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SYSTEMATIC LITERATURE REVIEW

Impact of Cardiovascular Disease on the Bone-Vascular Axis: A Systematic Review of Musculoskeletal Deficiencies and Therapeutic Implications

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Introduction

Recent advances in medical research reveal how cardiovascular diseases, the leading cause of death worldwide, have substantial effects on other body systems. Cardiovascular diseases like arteriosclerosis and coronary artery disease (CAD) are caused when coronary arteries are blocked by a buildup of atherosclerotic plaques, leading to reduced blood flow, ischemia, stroke, and myocardial infarction. Traditionally, CAD and arteriosclerosis are researched for their prevalent effects on the cardiovascular system. However, they also impact many other systems, including the musculoskeletal system.

Musculoskeletal deficiencies, leading causes of disability and chronic pain worldwide, are conditions impairing the musculoskeletal system's structure and functionality, including bones, muscles, tendons, and ligaments. The deficiencies lead to decreased mobility and strength. As the musculoskeletal system provides structural support and enables movement, deficiencies here lead to chronic pain, reduced movement, and increased vulnerability to injuries like fractures.

Subtypes of musculoskeletal deficiencies affect specific tissues like joint degeneration (osteoporosis), connective tissue diseases (tendinopathy), and muscles (sarcopenia) [1]. Musculoskeletal deficiencies, particularly osteoporosis, have recently been found to be another complication of different types of cardiovascular disease. These deficiencies are a result of disruptions within the bone vascular axis - an interplay between bone and blood vessels that impacts both bone and vascular health. Cardiovascular diseases can cause damage to this axis in different ways, such as coronary arterial calcification, chronic inflammation, and metabolic dysregulation, which not only lead to vascular diseases but also affect bone remodeling and growth.

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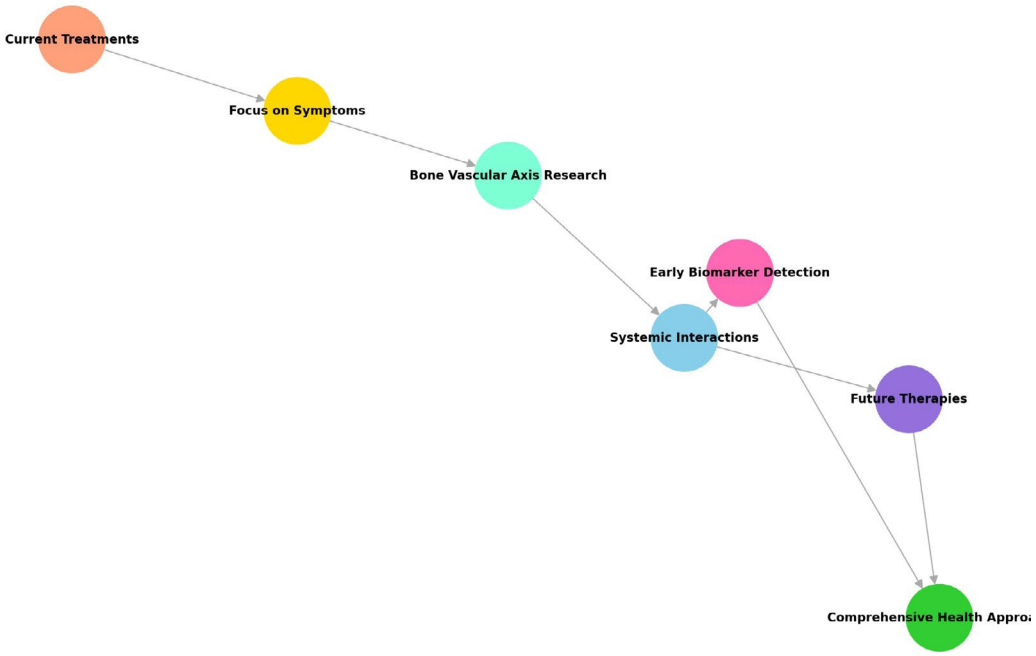
Aspect	Cardiovascular Diseases	Musculoskeletal Deficiencies	Impact on Systems
Conditions	Arteriosclerosis, CAD	Osteoporosis, Tendinopathy, Sarcopenia	Leads to ischemia, stroke, heart attack
Cause	Blocked coronary arteries	Impaired bones, muscles, tendons, ligaments	Disrupted blood flow, inflammation, dysregulation
Impact on Musculoskeletal System	May affect bone health (osteoporosis, fractures)	Joint degeneration, bone loss, muscle atrophy	Atherosclerosis and CAD damage bone remodeling
Resulting Complications	Stroke, heart attack, reduced mobility	Chronic pain, fractures, reduced movement	Both systems experience chronic pain and increased injury risk

Aim of Literature Review

Current treatments for such deficiencies, like osteoporosis, use bisphosphonates, selective estrogen receptor modulators (SERMs) like Raloxifene, vitamin D supplementation, and lifestyle interventions [1]. The problem is that these treatments primarily focus on stopping symptoms like preventing fractures rather than addressing the underlying cause of the deficiency. That is why this literature review aims to find how cardiovascular diseases affect the bone vascular axis, as understanding the systemic interactions between the vascular and skeletal systems will be crucial in developing treatments and strategies that go beyond treating symptoms but the disease.

By using this knowledge of the bone vascular axis in clinical practice, we may be able to change the way we think about musculoskeletal and cardiovascular health. Understanding the interdependence of both systems may lead to more comprehensive approaches in future therapies that prevent or delay the development of both vascular disorders and bone deficits at the same time. This combined strategy may also aid in the early detection of biomarkers for bone-related and cardiovascular disorders, enabling earlier intervention and maybe lowering the need for more invasive procedures or long-term drug usage. Improving our comprehension of these systemic linkages may ultimately result in longer-term, more effective remedies that deal with the underlying causes of these disorders rather than just treating their symptoms.

