Unraveling the links underlying arterial stiffness, bone demineralization, and muscle loss

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Title: Unraveling the links underlying arterial stiffness, bone demineralization and muscle loss

Running title: Links between arterial, bone and muscle aging

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Abstract

The effects of elevated arterial stiffness on cardiovascular outcomes are widely studied, whereas the relation to non-cardiovascular outcomes relevant to older persons, such as the effect on bones and muscles, is less well established. Arterial stiffness, bone demineralization and muscle loss are all age-related processes with common risk factors, however, whether these are just parallel age-related alterations or whether these processes share common pathways is not yet understood. In this review, we outline previous literature using different assessments of arterial stiffness in various populations across the world in order to produce a comprehensive overview. While there are many studies showing an association between arterial stiffness and loss of bone and muscle, the majority are cross-sectional and there is limited longitudinal evidence to justify causal conclusions. We also give an in-depth review of hypotheses and possible mechanisms which may underlie these associations including hormone dysregulation, impaired glucose metabolism and inflammation. This narrative review highlights the associations between vessels, bones and muscles with aging, offering insights into possible shared pathways.

Keywords

Arterial stiffness; Bone density; Muscles strength; Osteoporosis; Sarcopenia; Aging
Introduction

Aging brings a variety of molecular, physiological and organ-level changes. At the cellular level genomic instability, cell senescence and mitochondrial dysfunction are amongst its hallmarks,\(^1\) while alterations in hormone levels and increased levels of cytokines have led to the concept of aging as a low grade inflammatory state.\(^2\) Arterial stiffness is an age-related process which can be accelerated by several conditions such as hypertension, diabetes mellitus, the metabolic syndrome and chronic inflammation.\(^3\)-\(^8\) Elevated arterial stiffness leads to changes of the blood pressure profile and an increased pulsatile pressure and flow load, which can affect target organs, such as the heart, brain and kidneys\(^9\)-\(^11\) and therefore, increases the risk of cardiovascular morbidity and mortality.\(^12\) Bones and muscles also deteriorate with age;\(^13,\ 14\) In the aging bone, the balance between bone resorption and bone formation has changed as result of an increase in bone-resorbing osteoclasts and pro-osteoclastogenic interleukins, subsequently leading to loss of bone tissue and reduced mineral content with aging.\(^15\) The loss of skeletal muscle occurs universally with age and is characterized by decreased quantity and quality of muscle leading to functional impairment. Animal models have shown changes in protein synthesis and breakdown, mitochondrial dysfunction and elevated reactive oxidant species (ROS) with fatty and fibrotic changes.\(^16\) These age-related changes in the bones and muscles appear to share common risk factors with the process of vascular aging.\(^17\)-\(^20\) We have shown in a cohort of older men that the combination of high lean mass and low fat mass was associated with the best arterial and bone profiles i.e. the lowest arterial stiffness and the highest bone mineral density (BMD).\(^19\) Hitherto, there is a paucity of studies
investigating whether arterial stiffness and both bone and muscle deterioration are just parallel age-related processes or whether these processes share common pathways and directly influence one another.

In this narrative review, we give an overview of the literature in order to clarify the possible relationship between arterial stiffness and age-related non-cardiovascular outcomes, namely bone demineralization and muscle loss. We mainly focus on the clinical and epidemiological studies exploring the associations of arterial stiffness with manifestations of bone and muscle aging before concluding with a more in-depth overview of hypotheses underlying these associations including pre-clinical studies to describe potential mechanisms.

**Methodological approaches**

*Arterial stiffness*

In most of the clinical studies, arterial stiffness has been assessed using pulse wave velocity (PWV) either the brachial-ankle PWV (baPWV), an indicator of global arterial stiffness, or the carotid-femoral PWV (cfPWV) which assesses stiffness of the central arteries. In some studies, arterial stiffness was assessed with other validated methods, such as central or peripheral pulse pressure (cPP or pPP) and cardio-ankle vascular index (CAVI).

*Bone Mineral Density (BMD)*

BMD has been assessed with Dual-energy X-ray absorptiometry (DEXA) scans in most studies, the gold standard for BMD quantification. Some
studies have used computed tomography (CT) scans to assess BMD, whereas other studies have used the Achilles quantitative ultrasound system (QUS) which measures the speed of sound and the frequency-dependent broadband ultrasound attenuation (BUA). Levels of bone alkaline phosphatase (BAP), a sensitive and reliable indicator of bone metabolism, were also used to assess bone (de)mineralization.

Muscle mass and function

Muscle mass was assessed in most studies using CT/DEXA imaging or Bioimpedance Analysis (BIA). These modalities for determining muscle quantity are frequently combined with measures of function such as grip strength.

