC is associated with higher mortality (mainly cardiovascular one). Therefore, in the longer follow-up, the competing risk of death should be taken into account in the analysis of the fracture risk.

Carotid artery calcification and bone

A large number of studies assessed the associations between bone status and atherosclerosis in the carotid common and internal artery. Carotid artery intima-media thickness (CIMT) and carotid plaque number, size, echogenicity and calcification are assessed by ultrasonography. Carotid artery calcification can be also assessed using panoramic radiography.

Overall, the results of the studies were inconsistent. Greater CIMT was associated with lower areal BMD in some [68–77], but not all [78–84], studies. For instance, in postmenopausal women from the Japanese Population-based Osteoporosis Cohort Study, osteoporotic women had 28 % (0.85SD) higher CIMT compared with the women with normal BMD [71]. Similarly, cross-sectional studies on the association between and BMD and carotid plaques provided inconsistent results. In some studies, lower areal and volumetric BMD (or diagnosis of osteoporosis) was associated with higher prevalence of echogenic/calcified carotid plaques [74,85–

Figure 4 | Prospective study of the association between abdominal aortic calcification (AAC) severity at baseline and the risk of fracture during a 5-year follow-up in a cohort of 1 724 postmenopausal Chinese women. Fracture-free survival according to the AAC score: AAC = 0, AAC = 1–2, AAC = 3–6, AAC > 6.
Reproduced from [45]



87]. For instance, in a large cohort of older men and women (Tromso study), individuals with echogenic carotid plaques had 3.4 % lower distal forearm BMD compared with the individuals without plaques, whereas BMD did not differ between the subjects with echolucent plaques and those without plaques [86]. Similarly, in older men and women from the MESA study, volumetric BMD at the lumbar spine decreased significantly with the increasing echogenicity of the carotid plaques (p for trend < 0.05) and was 7–8 % lower in the individuals with calcified carotid plaques vs those who did not have plaques [85].

Other studies found significant negative associations only for some but not all the skeletal sites of BMD measurement [57,68,88]. The patterns differed according to the ethnicity, sex and hormone replacement therapy [88]. Finally, studies performed in smaller groups did not find any association between areal BMD (lumbar spine, hip) and the presence of echogenic/calcified carotid plaques [75,89–90].

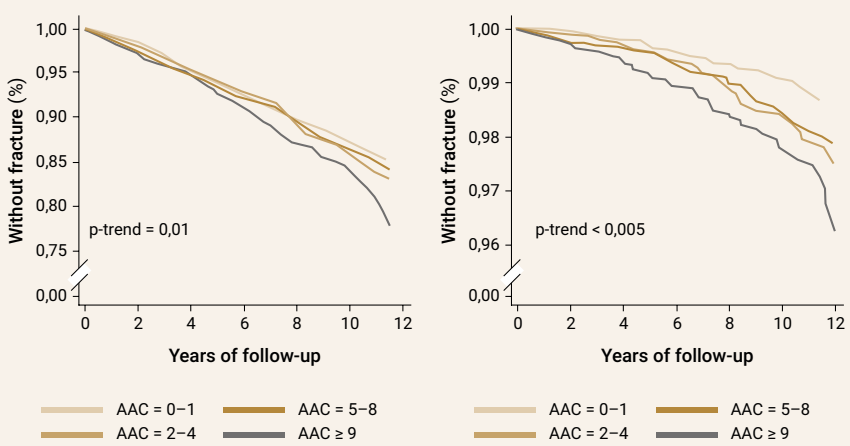
Furthermore, presence of echogenic/calcified carotid plaques was associated with higher prevalence of osteoporotic fractures (mainly vertebral fractures) in some [89,91], but not all [80, 87], studies. In a large cohort of elderly women followed up prospectively for 20 years, higher CIMT was associated with a significantly higher risk of hip fracture after adjustment for clinical confounders [84]. Similarly, after adjustment for confounders including BMD, presence of echogenic carotid plaques was associated with a slightly higher risk of non-vertebral fracture in postmenopausal women [92]. Conversely, lower lumbar spine BMD and prior osteoporotic fracture were associated with higher risk of developing an incident echogenic plaque [91,93]. In a large cohort of older Chinese women, lower lumbar spine BMD (lowest quartile) was associated with a higher risk of developing calcified carotid plaque in comparison with the highest BMD quartile after adjustment for confounders (HR = 2.68, 95% CI: 1.52–3.98) [93].

Several factors may contribute to the discordances between the studies. The associations between CIMT and BMD were negative and significant in postmenopausal women and older men, but not in premenopausal women and young men [82,94–95]. However, one study found positive link between CIMT and BMD in a large cohort of elderly men and women [84]. The associations were similar regardless of the ethnicity and of the health status at baseline (general population, diabetes mellitus, systemic lupus erythematosus). The associations were significant mainly for calcified carotid plaques [57,85–87,93]. By contrast, they were less consistent for CIMT and for somewhat vaguely characterized carotid plaques (present vs absent, echogenic vs echolucent) [71,80–81,89]. The results could also depend on the confounders used in the statistical models. Some significant associations were found in models poorly controlled for confounders.

Coronary artery calcification and bone

A substantial number of studies assessed the association between coronary artery calcification (CAC) and BMD in both sexes. Overall, the majority of the

Figure 5 | Fracture-free survival in 5 400 men aged ≥ 65 from the MrOS cohort followed up prospectively for the median of 10.5 years (interquartile range, 8.5–11.2). Fracture-free survival is presented according to the quartiles of the AAC score (adjusted for age, body mass index, center, race, hip bone mineral density, fall history, prior fracture, smoking, and co-morbidities): (A) non-vertebral fractures (n = 805 men); (B) hip fractures (n = 178 men). Reproduced from [117]



AAC — abdominal aortic calcification assessed using the 24-point Kauppila's score

studies found no association between CAC and areal BMD measured by DXA in the multivariable models [42,88,96–104]. However, a significant negative link between greater CAC and lower areal BMD in some other studies [39,105–110]. For instance, in a group of postmenopausal Chinese women, average CAC score was fourfold higher in women who were osteoporotic at the femoral neck compared to the women who had normal BMD [108].