Visual Graph: Current and Future Approaches to Bone and Vascular Health



Methods (Following PRISMA Guidelines)

To evaluate how cardiovascular diseases, like coronary artery disease (CAD) and arteriosclerosis, affect the bone vascular axis leading to musculoskeletal deficiencies, a focused literature search was conducted. The search specifically included articles published between 2000 and 2024, highlighting recent advancements in studying the

effects of cardiovascular disease on the bone vascular axis. PubMed and Google Scholar were among the resources utilized to select publications. “Cardiovascular disease and bone vascular axis,” “musculoskeletal deficiencies treatments,” “bone remodeling cardiovascular disease,” “cardiovascular disease and musculoskeletal health,” and “cardiovascular disease treatments for musculoskeletal system” were the search terms.

Authors & Year	Title	Journal	DOI
Azeez, T.A. (2023)	Osteoporosis and cardiovascular disease: a review	Mol Biol Rep	10.1007/s11033-022-08088-4
Sfyri, P., & Matsakas, A. (2017)	Crossroads between peripheral atherosclerosis, western-type diet and skeletal muscle pathophysiology	J Biomed Sci	10.1186/s12929-017-0346-8
Thompson, B., & Towler, D.A. (2012)	Arterial calcification and bone physiology: role of the bone-vascular axis	Nat Rev Endocrinol	10.1038/nrendo.2012.36
Wang, Y., Wang, R., Liu, Y. et al. (2021)	Associations between bone mineral density in different measurement locations and coronary artery disease	Arch Osteoporos	10.1007/s11657-021-00940-7
Jørgensen, L., Joakimsen, O., Mathiesen, E.B., et al. (2006)	Carotid Plaque Echogenicity and Risk of Nonvertebral Fractures in Women	Calcif Tissue Int	10.1007/s00223-006-0071-x
Kim, H., Lee, J., Lee, K.-B. et al. (2022)	Low bone mineral density is associated with coronary arterial calcification progression	Clin Kidney J	10.1093/ckj/sfab138

LeBoff, M. S., et al.	2022	Prevention and treatment of osteoporosis	Osteoporosis treatments	Guidelines for managing osteoporosis
Pittman, C. B., et al.	2014	Myocardial infarction risk in bisphosphonate users	Bisphosphonates and CVD risk	Bisphosphonate use linked to higher myocardial infarction risk
Sfyri, P., & Matsakas, A.	2017	Peripheral atherosclerosis and muscle pathophysiology	Atherosclerosis and musculoskeletal effects	Atherosclerosis leads to muscle atrophy and dysfunction
Tankó, L. B., et al.	2005	Osteoporosis and cardiovascular disease in postmenopausal women	Postmenopausal osteoporosis and CVD risk	Osteoporotic women have a higher risk of cardiovascular events
Thompson, B., & Towler, D. A.	2012	Arterial calcification and bone physiology	Bone-vascular axis mechanisms	Bone health and vascular calcification are interrelated
Wang, Y., et al.	2021	BMD and coronary artery disease	CAD and bone density	Low BMD correlates with increased CAD risk
Wiegandt, Y. L., et al.	2019	BMD and coronary calcification in men and women	BMD and CAC relationship	Low BMD is linked to higher coronary calcification in both genders

Wu, S. T., et al.	2021	Bisphosphonates and cardiovascular risk	Osteoporosis treatment and CVD	Bisphosphonates may increase cardiovascular mortality risk
Yang, Y., & Huang, Y.	2023	BMD and cardiovascular disease in older adults	Osteoporosis and CVD risk	Older adults with low BMD have a higher risk of CVD

The inclusion criteria for this review encompassed studies that focused on the effects of cardiovascular disease on the musculoskeletal system, specifically related to disruptions within the bone vascular axis, provided data on prognostic indicators and progression rates of patients with musculoskeletal deficiencies due to vascular issues, and included original research, systematic reviews, or meta-analyses published through 2000 to 2024. The exclusion criteria rejected studies that did not specifically mention the relationship between cardiovascular disease and the bone vascular axis. Further studies were excluded due to not offering empirical data on musculoskeletal or cardiovascular treatments and those that did not discuss cardiovascular disease's systemic effects.

A PRISMA flowchart was utilized to depict the study selection process, demonstrating how many articles were identified, verified, removed, and ultimately included in this review.

Data from the studies mentioned were collected methodically, emphasizing study characteristics such as author(s), year of publication, study design, and sample size. Key data points extracted included how different types of cardiovascular disease impact bone and vascular health, the effects of coronary arterial calcification and chronic inflammation, development of musculoskeletal deficiencies in cardiovascular disease patients, and effectiveness of musculoskeletal treatments like bisphosphonates, selective estrogen receptor modulators (SERMs) like Raloxifene, vitamin D supplementation, and lifestyle interventions in comparison to cardiovascular disease treatments on musculoskeletal health affecting bone mineral density (BMD), fracture susceptibility, and muscle strength.

Mechanism	Impact on CVDs	Impact on Bone Health
Chronic inflammation	Promotes plaque formation and vascular remodeling	Increases bone resorption and reduces formation
Oxidized LDL	Increases atherosclerosis progression	Reduces osteoblast growth and promotes apoptosis
Endothelial dysfunction	Plaque development and vascular dysfunction	Disrupts bone remodeling processes
Elevated homocysteine	Vascular damage and remodeling	Affects osteoblast activity and bone health
Lipid peroxidation	Triggers oxidative stress and inflammation	Induces bone tissue damage and resorption