Results of the clinical and epidemiological studies

A. Arterial stiffness and BMD

Table 1 gives an overview on studies included in this study investigating associations between arterial stiffness and BMD. The baPWV has been used as marker of arterial stiffness in predominately Asian populations for studying the relationship between arterial stiffness and BMD. In hypertensive men in China (mean age 67.7±9.6 years), baPWV was inversely correlated with femoral neck (FN) BMD in univariate and multivariate analyses, whereas no association was found in age-matched non-hypertensive men. The authors describe that this difference between groups may lie in excessive urinary calcium excretion in persons with hypertension which could decrease serum calcium, lead to secondary hyperparathyroidism and thus increase the calcium release from the bone into the blood. In Japanese women, lumbar spine (LS)
BMD and baPWV were negatively correlated, whereas a positive correlation was found between BAP levels and baPWV. Although correlations were the strongest in subjects with normal body mass index and blood pressure, no correlations were found in adjusted analysis. Within the framework of the JPOS-study, one of the few longitudinal studies, it was investigated whether BMD had a role in the development of increased baPWV in Japanese middle-aged and elderly women during 10-years of follow-up. Participants with increased arterial stiffness after 10 years showed lower BMD values at baseline than participants with a less pronounced increase in arterial stiffness. Low BMD at the level of the total hip (TH) remained different between groups after additional adjustments, suggesting an independent role of BMD in determining elevated arterial stiffness.

cfPWV has been shown to be predictive for morbidity, progression of end-organ diseases and even mortality. The possible association between cfPWV and BMD has also been previously investigated. Within the framework of the Baltimore longitudinal study of aging, a prospective study of normative aging in healthy volunteers, no correlation was found between BMD and cfPWV in men, whereas, in women, an inverse correlation was found between BMD and cfPWV. This sex-specific relationship suggests that mediators of this association are probably differentially regulated between men and women. Several studies have investigated the possible relationship between cfPWV and BMD in patients with CKD or on dialysis, populations that are known to have increased vascular calcification and arterial stiffness. In patients with CKD, a negative correlation was found between vascular calcification and BMD scores in the femoral region, whereas no association was found between cfPWV and BMD. However, the small sample size might have affected the results. In a study of hemodialysis
patients, using quantitative CT scan (QCT) to assess BMD, participants with progressively lower BMD were more likely to have a PWV≥9 m/s, even after adjustments, which supports the concept of a close interaction of vascular and bone disease in dialysis patients. The authors suggest that mineral metabolism and alterations in bone remodeling might be factors influencing vascular properties in this specific patient group, however since this was a cross-sectional analysis, no conclusion can be drawn about causality.

To the best of our knowledge, only one study investigated the effect of arterial stiffness on bone metabolism during follow-up; in a hyperhomocysteinemic population, arterial stiffness measured as cfPWV and cPP did not have an effect on changes in BMD within 2 years. The authors hypothesized that hyperhomocysteinemia, which is associated with both cardiovascular disease and osteoporosis, could be part of a common pathway in the association between arterial stiffness and bone demineralization, however, they were not able to confirm this hypothesis.

In a large population-based cohort study in Canada, individuals between 40-70 years old were included in which it was observed that levels of cPP and pPP were inversely associated with BMD values. Associations remained significant in multivariate analysis, implying an independent association between these parameters which further suggests that arterial stiffness and low BMD are both part of an accelerated aging process.
Only one study explored the possible association between BMD and CAVI, a blood pressure-independent parameter of overall vascular stiffness;\textsuperscript{39} in middle-aged and older Chinese inpatients, FN BMD and TH BMD were negatively correlated with CAVI values. After adjusting for several confounders, this correlation was still present between TH BMD and CAVI values. The authors state that there might be an interaction between bone and vascular metabolic mechanisms, such as changes in hormone levels and an increase in proinflammatory cytokines with aging.

There seems to be increasing evidence linking arterial stiffness to bone demineralization, however, results are controversial. Associations may be strongly dependent on the tools which were used to assess arterial stiffness and BMD and on the study population in which associations were studied. Most studies have limited sample size, which limits the possibility of adjustment for potential confounders and therefore of investigating a potential independent association. Also, only a few longitudinal studies were conducted to establish causality. Therefore, the question whether these processes share common pathways or whether the same risk factors contribute to these age-related alterations still remains.