Overall, such trends were found mainly in postmenopausal women, but not in men, probably because women have greater bone loss compared with men of similar age [106]. The links were significant mainly at the hip, but less consistently at the lumbar spine [106,109–110], probably because, in older individuals, lumbar spine areal BMD may be influenced by osteoarthritis. However, these weak (although significant) associations may be also due to the type I statistical error (false positive) or due to insufficient control for potential confounders such as shared determinants of the studied variables (age, smoking, diabetes mellitus, low grade inflammatory syndrome, hormones replacement therapy).

Several [35,55,57,88,111–114], but not all [25,115], studies showed that more severe CAC are associated with lower trabecular volumetric BMD at the thoracic and lumbar spine. For instance, in a group of patients with type 2 diabetes mellitus, the presence of calcified coronary artery plaque was associated with a significantly lower trabecular volumetric BMD at the lumbar spine and at the thoracic spine after adjustment for multiple confounders [57]. Again, this negative association was found mainly in postmenopausal women and less frequently in older men [35, 55,57, 88, 112–114]. However, the associations were very weak and the data were inconsistent. By contrast, the association between CAC severity and cortical volumetric BMD was not significant [35] or even astonishingly, positive [112].

In addition, after adjustment for confounders, individuals with severe CAC (Agatston > 400U) had twofold higher odds of prevalent vertebral fractures [116]. By contrast, CAC was not associated with the risk of incident fracture in the prospective studies [102,116].

The association between CAC and BMD seems to be overall weak and determined mainly by the significant negative link between CAC and trabecular volumetric BMD in postmenopausal women. In this population bone loss is relatively rapid, in particular in the trabecular compartment, which has a larger metabolically available surface than cortical bone. Thus, trabecular compartment may be more sensitive to various pathogenic factors, e.g. sex steroid deficit, heavy smoking or inflammatory cytokines.

Vascular calcification and osteoporosis – clinical perspective

Overall, the available data show a significant association between cardiovascular diseases and osteoporosis. Patients with low BMD or prior osteoporotic fracture have higher risk of major cardiovascular event, e.g. myocardial infarction or stroke. Patients with severe cardiovascular disease have higher risk of major osteoporotic fracture, mainly hip or vertebral fracture. These two groups of diseases share risk factors, e.g. smoking, sedentary lifestyle, diabetes mellitus, sex steroid deficit, vitamin D deficit, poor renal function, dyslipidaemia, oxidative stress, low grade inflammatory syndrome, long-term use of systemic glucocorticoids. Osteoporosis and vascular calcification may share underlying pathophysiological mechanisms [117]. Some consequences of one disease may increase the risk of the other one. For instance, prior stroke or arrhythmias are associated with higher risk of dangerous fall, which may result in a fracture [14]. An emergency surgery after a hip fracture may be associated with higher risk of cardiovascular complications compared to an elective surgery for hip osteoarthritis [118].

Thus, a patient with severe osteoporosis may have high risk of cardiovascular disease and *vice versa*. However, there are no official guidelines for the clinical management of these patients. Intuitively, history of myocardial infarction may be considered an indication for the assessment of FRAX, bone densitometry and other exams of bone status. Conversely, a patient with a hip or vertebral fracture would benefit from an in-depth assessment of the cardiovascular status. Of note, severe AAC found incidentally on a radiograph is a signal of higher cardiovascular risk and of higher risk of fracture.

Modification of the lifestyle (cessation of smoking, regular leisure physical activity), optimal pharmacological control of hypertension, arrhythmias or diabetes mellitus as well as reduction of systemic glucocorticoid dose may be beneficial for bone and vascular health. The use of medications increasing fracture risk (e.g. furosemide, selective serotonin uptake inhibitors, proton pump inhibitors) is to be considered with caution in patients with severe cardiovascular diseases [119–120], especially if they also have higher fracture risk for other reasons.

However, these suggestions are only common sense, because no clinical study assessed the impact of modifications of the clinical practice on the incidence of fragility fractures and of cardiovascular events. Further studies are needed to develop clinical recommendations which could improve the clinical management of patients at high risk of these diseases.

References

1. Veronese N, Stubbs B, Crepaldi G et al. Relationship between Low Bone Mineral Density and Fractures With Incident Cardiovascular Disease: A Systematic Review and Meta-Analysis. J Bone Miner Res 2017; 32(5): 1126–1135. Available on: <http://dx.doi.org/10.1002/jbmr.3089>.

2. Lee FY, Chen WK, Lin CL et al. Risk of aortic dissection, congestive heart failure, pneumonia and acute respiratory distress syndrome in patients with clinical vertebral fracture: a nationwide population-based cohort study in Taiwan. BMJ Open 2019; 9(11): e030939. Available on: <http://dx.doi.org/10.1136/bmjopen-2019–030939>.

3. Tankó LB, Christiansen C, Cox DA et al. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res 2005; 20: 1912–1920. Available on: <http://dx.doi.org/10.1359/JBMR.050711>. Erratum in J Bone Miner Res 2006; 21(2):352.

4. Pedersen AB, Ehrenstein V, Szépligeti SK et al. Hip Fracture, Comorbidity, and the Risk of Myocardial Infarction and Stroke: A Danish Nationwide Cohort Study, 1995–2015. J Bone Miner Res 2017; 32(12): 2339–2346. Available on: <http://dx.doi.org/10.1002/jbmr.3242>.