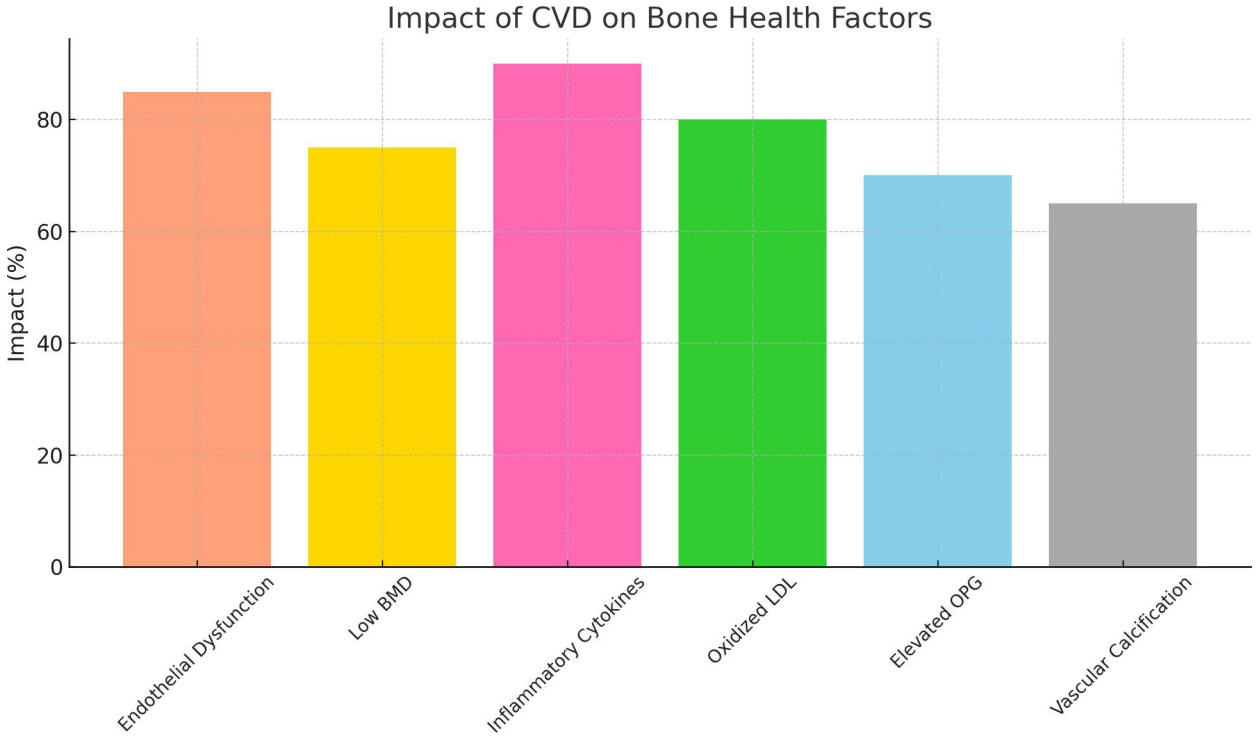
Prognostic outcomes such as BMD, fracture susceptibility, mobility, myocardial infarction, and stroke were among the measures assessed. Important findings about cardiovascular disease, the bone vascular axis, and musculoskeletal deficiencies were documented and synthesized to provide insights into the effectiveness of the bone and vascular treatments for these deficiencies.

The methodological quality of the included research was assessed using standardized instruments appropriate for the kind of study examined, such as QUADAS-2 for diagnostic accuracy studies and ROBINS-I for non-randomized studies. This evaluation considered variables such as study design, bias risk, and data generalizability. The quality assessment findings influenced discussions concerning the strength of the data indicating the potential of cardiovascular disease's impact on the musculoskeletal system and its potential treatments to address deficiencies.

Impact of Cardiovascular Disease on Musculoskeletal Health

Cardiovascular diseases (CVDs), including coronary artery disease (CAD) and arteriosclerosis, are known for their effects on the cardiovascular system, but scientific research has revealed their impact on the musculoskeletal system and bone health. Specifically, osteoporosis, a common type of musculoskeletal deficiency, has many pathophysiological mechanisms shared between CVDs. Osteoporosis results when there is an imbalance between osteoclastic bone resorption and osteoblastic bone formation, where there is more bone resorption than bone

formation. Common features of osteoporosis are chronic low-grade inflammation, elevated homocysteine, lipid peroxidation, and calcium deposition-which are also found in coronary artery disease [2]. Endothelial dysfunction, a sign of CAD, has been found to disrupt bone health. Azeez [2] identified that endothelial dysfunction is crucial in the formation of coronary artery plaques, and it has been deemed to affect osteoblast activity, leading to an imbalance in bone resorption and formation. Additionally, osteoporosis and CVDs share critical proteins that affect bone and vascular health. As noted by Azeez [2], bone mineral density is directly proportional to high-density lipoprotein cholesterol (HDL-C) and low HDL-C is found in osteoporosis, and coincidently low HDL-C is a risk factor for CAD. Lipid oxidation is a key factor in the development of coronary artery atherosclerosis, and oxidized low-density lipoprotein (LDL) is recognized for disrupting the growth of osteoblasts and increasing their rate of apoptosis. Elevated levels of osteoprotegerin (OPG), a protein that affects both bone and vascular metabolism, have been found in osteoporosis and CAD. Finally, inflammatory cytokines that depend on caspases, like IL-1β, IL-6, and IL-18, play a role in both the development of plaques and the breakdown of bone. These findings suggest that similar mechanisms put individuals at risk of both CVDs and musculoskeletal deficiencies, displaying a relationship between the two.



Protein/Marker	Role in CVDs	Role in Bone Health
Osteoprotegerin (OPG)	Promotes vascular calcification	Regulates bone metabolism
IL-6	Drives inflammation and smooth muscle growth	Increases bone resorption
Sclerostin	Elevated levels in vascular calcification	Inhibits bone formation
Nitric Oxide (NO)	Dysregulation leads to vascular dysfunction	Maintains bone remodeling balance
CRP (C-reactive protein)	Marker of systemic inflammation in vascular disease	Triggers osteoclast activity and bone resorption

CVDs have more direct impacts on bone health as well. Peripheral atherosclerosis compromises homeostasis and functional capacity of skeletal muscle. It causes myopathy, fibrosis, mitochondrial de-regulation, oxidative stress, inflammation, and apoptosis. This leads to impaired capillary density and chronic ischemia-reducing blood flow. According to Sfyri and Matsakas [3], the metabolic hypothesis suggests a direct relationship between local blood flow and the metabolic demand of muscle. This can be seen when chronic ischemia results in a lack of oxygen and nutrients, which brings about various changes in skeletal muscle metabolism. These include a reduction in mitochondrial respiration, an elevation in reactive oxygen species (ROS) production, a buildup of metabolic byproducts such as hydrogen ions (H^+) and calcium ions (Ca^+), and an imbalance in intracellular ions (like potassium