**B. Arterial stiffness and muscle mass and function**

The baPWV has been the most commonly used tool in studies of muscle function and arterial stiffness, with large cross-sectional studies finding significant associations across predominately Asian populations.\textsuperscript{40-42} In table 2, an overview is presented on previous studies investigating
associations between arterial stiffness and muscle mass and function. The J-SHIPP study explored the relationship of arterial stiffness with sarcopenia, finding the strongest association with baPWV compared to central pulse pressure and suggesting that sarcopenic obesity poses the biggest risk, although neither study presents a postulated mechanism. Similarly, using baPWV in community-dwelling Chinese older adults, Zhang found an association between arterial stiffness and sarcopenia according to the Asian Working Group on Sarcopenia definition, with an increase of 11% in the odds of being sarcopenic per 1 standard deviation increase in baPWV. In this study, the relationship was only significant in men after adjustment, but not in women, suggesting that testosterone may be an important factor in the underlying mechanism, as sex discrepancies have been a common theme in the investigation of sarcopenia.

There have been relatively few studies using the gold standard tool for assessing arterial stiffness, cfPWV. The Health ABC study demonstrated an independent negative association of cfPWV with muscle parameters in men and white women based on CT and DEXA assessments. The authors proposed that reduction in blood flow to limbs due to stiff arteries led to muscle decline, suggesting an additional role for microvascular dysfunction. Meanwhile, a small study of 54 patients in Portugal found significant inverse correlations between aortic PWV with both quantity (total lean mass) and quality of muscle (handgrip strength and sit-to-stand test). However, the full results have yet to be published, and it is unclear if these correlations remain significant after adjustment for confounders such as age and blood pressure. A meta-analysis of cross-sectional studies found a pooled negative correlation of muscle mass and PWV, although this included studies from varying geographical locations, age ranges (from mean age 23 in one study to 74 in another) and using different methods of assessing both muscle
mass and arterial stiffness (baPWV, cfPWV and carotid-ankle PWV). They offer a variety of possible mechanisms including oxidative stress and insulin dysregulation as common pathways in muscle loss and arterial stiffening.

Our UK study in older adults found a much stronger association of sarcopenia with the CAVI compared to cfPWV, showing significant correlations for CAVI with all criteria for defining sarcopenia, which were stronger in women than in men, again suggesting a role for sex hormones in mediating these changes. Similar findings were seen in a smaller Japanese study, showing a negative correlation of CAVI with skeletal muscle index (SMI) in both men and women. A Korean study of middle aged men found that higher grade muscle mass deficit on BIA was associated with increased odds ratio (OR) for being in a high CAVI group. However, the OR became non-significant after full adjustment for confounders, and the binary assessment of CAVI as low or high coupled with low age range of the sample (40-64 years) limits its comparability. In a Japanese study, CAVI was found to be associated with hand-grip strength in non-hypertensive women, but not in hypertensive women or men. Finally, Xue found a significant association between CAVI and frailty as defined by Fried’s frailty index in geriatric inpatients on multivariate regression, stating that arterial stiffness contributes to frailty on multiple levels.

A study of post-menopausal women showed higher baPWV in women with reduced muscle indices compared to normal. This study also suggested an exaggerated BP response to post-exercise muscle ischaemia in the sarcopenic group with menopause triggering an enhanced level of metaboreflex activation. Ochi found a significant negative association between carotid intimal thickness and sarcopenia in men, and
showed baPWV as a modest predictor of sarcopenia in addition to age, height, low physical activity, free testosterone level, again suggesting sex differences which may result from different hormonal constitutions.\textsuperscript{54}

Thus, while the evidence linking sarcopenia with arterial stiffness is irrefutable, the best method for assessing this relationship is, as yet, unclear. Both baPWV and CAVI include muscular and elastic arteries, rather than solely central aortic stiffness, thus may be better tools to evaluate the universal loss of muscle tissue in sarcopenia and highlight its cardiovascular repercussions.

**Possible mechanisms**

**A. Arterial stiffness and BMD**

There is no clear consensus on how the processes of arterial stiffness and bone demineralization interact, however there are several hypotheses that link both processes. Large population-based studies have found that arterial calcifications changes arterial structural and functional properties and that those with the greatest bone loss have the most severe progression of aortic calcification.\textsuperscript{55, 56} Non-collagenous proteins are important in the process of bone mineralization and have also been found in calcification of the arteries,\textsuperscript{57} suggesting that vascular mineralization and bone demineralization might have a common etiology. We outline the commonly described hypotheses in **figure 1** and below, including inflammation, hormonal dysregulation and impaired glucose metabolism.
Inflammation

The immunosenescence in aging results in remodeling of specific cell types and more importantly seems to induce a permanent state of chronic inflammation.\textsuperscript{58} Chronic inflammation and oxidative stress increase with age and might underlie both changes in blood vessel structure and bone mineralization.\textsuperscript{59} Levels of C-reactive protein and pro-inflammatory cytokines, such as interleukins and TNF-alpha are associated with elevated arterial stiffness,\textsuperscript{60, 61} possibly due to their role in endothelial dysfunction by inhibiting endothelium-dependent vasodilatation. The same cytokines have been shown to increase osteoclast activity and thus bone resorption.\textsuperscript{62} Inflammatory cytokines increase the level of RANKL, which activates osteoclasts, and cause bone resorption and calcium to transfer from bone to the vessels wall.\textsuperscript{63} RANKL is usually undetectable in normal vasculature, whereas significant amounts of RANKL have been detected in atherosclerotic tissue inducing angiogenesis and stimulating osteogenic differentiation and calcification in vascular smooth muscle cells.