5. Chiang CH, Liu CJ, Chen PJ ET al. Hip fracture and risk of acute myocardial infarction: a nationwide study. J Bone Miner Res 2013 28(2): 404–411. Available on: <http://dx.doi.org/10.1002/jbmr.1714>.

6. Dodd AC, Bulka C, Jahangir A et al. Predictors of 30-day mortality following hip/pelvis fractures. Orthop Traumatol Surg Res 2016; 102(6):707–10. Available on: <http://dx.doi.org/10.1016/j.otsr.2016.05.016>.

7. Ye C, Xu M, Wang S et al. Decreased Bone Mineral Density Is an Independent Predictor for the Development of Atherosclerosis: A Systematic Review and Meta-Analysis. PLoS One 2016; 11(5): e0154740. Available on: <http://dx.doi.org/10.1371/journal.pone.0154740>.

8. Nordström A, Eriksson M, Stegmayr B et al. Low bone mineral density is an independent risk factor for stroke and death. Cerebrovasc Dis 2010; 29(2): 130–136. Available on: <http://dx.doi.org/10.1159/000262308>.

9. Fohtung RB, Brown DL, Koh WJ et al. Bone Mineral Density and Risk of Heart Failure in Older Adults: The Cardiovascular Health Study. J Am Heart Assoc 2017; 6(3). pii: e004344. Available on: <http://dx.doi.org/10.1161/JAHA.116.004344>.

10. Fiechter M, Bengs S, Roggo A et al. Association between vertebral bone mineral density, myocardial perfusion, and long-term cardiovascular outcomes: A sex-specific analysis. J Nucl Cardiol 2019. Available on: <http://dx.doi.org/10.1007/s12350–019–01802-z>.

11. Browner WS, Pressman AR, Nevitt MC et al. Association between low bone density and stroke in elderly women. The study of osteoporotic fractures. Stroke 1993; 24: 940–946. Available on: <http://dx.doi.org/10.1161/01.str.24.7.940>.

12. Lai SW, Liao KF, Lai HC et al. Risk of major osteoporotic fracture after cardiovascular disease: a population-based cohort study in Taiwan. J Epidemiol 2013; 23(2): 109–114. Available on: <http://dx.doi.org/10.2188/jea.je20120071>.

13. Sennerby U, Melhus H, Gedeborg R et al. Cardiovascular diseases and risk of hip fracture. JAMA 2009; 302(15): 1666–1673. Available on: <http://dx.doi.org/10.1001/jama.2009.1463>.

14. Luan L, Li R, Wang Z et al. Stroke increases the risk of hip fracture: a systematic review and meta-analysis. Osteoporos Int 2016; 27(11): 3149–3154. Available on: <http://dx.doi.org/10.1007/s00198–016–3632–5>.

15. Ge G, Li J, Wang Q. Heart failure and fracture risk: a meta-analysis. Osteoporos Int 2019; 30(10): 1903–1909. Available on: <http://dx.doi.org/10.1007/s00198–019–05042–2>.

16. Xu B, Han L, Liu H et al. Cardiovascular disease and hip fracture among older inpatients in Beijing, China. Biomed Res Int 2013; 2013: 493696. Available on: <http://dx.doi.org/10.1155/2013/493696>.

17. Ungprasert P, Wijarnpreecha K, Thongprayoon C et al. Peripheral arterial disease and risk of hip fracture: A systematic review and meta-analysis of cohort studies. J Postgrad Med 2018; 64(4): 220–225. Available on: <http://dx.doi.org/10.4103/jpgm.JPGM_685_17>

18. Lin SM, Wang JH, Liang CC et al. Statin Use Is Associated With Decreased Osteoporosis and Fracture Risks in Stroke Patients. J Clin Endocrinol Metab 2018; 103(9): 3439–3448. Available on: <http://dx.doi.org/10.1210/jc.2018–00652>.

19. Puttnam R, Davis BR, Pressel SL et al. Association of 3 Different Antihypertensive Medications With Hip and Pelvic Fracture Risk in Older Adults: Secondary Analysis of a Randomized Clinical Trial. JAMA Intern Med 2017; 177(1): 67–76. Available on: <http://dx.doi.org/10.1001/jamainternmed.2016.6821>.

20. Kauppila LI, Polak JF, Cupples LA et al. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis 1997; 132(2): 245–250. Available on: <http://dx.doi.org/10.1016/s0021–9150(97)00106–8>.

21. Schousboe JT, Wilson KE, HangartnerTN. Detection of aortic calcification during vertebral fracture assessment (VFA) compared to digital radiography. PLoS ONE 2007; 2(8): e715. Available on: <http://dx.doi.org/10.1371/journal.pone.0000715>.

22. Schousboe JT, Wilson KE, Kiel DP. Detection of abdominal aortic calcification with lateral spine imaging using DXA. J Clin Densitom 2006; 9(3): 302–308. Available on: <http://dx.doi.org/10.1016/j.jocd.2006.05.007>.

23. Setiawati R, Di Chio F, Rahardjo P et al. Quantitative assessment of abdominal aortic calcifications using lateral lumbar radiograph, dual-energy X-ray absorptiometry, and quantitative computed tomography of the spine. J Clin Densitom 2016; 19(2): 242–249. Available on: <http://dx.doi.org/10.1016/j.jocd.2015.01.007>.

24. Schousboe JT, Lewis JR, Kiel DP. Abdominal aortic calcification on dual-energy X-ray absorptiometry: Methods of assessment and clinical significance. Bone 2017; 104: 91–100. Available on: <http://dx.doi.org/10.1016/j.bone.2017.01.025>.