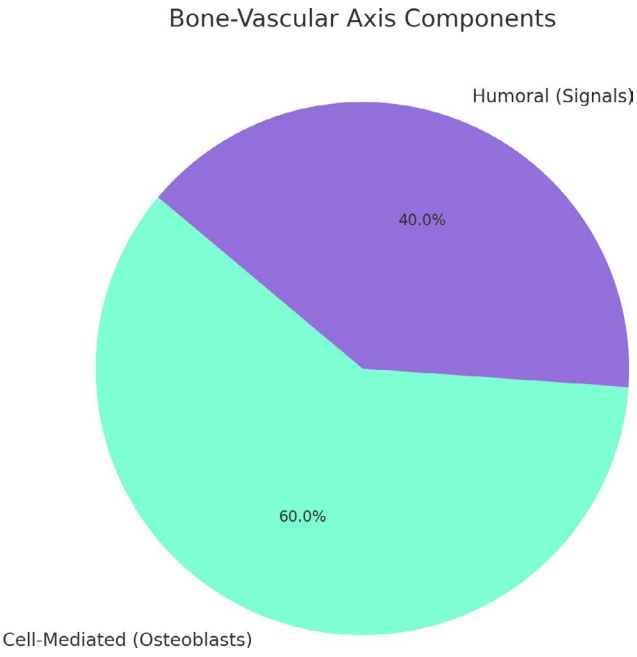
and sodium) that further hinders cellular function. All of these issues lead to musculoskeletal issues.

Effect	Mechanism	Outcome
Myopathy	Reduced blood flow to skeletal muscle	Muscle atrophy and fibrosis
Chronic ischemia	Impaired oxygen and nutrient supply	Reduced metabolic function
Oxidative stress	Increased ROS production	Tissue damage and inflammation
Mitochondrial deregulation	Altered mitochondrial respiration	Energy production inefficiency

One of the most important connections between CVDs and musculoskeletal deficiencies is the bone vascular axis, where blood vessels assist in musculoskeletal functions, while cell types derived from bone and various signaling molecules influence vascular health. According to Thompson and Towler [4], there are two arms of the bone vascular axis-one being cell-mediated and the other being humoral. The cell-mediated component includes osteoblasts, which are the cells responsible for building bone. These osteoblasts release signals that affect other cells in the bone marrow and influence their movement. The humoral component involves the signals that osteoblasts and osteocytes secrete into the bloodstream. These signals play a crucial role in regulating processes such as phosphate excretion by the kidneys, the production of parathyroid hormone (PTH), and the interaction between blood vessels and bone remodeling.

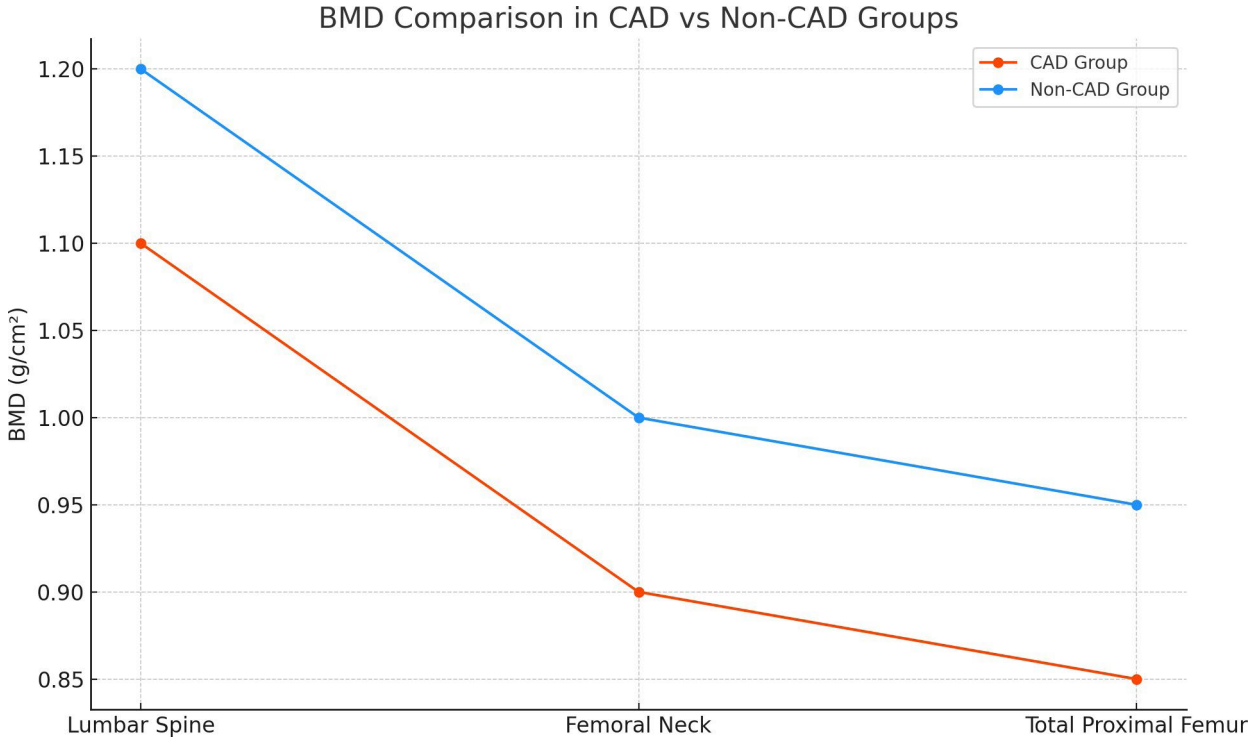
Together, these two pathways help to sustain both bone health and vascular health. From this, Thompson and Towler [4] envisioned three relationships to describe diseases of the bone vascular axis. Firstly, oxylipids contribute to the process of arteriosclerotic calcification, inhibit bone formation, and enhance the development of osteoclasts, leading to the simultaneous and independent progression of arteriosclerosis and musculoskeletal disease. Secondly, arteriosclerosis can negatively affect the bone's anabolic functions critical for maintaining skeletal homeostasis and repairing fractures via vessel stiffening and decreased endothelium-dependent regulation of bone blood flow - leading to musculoskeletal deficiencies. Finally, since osteoblasts, osteocytes, and other cellular components within the bone and bone marrow produce elements and hormonal signals that combat arteriosclerotic changes and support vascular health, primary bone diseases may initiate or exacerbate arteriosclerotic conditions.