Hormonal dysregulation

Parathyroid hormone (PTH) has an important role in regulating calcium-phosphate metabolism by stimulating osteoclastogenesis through activation of the osteoblastic cell, resulting in resorption of the bone matrix and secondary increase of serum calcium.\textsuperscript{64} PTH has also been linked to vascular calcification, which might be a direct effect of PTH or a more indirect result of hyperphosphatemia or hypercalcemia.\textsuperscript{65} Directly, PTH induces an acute vasodilatory response of the vasculature by binding on the PTH receptors on the vascular smooth muscle cells (VSMCs).\textsuperscript{66} Moreover, PTH is found to be a significant prosclerotic factor in these VSMCs, since it has a direct effect on production and
reorganization of collagen. More indirectly, hyperphosphatemia increases activity of sodium-dependent cotransporters, which upregulates genes involved in matrix mineralization.\textsuperscript{67} Both hyperphosphatemia and hypercalcemia can increase the release of matrix vesicles resulting in deposition of calcium phosphate mineral in the extracellular matrix, increasing vascular calcification and arterial stiffening.\textsuperscript{68} Estrogen also has an important role in vascular health and bone metabolism. Estrogen has protective effects on the cardiovascular system by altering serum lipid concentrations;\textsuperscript{69} estrogen can lower phosphorus levels and reduce the production of inflammatory cytokines.\textsuperscript{70, 71} Moreover, estrogen receptors are found on both vascular endothelial and smooth muscle cells, osteoblasts and osteoclasts,\textsuperscript{72-74} which suggests a direct effect of estrogen on vascular structures and bone cells as well. Therefore, estrogen might be a mediator in the sex-specific association between arterial stiffness and bone demineralization.\textsuperscript{31} 

\textit{Impaired glucose metabolism}

Changes in insulin regulation and glucose metabolism may be another underlying factor in both processes. Diabetes mellitus, impaired glucose regulation and metabolic syndrome are associated with elevated stiffness as result of accumulation of glycation end-products (AGEs) in the vessel wall.\textsuperscript{75} Insulin resistance is found to be associated with lower bone strength independent of body weight or other potential confounders, suggesting that hyperinsulinemia (and not hyperglycemia) negatively affects bone structure.\textsuperscript{76} It has been suggested that osteoblasts are insulin target cells and that bone resorption is stimulated by insulin signaling in osteoblasts.\textsuperscript{77} Also, adipocytes and osteoblasts have a common progenitor and the differentiation is modulated by various shared pathways in which hormones and inflammatory mediators stimulate and
inhibit both type of cells.\textsuperscript{78} Therefore, impaired glucose metabolism including metabolic syndrome seems to concurrently influences both arterial stiffness and bone demineralization.

\textit{Other hypotheses}

An optimal blood flow is essential in the formation of capillaries and angiogenic growth of the bone vasculature, in which Notch signaling in the endothelium of the bone plays a key role;\textsuperscript{79} Notch promotes blood vessel growth and couples angiogenesis and osteogenesis.\textsuperscript{80} Since a non-optimal blood flow downregulates Notch signaling, this can result in defective angiogenesis and negatively affect bone homeostasis and repair. The renin-angiotensin-aldosterone system (RAAS), a critical regulator of blood volume and a determinant of arterial stiffness,\textsuperscript{81} might also play a role in bone homeostasis, where angiotensin II increases the osteoclastogenesis and inhibits osteoblastic activity resulting in a decrease in bone mineral density.\textsuperscript{82} There may also be a role for transcription factors involved in cell differentiation, such as peroxisome proliferator-activated receptor gamma (PPAR-\textgreek{y}), which is a positive promotor of adipogenesis and a negative regulator of osteoblastogenesis.\textsuperscript{83} It is shown that PPAR-\textgreek{y} agonists reduce inflammation, adhesion molecules and arterial stiffness by improving insulin sensitivity,\textsuperscript{84} which makes it a relevant factor for future research.

\textbf{B. Arterial stiffness and muscle mass and function}
In terms of the potential mechanism whereby sarcopenia and vascular stiffness interact, there is no clear consensus, with manifold theories and likely multiple highly interrelated factors. While some studies have suggested chronic ischaemia from stiff vessels as the cause of muscle breakdown, others have highlighted the impact of atrophic myocytes on the body’s oxidative state, resulting in chronic inflammation and augmenting vascular stiffening. The most commonly hypothesized mechanisms are outlined in figure 1 and below.