25. Farhat GN, Cauley JA, Matthews KA et al. Volumetric BMD and vascular calcification in middle-aged women: the Study of Women's Health Across the Nation. J Bone Miner Res 2006; 21(12): 1839–1846. Available on: <http://dx.doi.org/10.1359/jbmr.060903>.

26. Courand PY, Pereira H, Del Giudice C et al. Abdominal Aortic Calcifications Influences the Systemic and Renal Hemodynamic Response to Renal Denervation in the DENERHTN (Renal Denervation for Hypertension) Trial. J Am Heart Assoc 2017; 6(10). pii: e007062. Available on: <http://dx.doi.org/10.1161/JAHA.117.007062>.

27. Toussaint ND, Lau KK, Strauss BJ et al. Determination and validation of aortic calcification measurement from lateral bone densitometry in dialysis patients. Clin J Am Soc Nephrol 2009; 4(1):119–127. Available on: <http://dx.doi.org/10.2215/CJN.03410708>.

28. Cecelja M, Hussain T, Greil G et al. Multimodality imaging of subclinical aortic atherosclerosis: relation of aortic stiffness to calcification and plaque in female twins. Hypertension. 2013; 61(3): 609–614. Available on: <http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.00024>.

29. Confavreux CB, Szulc P, Casey Ret al. Higher serum osteocalcin is associated with lower abdominal aortic calcification progression and longer 10-year survival in elderly men of the MINOS cohort. J Clin Endocrinol Metab 2013; 98(3): 1084–1092. Available on: <http://dx.doi.org/10.1210/jc.2012–3426>.

30. Samelson EJ, Miller PD, Christiansen C et al. RANKL inhibition with denosumab does not influence 3-year progression of aortic calcification or incidence of adverse cardiovascular events in postmenopausal women with osteoporosis and high cardiovascular risk. J Bone Miner Res 2014; 29(2): 450–457. Available on: <http://dx.doi.org/10.1002/jbmr.2043>.

31. Tankó LB, Qin G, Alexandersen P et al. Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. Osteoporos Int 2005; 16(2):184–190. Available on: <http://dx.doi.org/10.1007/s00198–004–1662-x>.

32. Miwa Y, Tsushima M, Arima H et al. Pulse pressure is an independent predictor for the progression of aortic wall calcification in patients with controlled hyperlipidemia. Hypertension 2004; 43(3): 536–540. Available on: <http://dx.doi.org/10.1161/01.HYP.0000117153.48029.d1>.

33. Naves-Díaz M, Cabezas-Rodríguez I, Barrio-Vázquez S et al. Low calcidiol levels and risk of progression of aortic calcification.

Osteoporos Int 2012; 23(3):1177–1182. Available on: <http://dx.doi.org/10.1007/s00198–011–1550–0>.

34. Raggi P, Cooil B, Hadi A et al. Predictors of aortic and coronary artery calcium on a screening electron beam tomographic scan. Am J Cardiol 2003; 91(6): 744–746. Available on: <http://dx.doi.org/10.1016/s0002–9149(02)03421–5>.

35. Chan JJ, Cupples LA, Kiel DP et al. QCT Volumetric Bone Mineral Density and Vascular and Valvular Calcification: The Framingham Study. J Bone Miner Res 2015; 30(10): 1767–1774. Available on: <http://dx.doi.org/10.1002/jbmr.2530>.

36. Mori S, Takaya T, Kinugasa M et al. Three-dimensional quantification and visualization of aortic calcification by multidetector-row computed tomography: a simple approach using a volume-rendering method. Atherosclerosis 2015; 239(2): 622–628. Available on: <http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.041>.

37. Nakayama K, Nakao K, Takatori Y et al. Long-term effect of cinacalcet hydrochloride on abdominal aortic calcification in patients on hemodialysis with secondary hyperparathyroidism. Int J Nephrol Renovasc Dis 2013; 7: 25–33. Available on: <http://dx.doi.org/10.2147/IJNRD.S54731>.

38. Wada K, Wada Y. Evaluation of aortic calcification with lanthanum carbonate vs. calcium-based phosphate binders in maintenance hemodialysis patients with type 2 diabetes mellitus: an open-label randomized controlled trial. Ther Apher Dial 2014; 18(4): 353–360. Available on: <http://dx.doi.org/10.1111/1744–9987.12153.>.

39. Paccou J, Mentaverri R, Renard C et al. The relationships between serum sclerostin, bone mineral density, and vascular calcification in rheumatoid arthritis. J Clin Endocrinol Metab 2014; 99(12): 4740–4748. Available on: <http://dx.doi.org/10.1210/jc.2014–2327>.

40. Szulc P, Samelson EJ, Sornay-Rendu E et al. Severity of aortic calcification is positively associated with vertebral fracture in older men--a densitometry study in the STRAMBO cohort. Osteoporos Int 2013; 24(4): 1177–1184. Available on: <http://dx.doi.org/10.1007/s00198–012–2101-z>.

41. Flipon E, Liabeuf S, Fardellone P et al. Is vascular calcification associated with bone mineral density and osteoporotic fractures in ambulatory, elderly women? Osteoporos Int 2012; 23(5):1533–1539. Available on: <http://dx.doi.org/10.1007/s00198–011–1762–3>.

42. Wang TK, Bolland MJ, van Pelt NC et al. Relationships between vascular calcification, calcium metabolism, bone density, and fractures. J Bone Miner Res 2010; 25(12): 2777–2785. Available on: <http://dx.doi.org/10.1002/jbmr.183>.

43. Aoyagi K, Ross PD, Orloff J et al. Low bone density is not associated with aortic calcification. Calcif Tissue Int 2001; 69(1):20–4. Calcif Tissue Int 2001; 69(1): 20–24. Available on: <http://dx.doi.org/10.1007/s002230020003>.