These findings support the link between bone health and vascular disease.



This link is displayed by a study conducted by Wang, et al. [5], where participants with or without CAD had their bone mineral density (BMD) measured at 8 locations like the lumbar spine and femoral neck. The results showed that the BMD (measured in g/cm^2, T-score) in the CAD group across three sites (the mean of the first to fourth lumbar spine, the average of both femoral necks, and the total proximal femur) was notably lower compared to the non-CAD group [5]. The study went on to highlight the involved aspects that may be causing the related mechanism between low BMD and the occurrence of CAD. In patients with osteoporosis, pro-inflammatory factors, such as CRP, TNF-α, and IL-6, are expressed, which harms the vascular endothelium, contributes to the growth of smooth muscle cells, speeds up vascular remodeling, and worsens the development of CAD. Abnormalities in proteins like

sclerostin, osteoprotegerin, and GLA, which inhibit bone resorption and stimulate bone formation, also promote vascular calcification. Lastly, Wang, et al. [5] mention the disruption in the regulation of the bone-vascular axis, which includes issues with endothelial function and elevated levels of nitric oxide- leading to bone and vascular disease.

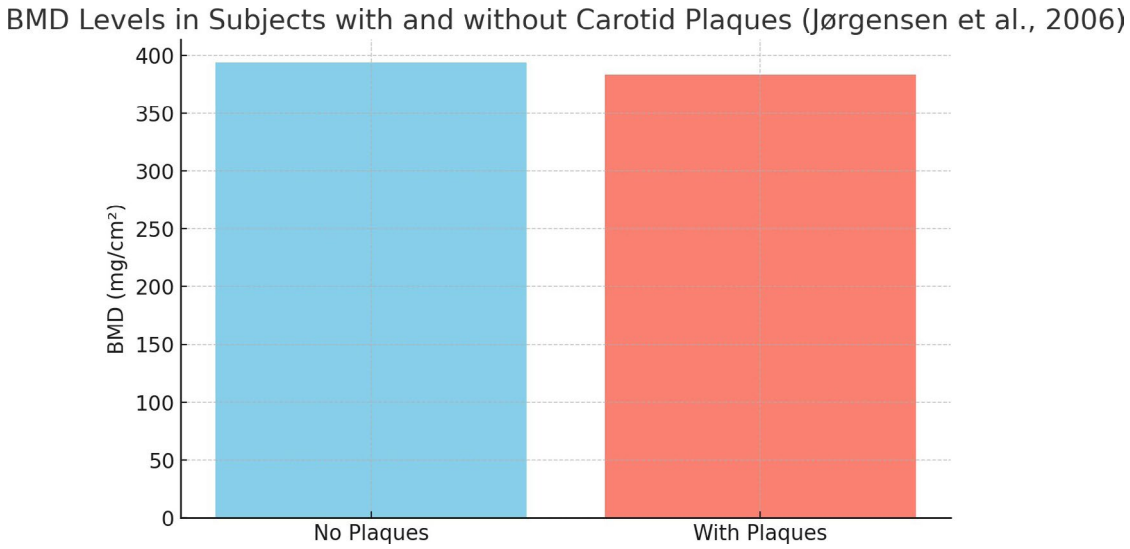


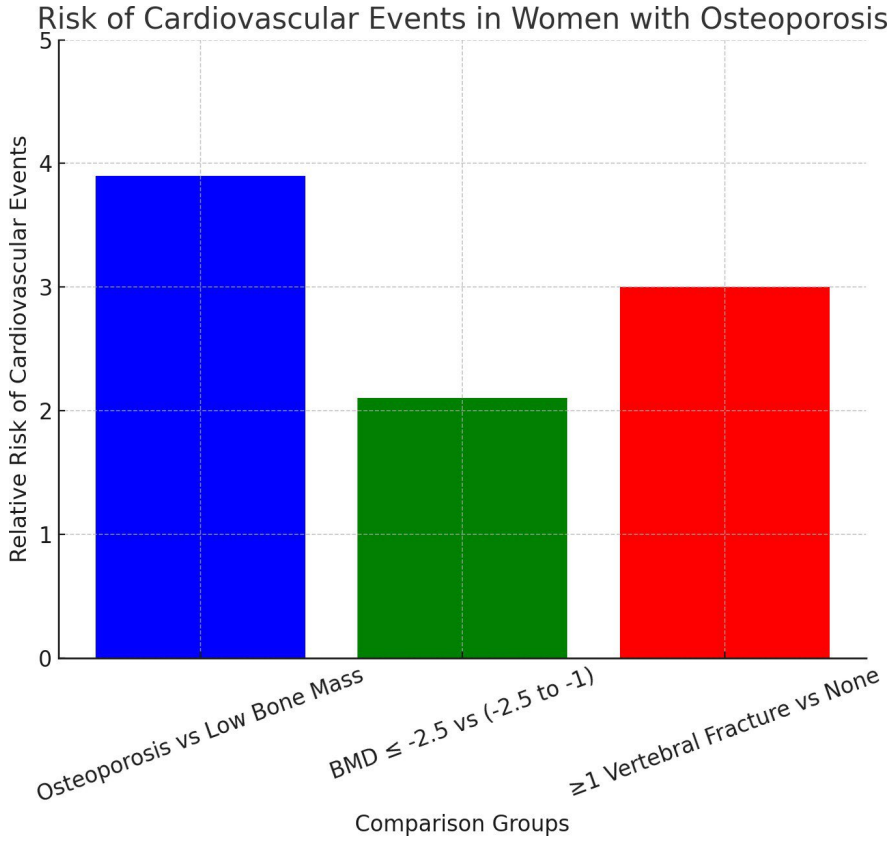
A further study by Jørgensen, et al. [6] looked into the relationship between fracture risk and carotid plaque echogenicity in a longitudinal study. They found that BMD in subjects without plaques was higher than in subjects with plaques, with 394.0 mg/cm^2 and 383.2 mg/cm^2 levels, respectively. Fractures were also sorted according to the prevalence of plaques, with 9.2% having fractures in subjects without plaques and 11.5% in subjects with plaques. Thus, Jørgensen, et al. [6] concluded that women with echogenic carotid plaques had an increased risk of nonvertebral fractures compared to women without plaques, suggesting cardiovascular disease played a part in creating musculoskeletal deficiencies leading to fractures.