Inflammation

Chronic inflammation and oxidative stress are frequently postulated to underlie changes in muscle and blood vessels with age. Aging cells show mitochondrial dysfunction, for example changes in peroxisome proliferator-activated receptor-γ coactivator-1α pathways, leading to increased production of reactive oxidant species, further mitochondrial damage and reduced proliferative capacity, particularly in high oxygen consumption tissues such as skeletal muscle. Deficient autophagy in muscle stem cells can exacerbate inflammation and impaired antioxidant molecules such as Sestrin have been implicated in skeletal muscle decline with age in animal models. Increased CRP has been shown to predict loss of muscle, while imbalanced production of reactive oxygen species can impair muscle cell maintenance. Inflammatory mediators can act directly on muscle receptors to increase breakdown or indirectly by impairing production of anabolic proteins such as growth hormone. In arteries, an inflammatory state can reduce elastin and increase stiffness, and these changes result in further release of inflammatory mediators. Whether low level inflammation is the cause or effect of muscle breakdown and arterial stiffening is yet to be determined.
Hormonal dysregulation

Testosterone has also been proposed as a link between cardiovascular risk and sarcopenia, with androgen-deprivation therapy resulting in increased fat and loss of muscle. Ochi found an association of free testosterone with both loss of muscle mass and increased arterial stiffness, suggesting this may underlie the association in men. However, this study used thigh muscle CT to define sarcopenia, showing a higher reduction in this parameter with age in men compared to women and thus possibly explaining the lack of association with arterial stiffness in women. Using whole body measures of muscle mass may be more useful in assessing the relationship in both sexes. Testosterone may increase the levels of type 1 and type 2 muscle fibers, possibly through increasing IGF-1 levels, and its effect on arterial stiffness may also relate to changes in the muscular wall, although other theories include a vasodilatory effect or increase in inflammatory mediators. Although there is some evidence to suggest testosterone therapy improves body composition, concerns over cardiovascular and prostate disease mean it is not currently recommended.

Impaired glucose metabolism

Other studies have suggested that changes in insulin regulation as the common underlying factor in these processes. Indeed, the association of sarcopenia and coronary artery calcification was reduced by adjustment for insulin resistance. The exact mechanism for muscles is unidentified, as dysfunctional insulin signalling can cause muscle breakdown via resistance to insulin’s anabolic activation of MAPK pathways, while muscle loss and change in proportion of type 1 to type 2 muscle fibers can act to reduce insulin sensitivity, with both elements likely
exerting an amplifying effect. Insulin may induce its anabolic effect on skeletal muscle by increasing endothelial-derived nitric oxide to increase amino acid delivery via vasodilation. Aging may lead to impaired endothelial responsiveness to insulin (due to increased endothelin1, reduced nitric oxide and systemic inflammation), thereby mediating one element of insulin resistance on muscle. S6K1 has also been implicated as a possible causal pathway linking impaired skeletal muscle responses to insulin signalling, which may be involved in vascular stiffening in diabetes. A recent meta-analysis found increased prevalence of sarcopenia in diabetics with higher risk of developing diabetic complications, concluding there is likely a bi-directional interaction between muscle wasting and insulin dysregulation.

Other hypotheses

A study comparing the impact of sarcopenia on vascular function in Indian and Japanese patients suggested that baPWV in the Indian cohort and CAVI in the Japanese cohort was found to be only associated with loss of muscle in non-hypertensive individuals, postulating that differential activity of CD34 cells and platelets induced by hypertension may enhance angiogenesis and enable the maintenance of grip-strength despite underlying endothelial dysfunction. One small study of neural tracts using diffusion tensor tractography found a deterioration of associated neural tracts for motor function in sarcopenic women compared to non-sarcopenic, proposing elevated arterial stiffness as the underlying mechanism for microscopic changes in neural structures leading to subsequent muscle atrophy. The ability of ACE inhibitors to increase anabolism and reduce arterial stiffness has led some to consider the role of the renin-angiotensin-aldosterone system in the development of sarcopenia, with sarcopenic patients showing higher rates of urinary angiotensinogen excretion. Cardiovascular
medications have shown some benefits in reducing sarcopenia, including espindolol (thought to reduce catabolic and increase anabolic sympathetic signalling) and ACE inhibitors (thought to have an as yet unspecified direct effect on skeletal muscle as well as their effect on insulin sensitivity and inflammation). The RAS system may influence anabolic signalling cascades, thus offering a potential treatment option in the future to reduce both sarcopenia and cardiovascular risk. Sarcopenia also seems to be linked to atherosclerosis, with BIA-derived sarcopenia associated with an increased trend in coronary artery calcification scores.