44. El Maghraoui A, Rezqi A, Mounach A et al. Vertebral fractures and abdominal aortic calcification in postmenopausal women. A cohort study. Bone 2013; 56(1): 213–219. Available on: <http://dx.doi.org/10.1016/j.bone.2013.05.022>.

45. Zhou R, Zhou H, Cui M et al. The association between aortic calcification and fracture risk in postmenopausal women in China: the prospective Chongqing osteoporosis study. PLoS One 2014; 9(5): e93882. Available on: <http://dx.doi.org/10.1371/journal.pone.0093882>.

46. Simon SP, Fodor D, Muntean L et al. Bone mineral density, vertebral fractures and body mass index in postmenopausal women with abdominal aortic calcification. Endocr Res 2014; 39(1): 1–6. Available on: <http://dx.doi.org/10.3109/07435800.2013.794425>.

47. Szulc P, Blackwell T, Schousboe JT et al. High hip fracture risk in men with severe aortic calcification: MrOS study. J Bone Miner Res 2014; 29(4):968–975. Available on: <http://dx.doi.org/10.1002/jbmr.2085>.

48. Szulc P, Blackwell T, Kiel DP et al. Abdominal aortic calcification and risk of fracture among older women – The SOF study. Bone 2015; 81: 16–23. Available on: <http://dx.doi.org/10.1016/j.bone.2015.06.019>.

49. Frye MA, Melton LJ, Bryant SC et al. Osteoporosis and calcification of the aorta. Bone Miner 1992; 19(2): 185–194. Available on: <http://dx.doi.org/10.1016/0169–6009(92)90925–4>.

50. Bagger YZ, Tankó LB, Alexandersen P et al. Radiographic measure of aorta calcification is a site-specific predictor of bone loss and fracture risk at the hip. J Intern Med 2006; 259(6): 598–605. Available on: <http://dx.doi.org/10.1111/j.1365–2796.2006.01640.x>.

51. Szulc P, Kiel DP, Delmas PD. Calcifications in the abdominal aorta predict fractures in men: MINOS study. J Bone Miner Res 2008; 23(1): 95–102. Available on: <http://dx.doi.org/10.1359/jbmr.070903>.

52. Lewis JR, Eggermont CJ, Schousboe JT et al. Association Between Abdominal Aortic Calcification, Bone Mineral Density, and Fracture in Older Women. J Bone Miner Res 2019; 34(11): 2052–2060. Available on: <http://dx.doi.org/10.1002/jbmr.3830.

53. Schulz E, Arfai K, Liu X et al. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 2004; 89(9): 4246–4253. Available on: <http://dx.doi.org/10.1210/jc.2003–030964>.

54. Kim KJ, Kim KM, Park KH et al. Aortic calcification and bone metabolism: the relationship between aortic calcification, BMD, vertebral fracture, 25-hydroxyvitamin D, and osteocalcin. Calcif Tissue Int 2012; 91(6): 370–378. Available on: <http://dx.doi.org/10.1007/s00223–012–9642–1>.

55. Hyder JA, Allison MA, Wong N et al. Association of coronary artery and aortic calcium with lumbar bone density: the MESA Abdominal Aortic Calcium Study. Am J Epidemiol 2009; 169(2): 186–194. Available on: <http://dx.doi.org/10.1093/aje/kwn303>.

56. Li S, Yin L, Li K et al. Relationship of volumetric bone mineral density by quantitative computed tomography with abdominal aortic calcification. Bone 2020; 133: 115226. Available on: <http://dx.doi.org/10.1016/j.bone.2020.115226>.

57. Divers J, Register TC, Langefeld CD et al. Relationships between calcified atherosclerotic plaque and bone mineral density in African Americans with type 2 diabetes. J Bone Miner Res 2011; 26(7): 1554–1560. Available on: <http://dx.doi.org/10.1002/jbmr.389>.

58. Chow JT, Khosla S, Melton LJ et al. Abdominal aortic calcification, BMD, and bone microstructure: a population-based study. J Bone Miner Res 2008; 23(10):1601–1612. Available on: <http://dx.doi.org/10.1359/jbmr.080504>.

59. Kuipers AL, Zmuda JM, Carr JJ et al. Association of volumetric bone mineral density with abdominal aortic calcification in African ancestry men. Osteoporos Int 2014; 25(3):1063–1069. Available on: <http://dx.doi.org/10.1007/s00198–013–2486–3>.

60. Kiel DP, Kauppila LI, Cupples LA et al. Bone loss and the progression of abdominal aortic calcification over a 25 year period: the Framingham Heart Study. Calcif Tissue Int 2001; 68(5): 271–276. Available on: <http://dx.doi.org/10.1007/bf02390833>.

61. Naves M, Rodríguez-García M et al. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. Osteoporos Int 2008; 19(8):1161–1166. Available on: <http://dx.doi.org/10.1007/s00198–007–0539–1>.

62. Hak AE, Pols HA, van Hemert AM et al. Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. Arterioscler Thromb Vasc Biol 2000; 20(8): 1926–1931. Available on: <http://dx.doi.org/10.1161/01.atv.20.8.1926>.

63. Bristow SM, Gamble GD, Horne AM et al. Longitudinal changes in bone mineral density, bone mineral content and bone area at the lumbar spine and hip in postmenopausal women, and the influence of abdominal aortic calcification. Bone Rep 2018; 10:100190. Available on: <http://dx.doi.org/10.1016/j.bonr.2018.100190>.

64. Iwamoto J, Matsumoto H, Takeda T et al. A radiographic study on the associations of age and prevalence of vertebral fractures with abdominal aortic calcification in Japanese postmenopausal women and men. J Osteoporos 2010; 2010: 748380. Available on: <http://dx.doi.org/10.4061/2010/748380>.