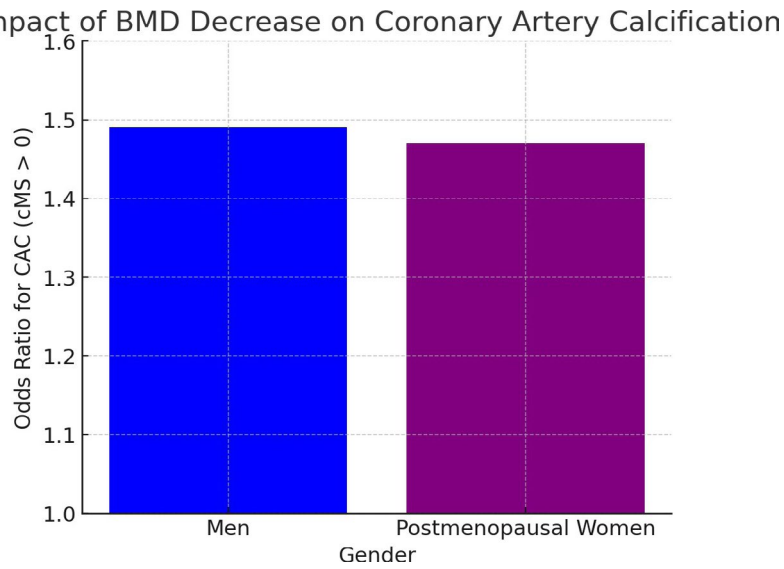
In another study that studies the relationship between musculoskeletal deficiencies and CVDs in women, Tankó, et al. [7] studied 2576 postmenopausal women and the association between the severity of osteoporosis events and the future risk of cardiovascular events. Individuals were classified as having osteoporosis if they had at least one vertebral fracture or a total hip bone mineral density (BMD) T score of -2.5 or lower at the beginning of the study. In contrast, those without vertebral fractures and with a total hip BMD T score ranging from -2.5 to -1 were categorized as having low bone mass. Tankó, et al. [7] found that women with osteoporosis had a 3.9 times more likely chance of a cardiovascular event than women with low bone mass. Similarly, a total hip BMD score ≤ -2.5 versus a T score between -2.5 and -1 was associated with a 2.1-fold increase in risk, and the presence of at least one vertebral fracture versus no vertebral fractures at baseline was associated with a 3.0-fold increase in risk. From these results, the study concluded that postmenopausal women with osteoporosis are at an increased risk of cardiovascular events [7], supporting the link between bone and vascular health.

They also determined that the treatment of postmenopausal osteoporosis should take into account measures to mitigate cardiovascular risks, which will be covered in our next section regarding treatments for osteoporosis and their effects.

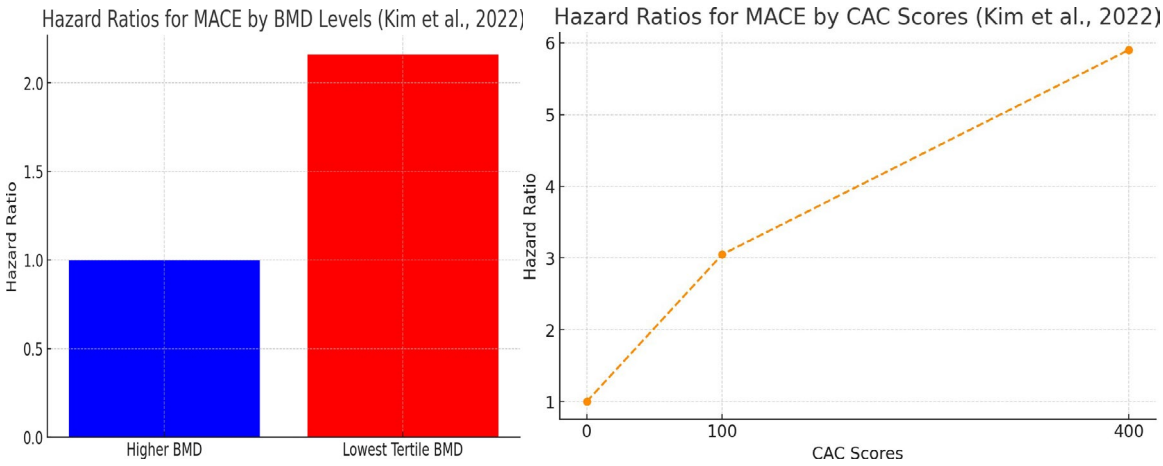
Is the relationship between bone and vascular health different between men and women? A study by Wiegandt, et al. [8] sought to answer this by looking into the relationship between volumetric thoracic bone mineral density and coronary calcification in men and women. In this study of 1163 men and 1385 women, coronary artery calcification (CAC) was measured using a calibrated mass score (cMS) and was split into two groups where cMS = 0 or cMS > 0. In men, a decrease in BMD of 100 mg/cm^3 was associated with an odd ratio of 1.49 for cMS > 0, meaning a 1.49 times greater risk of CAC. In postmenopausal women, a decrease in BMD of 100 mg/cm^3 was associated with an odds ratio of 1.47 for cMS > 0, meaning a 1.47 times greater risk for CAC [8]. These findings suggest that BMD and CAC are inversely related for both men and women, suggesting bone and vascular health are connected irrespective of gender.