It could be argued that genetic and lifestyle factors such as diet, exercise and smoking underlie increases in adipose tissue in the development of all these conditions, yet Campos found that lack of muscle rather than addition of fatty tissue, was the key driver in the atherosclerotic process in sarcopenic patients.

Conclusions

A large number of clinical studies report associations between arterial stiffness and bone and muscle loss. We have used pre-clinical studies to explore the common potential mechanisms linking the aging process in arteries, bones and muscle. However, considerable research is needed to establish the mechanisms that connect arterial stiffness with muscle and bone deterioration during the aging process. Experimental, longitudinal, long-term, large-scale studies with sequential simultaneous measurements of artery, muscle and bone clinical phenotypes are presently missing. Chronic inflammation, hormonal changes and metabolic disorders could be common mechanisms for increasing the pace of arterial, bone and muscle aging. Dysregulation of blood flow and tissue hypoperfusion due to arterial stiffness could also be an accelerator of
bone demineralization, whereas no such data exists on the possible effect of arterial stiffness on muscle mass and function. Regular exercise increases muscle and bone mass, and decreases arterial stiffness. It is possible that these actions are mediated through direct mechanical effects on muscle and bones but also through an effect of physical exercise on chronic inflammation and insulin resistance. Biomarkers of aging and of chronic inflammation will hopefully elucidate the mechanisms by which these complex processes of arterial stiffness, bone deterioration and muscle loss interact. The answer to these questions could determine new preventive and therapeutic targets in order to slow down these age-related degenerative processes and their multiple complications in older adults. A future meta-analysis on this topic would be of interest to establish the evidence from previous studies and could also confirm our conclusions.

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Disclosures

None
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**Figure 1.** Shared mechanisms underlying arterial stiffness, bone demineralization and muscle loss

**Abbreviations**: AGEs, Advanced glycation end products; CRP, C-reactive protein; IGF1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RANKL, Receptor activator of nuclear factor kappa-B ligand
### Table 1. Literature investigating associations between arterial stiffness and bone mineral density (BMD)

<table>
<thead>
<tr>
<th>Main publications on this topic</th>
<th>Design</th>
<th>Population</th>
<th>Country</th>
<th>Size</th>
<th>Age, years (SD)</th>
<th>Arterial stiffness</th>
<th>BMD</th>
<th>Associations in multivariate analyses</th>
<th>Covariates (if applicable)</th>
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<tr>
<td>Li XS 2016&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Hypertensive men (HTN) and control (no-HTN)</td>
<td>China</td>
<td>708</td>
<td>68.1 (9.5)</td>
<td>baPWV</td>
<td>*DEXA: LS,FN</td>
<td>HTN: baPWV-FN +++</td>
<td>Age, BMI, smoking, alcohol use, physical activity, SBP, DBP, DM, glucose, eGFR, cholesterol, triglycerides, antihypertensive medications, statins</td>
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<td>Mikumo M 2009&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Postmenopausal women</td>
<td>Japan</td>
<td>143</td>
<td>57.9 (8.3)</td>
<td>*baPWV</td>
<td>DEXA: LS</td>
<td>Blood: BAP</td>
<td>Age, height, SBP</td>
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<tr>
<td>Jaalkhorol M 2019&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Longitudinal (10 years)</td>
<td>Population-based</td>
<td>Japan</td>
<td>446</td>
<td>62.6 (7.9)</td>
<td>*baPWV</td>
<td>DEXA: LS, FN, TH</td>
<td>TH – baPWV +</td>
<td>baseline baPWV, Age, SBP</td>
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<tr>
<td>Giallauria F 2011&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Cross-sectional</td>
<td>Healthy adults</td>
<td>USA</td>
<td>633</td>
<td>66.5 (12.6)</td>
<td>*cfPWV</td>
<td>CT: cCSA</td>
<td>Women: cCSA-cfPWV +</td>
<td>Age, obesity, alcohol use, physical activity, MAP, menopause status, total estradiol, eGFR, calcium, antihypertensive medications, diuretics, HRT</td>
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<td>Cross-sectional</td>
<td>Patients with CKD</td>
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<td>64.5 (range 26-80)</td>
<td>cfPWV</td>
<td>*DEXA: LS,FN</td>
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<td>110</td>
<td>56.1</td>
<td>*cfPWV</td>
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<td>519</td>
<td>72.3 (5.4)</td>
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</tr>
<tr>
<td>2016</td>
<td>Cross-sectional</td>
<td>Longitudinal (2 years)</td>
<td>Patients with hyper-homocysteinemia</td>
<td>The Netherlands</td>
<td>519</td>
<td>72.3 (5.4)</td>
<td>cfPWV, cPP</td>
<td>*DEXA: LS, FN QUS: BUA calcaneus No associations Baseline BMD, Age, sex, BMI, smoking, alcohol use, hypertension, DM, cholesterol, eGFR, study center, treatment</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Cross-sectional</td>
<td>Population-based</td>
<td>Patients with hyper-homocysteinemia</td>
<td>The Netherlands</td>
<td>519</td>
<td>72.3 (5.4)</td>
<td>cfPWV, cPP</td>
<td>*DEXA: LS, FN QUS: BUA calcaneus No associations Baseline BMD, Age, sex, BMI, smoking, alcohol use, hypertension, DM, cholesterol, eGFR, study center, treatment</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>Cross-sectional</td>
<td>Geriatric inpatients</td>
<td>Patients with hyper-homocysteinemia</td>
<td>The Netherlands</td>
<td>519</td>
<td>72.3 (5.4)</td>
<td>cfPWV, cPP</td>
<td>*DEXA: LS, FN QUS: BUA calcaneus No associations Baseline BMD, Age, sex, BMI, smoking, alcohol use, hypertension, DM, cholesterol, eGFR, study center, treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BAP, bone alkaline phosphatase; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BUA, broadband ultrasound attenuation; CAVI, cardio-ankle vascular index; cCSA, cross-sectional cortical bone area; cfPWV, carotic-femoral pulse wave velocity; cPP, central pulse pressure; CVD, cardiovascular diseases; DEXA, dual energy x-ray absorptiometry; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FN, femoral neck; HDL, high density lipoprotein, HRT, hormone replacement therapy; LS, lumbar spine; MAP, mean arterial pressure, pPP, peripheral pulse pressure; SBP, systolic blood pressure; TH, total hip; TS, thoracic spine; QUS, quantitative ultrasound