65. El Maghraoui A, Rezqi A, Mounach A et al. Relationship between vertebral fracture prevalence and abdominal aortic calcification in men. Rheumatology (Oxford) 2012; 51(9):1714–1720. Available on: <http://dx.doi.org/10.1093/rheumatology/kes126>.

66. Iannotti N, Gazzola L, Savoldi A et al. Association between abdominal aortic calcifications, bone mineral density and vertebral fractures in a cohort of HIV-positive patients. J Int AIDS Soc

2014; 17(4 Suppl 3): 19715. Available on: <http://dx.doi.org/10.7448/IAS.17.4.19715>.

67. Samelson EJ, Cupples LA, Broe KE et al. Vascular calcification in middle age and long-term risk of hip fracture: the Framingham Study. J Bone Miner Res 2007; 22(9): 1449–1454. Available on: <http://dx.doi.org/10.1359/jbmr.070519>.

68. Värri M, Tuomainen TP, Honkanen R et al. Carotid intima-media thickness and calcification in relation to bone mineral density in postmenopausal women-the OSTPRE-BBA study. Maturitas 2014; 7(2): 304–309. Available on: <http://dx.doi.org/10.1016/j.maturitas.2014.05.017>.

69. Shaffer JR, Kammerer CM, Rainwater DL et al. Decreased bone mineral density is correlated with increased subclinical atherosclerosis in older, but not younger, Mexican American women and men: the San Antonio Family Osteoporosis Study. Calcif Tissue Int 2007; 81(6): 430–441. Available on: <http://dx.doi.org/10.1007/s00223–007–9079–0>.

70. Pennisi P, Russo E, Gaudio A et al. The association between carotid or femoral atherosclerosis and low bone mass in postmenopausal women referred for osteoporosis screening. Does osteoprotegerin play a role? Maturitas 2010; 67(4): 358–362. Available on: <http://dx.doi.org/10.1016/j.maturitas.2010.07.013>.

71. Tamaki J, Iki M, Hirano Y et al. Low bone mass is associated with carotid atherosclerosis in postmenopausal women: the Japanese Population-based Osteoporosis (JPOS) Cohort Study. Osteoporos Int 2009; 20(1): 53–60. Available on: <http://dx.doi.org/10.1007/s00198–008–0633-z>.

72. Sumino H, Ichikawa S, Kasama S et al. Relationship between carotid atherosclerosis and lumbar spine bone mineral density in postmenopausal women. Hypertens Res 2008; 31(6):1191–1197. Available on: <http://dx.doi.org/10.1291/hypres.31.1191>.

73. Kim SN, Lee HS, Nam HS et al. Carotid Intima-Media Thickness is Inversely Related to Bone Density in Female but not in Male Patients with Acute Stroke. J Neuroimaging 2016; 26(1): 83–88. Available on: <http://dx.doi.org/10.1111/jon.12284>.

74. Ajeganova S, Gustafsson T, Jogestrand T et al. Bone mineral density and carotid atherosclerosis in systemic lupus erythematosus: a controlled cross-sectional study. Arthritis Res Ther 2015; 17: 84. Available on: <http://dx.doi.org/10.1186/s13075–015–0595–4>.

75. Fodor D, Bondor C, Albu A et al. Relation between intima-media thickness and bone mineral density in postmenopausal women: a cross-sectional study. Sao Paulo Med J 2011; 129(3): 139–145. Available on: <http://dx.doi.org/10.1590/s1516–31802011000300004>.

76. de Almeida Pereira Coutinho M, Bandeira E, de Almeida JM et al. Low Bone Mass is Associated with Increased Carotid Intima Media Thickness in Men with Type 2 Diabetes Mellitus. Clin Med Insights Endocrinol Diabetes 2013; 6:1–6. Available on: <http://dx.doi.org/10.4137/CMED.S11843>.

77. Campos-Staffico AM, Freitas WM, Carvalho LSF et al. Lower bone mass is associated with subclinical atherosclerosis, endothelial dysfunction and carotid thickness in the very elderly. Atherosclerosis 2020; 292: 70–74. Available on: <http://dx.doi.org/10.1016/j.atherosclerosis.2019.11.007>.

78. Yamada S, Inaba M, Goto H et al. Associations between physical activity, peripheral atherosclerosis and bone status in healthy Japanese women. Atherosclerosis 2006; 188(1): 196–202. Available on: <http://dx.doi.org/10.1016/j.atherosclerosis.2005.10.036>.

79. Montalcini T, Emanuele V, Ceravolo R et al. Relation of low bone mineral density and carotid atherosclerosis in postmenopausal women. Am J Cardiol 2004; 94(2): 266–269. Available on: <http://dx.doi.org/10.1016/j.amjcard.2004.03.083>.

80. Mendoza-Pinto C, García-Carrasco M, Jiménez-Hernández M et al. Carotid atherosclerosis is not associated with lower bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Lupus 2015; 24(1):25–31. Available on: <http://dx.doi.org/10.1177/0961203314548247>.

81. Jiang Y, Fan Z, Wang Y et al. Low Bone Mineral Density Is Not Associated with Subclinical Atherosclerosis: A Population-Based Study in Rural China. Cardiology. 2018; 141(2): 78–87. Available on: <http://dx.doi.org/10.1159/000493166>.

82. Wang YQ, Yang PT, Yuan H et al. Low bone mineral density is associated with increased arterial stiffness in participants of a health records based study. J Thorac Dis 2015; 7(5): 790–798. Available on: <http://dx.doi.org/10.3978/j.issn.2072–1439.2015.04.47>.