BMD Levels in Subjects with and without Carotid Plaques (Jørgensen et al., 2006)
BMD (mg/cm²)
400
350
300
250
200
150
100
50
0
No Plaques
With Plaques

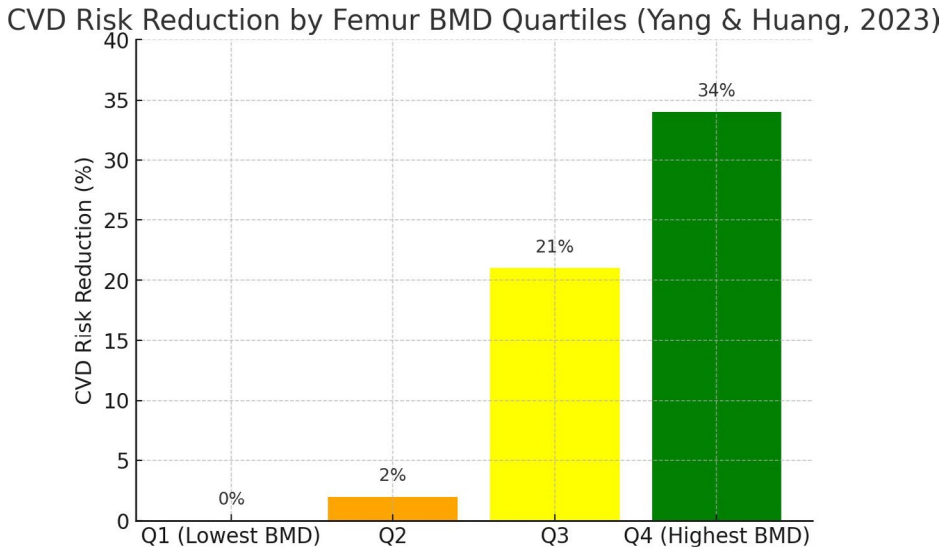

Risk of Cardiovascular Events in Women with Osteoporosis
Relative Risk of Cardiovascular Events
5
4
3
2
1
0
Osteoporosis vs Low Bone Mass
BMD ≤ -2.5 vs (-2.5 to -1)
≥1 Vertebral Fracture vs None
Comparison Groups


Impact of BMD Decrease on Coronary Artery Calcification
Odds Ratio for CAC (cMS > 0)
1.6
1.5
1.4
1.3
1.2
1.1
1.0
Men
Postmenopausal Women
Gender

Another study showed a similar correlation between coronary artery calcification and low BMD with subjects who have chronic kidney disease. In this prospective cohort study by Kim, et al. [9], 1957 patients with chronic kidney disease were measured for their BMD, coronary arterial calcification (CAC), and a major adverse cardiovascular event (MACE). The results showed that the lowest BMD tertile was significantly associated with an increased risk of MACE with a hazard ratio of 2.16. This means that individuals in the lowest tertile of BMD were more than twice as likely to suffer from a MACE than an individual from a higher tertile of BMD. Furthermore, in a subgroup of 977 patients, it was found that BMD was inversely related to accelerated CAC progression with an odds ratio of 0.75. This odds ratio means that with every unit increase of BMD, the likelihood of accelerated CAC progression decreases by 25%. This would imply that greater BMD is linked to a lower chance of rapid CAC progression. Kim, et al. [9] also found a relationship between CAC scores and the chance of a MACE. They found that patients with baseline CAC scores between 100 and 400 have a hazard ratio of 3.05, and those with CAC scores greater than 400 have a hazard ratio of 5.90, and these patients had a significantly increased risk of a MACE in comparison to those without CAC. These hazard scores suggest that these patients with CAC scores are three to almost six times more likely to experience a MACE than a patient without CAC scores. From this data, Kim, et al. [9] concluded that low BMD was associated with an increased risk of MACEs in patients with chronic kidney disease. Moreover, individuals with low BMD exhibited higher CAC scores and experienced quicker progression of CAC, both of which correlated significantly with an increased risk of MACEs.



The association between musculoskeletal deficiencies and CVDs is evident, especially in older adults. In a cross-sectional study by Yang & Huang [10], 2097 people over the age of 60 were studied to explore the relationship between BMD and cardiovascular events risk. In this study, the BMD was quartered in order from small to large (Q1, Q2, Q3, Q4). The results showed that a one-unit increase in femur BMD was associated with an 82% reduction in CVD risk. Similarly, using the lowest femur BMD (Q1) as the reference group, the risk of CVD was decreased by 2, 21, and 34% in Q2, Q3, and Q4 groups, respectively. This study found that osteoporosis was associated with a 2.05-fold higher risk of CVD than the normal group [10]. A similar study of 1250 participants of older adults by Fohtung, et al. [11] showed alike results. Among the nonblack men stratified group, total hip osteoporosis was associated with higher heart failure risk, with a hazard ratio of 2.83, compared with normal BMD [11]. Another study by Katano, et al. [12] delved into the link between bone and vascular health in patients with chronic heart failure (CHF). The study wanted to see how osteoporosis affects patients with CHF, specifically by measuring the number of adverse events-a death or readmission due to heart failure or arrhythmia. Katano, et al. [12] found that patients with osteoporosis had a hazard ratio of 2.40, suggesting that they had a significantly higher chance of adverse events, like death and hospitalization.