**Notes:** * marks dependent variable, +++ = p values < 0.001, ++ = p value < 0.01, + = p-value < 0.05
Table 2. Literature investigating associations between arterial stiffness and muscle loss

<table>
<thead>
<tr>
<th>Main publications on this topic</th>
<th>Design</th>
<th>Sample</th>
<th>Country</th>
<th>Size</th>
<th>Age, years (SD)</th>
<th>Arterial Stiffness</th>
<th>Muscle index</th>
<th>Associations in multivariate analyses</th>
<th>Covariates (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim TN 2011^40</td>
<td>Cross-sectional</td>
<td>Apparently healthy adults</td>
<td>Korea</td>
<td>510</td>
<td>53.6 (15.6)</td>
<td>*baPWV</td>
<td>CT+DEXA: MFR</td>
<td>MFR – baPWV +++</td>
<td>Age, sex, BMI, WC, smoking, alcohol use, physical activity, SBP, DBP, glucose, TG, HDL, cholesterol, ASM/height^2</td>
</tr>
<tr>
<td>Kohara K 2017^41</td>
<td>Cross-sectional</td>
<td>Healthy adults</td>
<td>Japan</td>
<td>1518</td>
<td>67.9 (6.8)</td>
<td>baPWV</td>
<td>*CT: thigh CSA</td>
<td>Analysis of variance: baPWV – CSA +++ baPWV – SMM +++ No multivariate analysis</td>
<td>-</td>
</tr>
<tr>
<td>Kohara K 2012^43</td>
<td>Cross-sectional</td>
<td>Healthy adults</td>
<td>Japan</td>
<td>1024</td>
<td>66.2 (8.7)</td>
<td>*baPWV</td>
<td>CT: thigh CSA, VFA</td>
<td>VFA – baPWV +++ Men:</td>
<td>Age, height, weight, BP, cholesterol, HDL, TG, glucose, CRP, smoking,</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>Population Description</td>
<td>Country</td>
<td>Sample Size</td>
<td>Age (Mean ± SD)</td>
<td>CSA – baPWV</td>
<td>Physical Activity, Antihypertensive Medication, Leptin</td>
<td></td>
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</tbody>
</table>
| Zhang L 2019<sup>45</sup>     | Cross-sectional    | Communit y-dwelling adults                                                              | China     | 1002        | 72.3 (5.2)      | baPWV             | *BIA: ASMI, HGS  
  baPWV – ASMI ++  
  baPWV – HGS + | Age, sex, BMI, smoking, alcohol use, BP, HR, cholesterol/HDL, HbA1C, CIMT, hypertension, DM, stroke |
| Abbatecola AM 2012<sup>46</sup> | Cross-sectional   | Communit y-based                                                                       | USA       | 2272        | 73.7 (3)        | cfPWV             | *CT: thigh CSA  
  DEXA: ALM to calculate sarcopenic index  
  Men: cfPWV – sarcopenic index ++  
  White women: cfPWV – sarcopenic index + | Age, BMI, SBP, PAD, CHD, IL-6, physical activity, fat mass, site, time, time<sup>2</sup>, race, PWV-race interaction |
| Rodriguez AJ 2017<sup>48</sup> | Meta-analysis      | Various                                                                                 | Various   | 8558        | Mean age ranges: 23 – 73.6 | Various: cfPWV, baPWV  
  Various: CT, DEXA, BIA | Pooled results: PWV – muscle tissue +++ | Various (meta-analysis) |
| Kirkham FA 2018<sup>49</sup>  | Cross-sectional    | Healthy adults and adults with cardiovascular risk factors                               | UK        | 366         | 70.8 (7.9)      | CAVI, crPWV, cfPWV | *BIA: SMI, HGS  
  CAVI – SMI +++ | Age, sex, DM, dyslipidemia, hypertension, ischemic heart disease, BP, smoking |