83. Uyama O, Yoshimoto Y, Yamamoto Y et al. Bone changes and carotid atherosclerosis in postmenopausal women. Stroke 1997; 28(9): 1730–1732. Available on: <http://dx.doi.org/10.1161/01.str.28.9.1730>.

84. Barzilay JI, Buzkova P, Cauley JA et al. The associations of subclinical atherosclerotic cardiovascular disease with hip fracture risk and bone mineral density in elderly adults. Osteoporos Int 2018; 29(10): 2219–2230. Available on: <http://dx.doi.org/10.1007/s00198–018–4611–9>.

85. Hyder JA, Allison MA, Barrett-Connor E et al. Bone mineral density and atherosclerosis: the Multi-Ethnic Study of Atherosclerosis, Abdominal Aortic Calcium Study. Atherosclerosis 2010; 209(1): 283–289. Available on: <http://dx.doi.org/10.1016/j.atherosclerosis.2009.09.011>.

86. Jørgensen L, Joakimsen O, Rosvold Berntsen GK et al. Low bone mineral density is related to echogenic carotid artery plaques: a population-based study. Am J Epidemiol 2004; 160(6): 549–556. Available on: <http://dx.doi.org/10.1093/aje/kwh252>.

87. Iwamoto Y, Uchida K, Sugino N et al. Osteoporosis, osteoporotic fractures, and carotid artery calcification detected on panoramic radiographs in Japanese men and women. Oral Surg Oral Med Oral Pathol Oral Radiol 2016; 121(6): 673–680. Available on: <http://dx.doi.org/10.1016/j.oooo.2016.02.006>.

88. Carr JJ, Register TC, Hsu FC et al. Calcified atherosclerotic plaque and bone mineral density in type 2 diabetes: the diabetes heart study. Bone 2008; 42(1):43–52. Available on: <http://dx.doi.org/10.1016/j.bone.2007.08.023>.

89. Kim SH, Kim YM, Cho MA et al. Echogenic carotid artery plaques are associated with vertebral fractures in postmenopausal women with low bone mass. Calcif Tissue Int 2008; 82(6): 411–417. Available on: <http://dx.doi.org/10.1007/s00223–008–9141–6>.

90. Hmamouchi I, Allali F, Khazzani H et al. Low bone mineral density is related to atherosclerosis in postmenopausal Moroccan women. BMC Public Health 2009; 9: 388. Available on: <http://dx.doi.org/10.1186/1471–2458–9-388>.

91. Hamada M, Kajita E, Tamaki J et al. Decreased bone mineral density and osteoporotic fractures are associated with the development of echogenic plaques in the carotid arteries over a 10-year follow-up period: The Japanese Population-based Osteoporosis (JPOS) Cohort Study. Maturitas 2020; 131: 40–47. Available on: <http://dx.doi.org/10.1016/j.maturitas.2019.10.010>.

92. Jørgensen L, Joakimsen O, Mathiesen EB et al. Carotid plaque echogenicity and risk of nonvertebral fractures in women: a longitudinal population-based study. Calcif Tissue Int 2006; 79(4):207–213. Available on: <http://dx.doi.org/10.1007/s00223–006–0071-x>.

93. Liu D, Chen L, Dong S et al. Bone mass density and bone metabolism marker are associated with progression of carotid and cardiac calcified plaque in Chinese elderly population. Osteoporos Int 2019; 30(9): 1807–1815. Available on: <http://dx.doi.org/10.1007/s00198–019–05031–5>.

94. Frysz M, Deere K, Lawlor DA et al. Bone Mineral Density Is Positively Related to Carotid Intima-Media Thickness: Findings From a Population-Based Study in Adolescents and Premenopausal Women. J Bone Miner Res 2016; 31(12): 2139–2148. Available on: <http://dx.doi.org/10.1002/jbmr.2903>.

95. Shaffer JR, Kammerer CM, Rainwater DL et al. Decreased bone mineral density is correlated with increased subclinical atherosclerosis in older, but not younger, Mexican American women and men: the San Antonio Family Osteoporosis Study. Calcif Tissue Int 2007; 81(6): 430–441. Available on: <http://dx.doi.org/10.1007/s00223–007–9079–0>.

96. Sinnott B, Syed I, Sevrukov A et al. Coronary calcification and osteoporosis in men and postmenopausal women are independent processes associated with aging. Calcif Tissue Int 2006; 78(4): 195–202. Available on: <http://dx.doi.org/10.1007/s00223–005–0244-z>.

97. Shen H, Bielak LF, Streeten EA et al. Relationship between vascular calcification and bone mineral density in the Old-order Amish.

Calcif Tissue Int 2007; 80(4): 244–250. Available on: <http://dx.doi.org/10.1007/s00223–007–9006–4>.

98. Yoon YE, Kim KM, Han JS et al. Prediction of Subclinical Coronary Artery Disease With Breast Arterial Calcification and Low Bone Mass in Asymptomatic Women: Registry for the Women Health Cohort for the BBC Study. JACC Cardiovasc Imaging 2019; 12(7 Pt 1): 1202–1211. Available on: <http://dx.doi.org/10.1016/j.jcmg.2018.07.004>.

99. Wilund KR, Tomayko EJ, Evans EM et al. Physical activity, coronary artery calcium, and bone mineral density in elderly men and women: a preliminary investigation. Metabolism 2008; 57(4): 584–591. Available on: <http://dx.doi.org/10.1016/j.metabol.2007.11.024>.

100. Liu Y, Fu S, Bai Y et al. Relationship between age, osteoporosis and coronary artery calcification detected by high-definition computerized tomography in Chinese elderly men. Arch Gerontol Geriatr 2018; 79: 8–12. Available on: <http://dx.doi.org/10.1016/j.archger.2018.07.002>.