| Sampaio RA                    | Cross-sectional    | Healthy                                                                                 | Japan     | 175         | > 65            | CAVI               | *BIA: SMI  
  CAVI – SMI + | Age, sex, BMI, MNA, grip |
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Design</th>
<th>Location</th>
<th>N</th>
<th>Age (SD)</th>
<th>Methodology</th>
<th>Predictor</th>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Cross-sectional</td>
<td>Adults</td>
<td>Korea</td>
<td>3356</td>
<td>48.9 (6.1)</td>
<td>*CAVI</td>
<td>BIA: MMD</td>
<td>MMD – CAVI</td>
<td>Age, BMI, MAP, HR, TG, GGT, leukocytes, HOMA-IR, alcohol use, smoking, regular exercise, medication</td>
</tr>
<tr>
<td>2017</td>
<td>Cross-sectional</td>
<td>Community dwelling men</td>
<td>Korea</td>
<td>3356</td>
<td>48.9 (6.1)</td>
<td>*CAVI</td>
<td>BIA: MMD</td>
<td>MMD – CAVI</td>
<td>Age, BMI, MAP, HR, TG, GGT, leukocytes, HOMA-IR, alcohol use, smoking, regular exercise, medication</td>
</tr>
<tr>
<td>2019</td>
<td>Cross-sectional</td>
<td>Geriatric inpatients</td>
<td>China</td>
<td>171</td>
<td>78.5 (9.2)</td>
<td>CAVI</td>
<td>*HGS and gait speed to determine frailty</td>
<td>CAVI – Frailty +++</td>
<td>Age, BMI, ADL, ABI, Hb, Albumin, eGFR, CRP, LDL</td>
</tr>
<tr>
<td>2016</td>
<td>Cross-sectional</td>
<td>Post-menopausal women</td>
<td>USA</td>
<td>36</td>
<td>58 (4)</td>
<td>*baPWV</td>
<td>DEXA: ASMI</td>
<td>T test: ASMI – baPWV ++</td>
<td>No multivariate analysis</td>
</tr>
<tr>
<td>2010</td>
<td>Cross-sectional</td>
<td>Apparently healthy adults</td>
<td>Japan</td>
<td>496</td>
<td>Middle aged</td>
<td>baPWV</td>
<td>*CT: thigh CSA</td>
<td>Men: baPWV – CSA ++</td>
<td>Age, height, SBP, cholesterol, HDL, TG, glucose, insulin, CRP, testosterone, antihypertensive medication, smoking, physical activity, alcohol, CIMT</td>
</tr>
</tbody>
</table>

**Abbreviations:** ABI, ankle brachial index; ADL, activities of daily living; ALM, appendicular lean mass; ASM(I), appendicular skeletal muscle mass (index); baPWV, brachial-ankle pulse wave velocity; BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; cfPWV, carotid-femoral pulse wave velocity; CHD, cardiac heart disease; CIMT, carotid intima-media thickness, CRP, c-reactive protein; crPWV, carotid-radial pulse wave velocity; CSA, cross-sectional area; CT, computerized tomography; DEXA, dual energy x-ray absorptiometry; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl
transferase; Hb(A1c), hemoglobin(A1c); HDL, high density lipoprotein; HGS, handgrip strength; HOMA-IR, homeostatic model assessment for insulin resistance; HR, heart rate; IL-6, interleukin-6; LDL, low density lipoprotein; MAP, mean arterial pressure; MFR, muscle-fat ratio; MMD, muscle mass deficit; MNA, mini-nutritional assessment; PAD, peripheral artery disease; SMI, skeletal mass index; SMM, skeletal muscle mass; SPB, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglycerides; VFA, visceral fat area; WC, waist circumference;

Notes: *marks dependent variable, +++ = p values < 0.001, ++ = p value < 0.01, + = p-value < 0.05