101. Lin T, Liu JC, Chang LY et al. Association between coronary artery calcification using low-dose MDCT coronary angiography and bone mineral density in middle-aged men and women. Osteoporos Int 2011; 22(2): 627–634. Available on: <http://dx.doi.org/10.1007/s00198–010–1303–5>.

102. Campos-Obando N, Kavousi M, Roeters van Lennep JE et al. Bone health and coronary artery calcification: The Rotterdam Study. Atherosclerosis 2015; 241(1): 278–283. Available on: <http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.013>.

103. Kim KI, Suh JW, Choi SY et al. Is reduced bone mineral density independently associated with coronary artery calcification in subjects older than 50 years? J Bone Miner Metab 2011; 29(3): 369–376. Available on: <http://dx.doi.org/10.1007/s00774–010–0229–5>.

104. Escota G, Baker J, Bush T et al. Aging Attenuates the Association Between Coronary Artery Calcification and Bone Loss Among HIV-Infected Persons. J Acquir Immune Defic Syndr 2019: 82(1): 46–50. Available on: <http://dx.doi.org/10.1097/QAI.0000000000002092>.

105. Lee HT, Shin J, Lim YH et al. The relationship between coronary artery calcification and bone mineral density in patients according to their metabolic syndrome status. Korean Circ J 2011; 41(2): 76–82. Available on: <http://dx.doi.org/10.4070/kcj.2011.41.2.76>.

106. Bakhireva LN, Barrett-Connor EL, Laughlin GA et al. Differences in association of bone mineral density with coronary artery calcification in men and women: the Rancho Bernardo Study. Menopause 2005; 12(6): 691–698. Available on: <http://dx.doi.org/10.1097/01.gme.0000184422.50696.ef>.

107. Lee SH, Park SJ, Kim KN et al. Coronary Calcification Is Reversely Related with Bone and Hair Calcium: The Relationship among Different Calcium Pools in Body. J Bone Metab 2016; 23(4): 191–197. Available on: <http://dx.doi.org/10.11005/jbm.2016.23.4.191>.

108. Xu R, Yang HN, Li YQ et al. Association of coronary artery calcium with bone mineral density in postmenopausal women. Coron Artery Dis 2016; 27(7): 586–91. Available on: <http://dx.doi.org/10.1097/MCA.0000000000000402>.

109. Choi SH, An JH, Lim S et al. Lower bone mineral density is associated with higher coronary calcification and coronary plaque burdens by multidetector row coronary computed tomography in pre- and postmenopausal women. Clin Endocrinol (Oxf) 2009; 71(5): 644–651. Available on: <http://dx.doi.org/10.1111/j.1365–2265.2009.03535.x>.

110. Barengolts EI, Berman M, Kukreja SC et al. Osteoporosis and coronary atherosclerosis in asymptomatic postmenopausal women. Calcif Tissue Int 1998; 62(3): 209–213. Available on: <http://dx.doi.org/10.1007/s002239900419>.

111. Wiegandt YL, Sigvardsen PE, Sørgaard MH et al. The relationship between volumetric thoracic bone mineral density and coronary calcification in men and women – results from the Copenhagen General Population Study. Bone 2019; 121: 116–120. Available on: <http://dx.doi.org/10.1016/j.bone.2019.01.010>.

112. Beckman JP, Camp JJ, Lahr BD, Bailey KR, Kearns AE, Garovic VD, Jayachandran M, Miller VM, Holmes DR 3rd. Pregnancy history, coronary artery calcification and bone mineral density in menopausal women. Climacteric. 2018 21: 53–59. Available on: <http://dx.doi.org/10.1080/13697137.2017.1406910>.

113. Ahmadi N, Mao SS, Hajsadeghi F et al. The relation of low levels of bone mineral density with coronary artery calcium and mortality. Osteoporos Int 2018; 29(7): 1609–1616. Available on: <http://dx.doi.org/10.1007/s00198–018–4524–7>.

114. Therkildsen J, Winther S, Nissen L et al. Sex Differences in the Association Between Bone Mineral Density and Coronary Artery Disease in Patients Referred for Cardiac Computed Tomography. J Clin Densitom. 2019; pii: S1094–6950(19)30143-X. Available on: <http://dx.doi.org/10.1016/j.jocd.2019.09.003>.

115. Miyabara Y, Camp J, Holmes D et al. Coronary arterial calcification and thoracic spine mineral density in early menopause. Climacteric 2011; 14(4): 438–444. Available on: <http://dx.doi.org/10.3109/13697137.2010.537409>.

116. van Dort MJ, Driessen JHM, Geusens P et al. Association between vertebral fractures and coronary artery calcification in current and former smokers in the ECLIPSE cohort. Osteoporos Int 2019; 31(2): 297–305. Available on: <http://dx.doi.org/10.1007/s00198–019–05218-w>.

117. Szulc P. Abdominal aortic calcification: A reappraisal of epidemiological and pathophysiological data. Bone 2016; 84: 25–37. Available on: <http://dx.doi.org/10.1016/j.bone.2015.12.004>.

118. Le Manach Y, Collins G, Bhandari M et al. Outcomes After Hip Fracture Surgery Compared With Elective Total Hip Replacement. JAMA 2015; 314(11): 1159–1166. Available on: <http://dx.doi.org/10.1001/jama.2015.10842>.

119. [FOCUS Trial Collaboration]. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet 2019; 393(10168): 265–274. Available on: <http://dx.doi.org/10.1016/S0140–6736(18)32823-X>.

120. Lin SM, Yang SH, Liang CC et al. Proton pump inhibitor use and the risk of osteoporosis and fracture in stroke patients: a population-based cohort study. Osteoporos Int 2018; 29(1): 153–162. Available on: <http://dx.doi.org/10.1007/s00198–017–4262–2>.