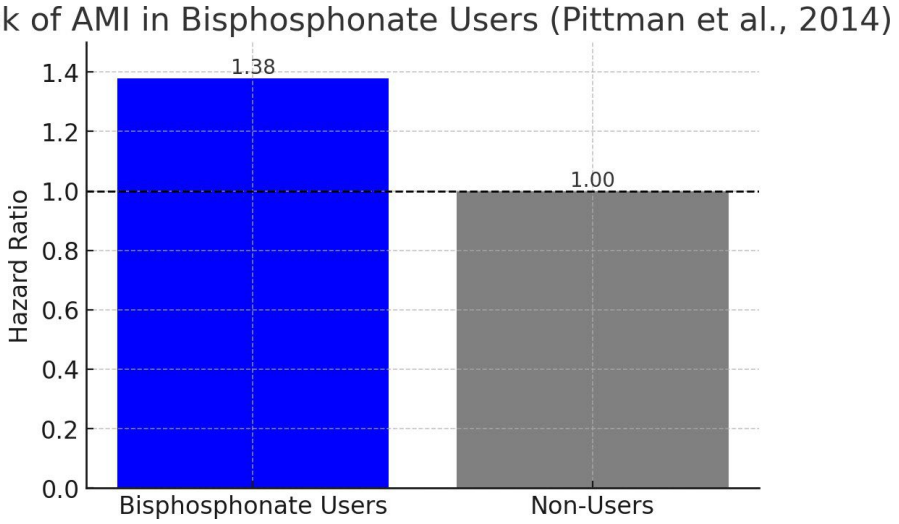


All these studies mentioned support the link between CVDs and musculoskeletal deficiencies. That is why bone and vascular health interplay needs to be further studied to create more effective therapies than current treatments for musculoskeletal health.

Study	Focus	Key Findings / Hazard Ratio
Pittman et al. (2014)	Bisphosphonates & AMI Risk	HR = 1.38 (↑ AMI Risk)
Wu et al. (2021)	Bisphosphonates & Atrial Fibrillation	HR = 1.76 (↑ Atrial Fibrillation)
Huang et al. (2010)	Alendronate vs. Raloxifene AMI Risk	HR = 2.24 (↑ AMI Risk with Alendronate)
Yang & Huang (2023)	BMD & CVD Risk Reduction	34% Risk Reduction (Highest BMD)
Fohtung et al. (2017)	Osteoporosis & Heart Failure Risk	HR = 2.83 (↑ Heart Failure Risk)
Katano et al. (2020)	Osteoporosis & Adverse CHF Events	HR = 2.40 (↑ Death/Hospitalization)

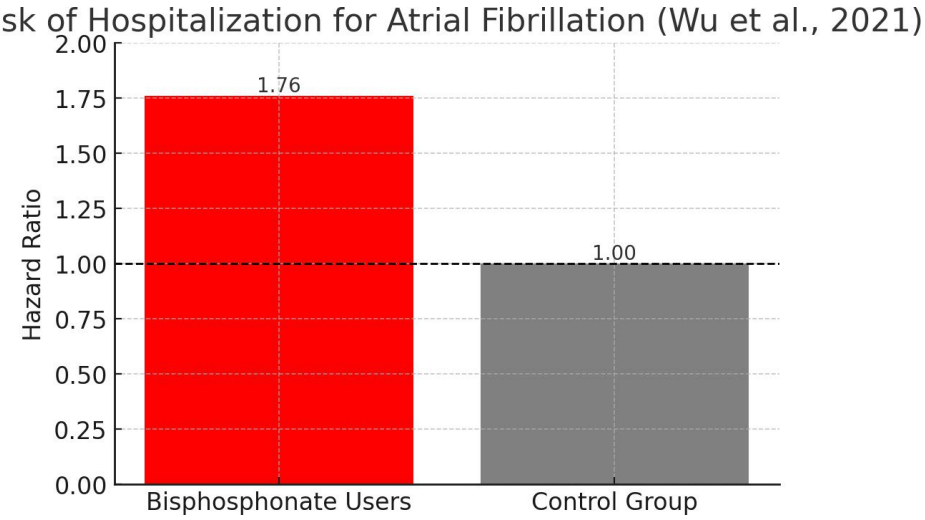
Current Issues with the Treatments of Musculoskeletal Deficiencies

Musculoskeletal deficiencies are the leading cause of chronic pain and disability in the world, meaning that effective therapies are necessary to help rejuvenate bone health and the quality of life of patients. Traditional treatments for such deficiencies use bisphosphonates, SERMs like Raloxifene, and hormone therapy. The problem is that these medications focus on strengthening bone to manage symptoms like fractures and don't look into underlying systemic effects that can cause musculoskeletal deficiencies. In doing so, these treatments may cause damage to other body systems due to not properly understanding the systemic interaction between the vascular and skeletal systems.

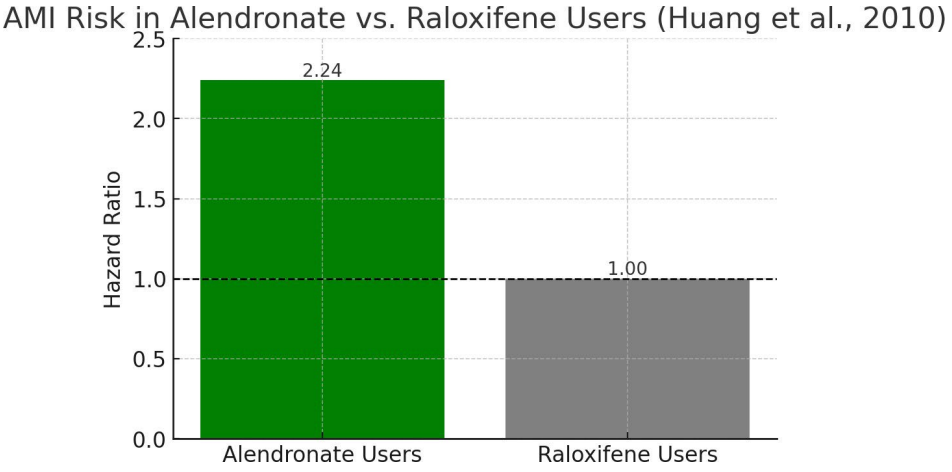


Many studies have looked into the risks of these treatments, particularly bisphosphonates, related to CVDs. In a retrospective administrative database study by Pittman, et al. [13], A cohort of 14,256 veterans 65 years or older with femoral or vertebral fractures were studied to see if there was a relationship between the use of bisphosphonates

and acute myocardial infarction (AMI). The results showed that bisphosphonate use was associated with an increased risk of AMI with a hazard ratio of 1.38. Pittman, et al. [13] concluded that there was a higher chance of AMI among patients prescribed bisphosphonates compared to those who were not.



Another study looked into how bisphosphonates impacted the survival of osteoporosis patients after acute coronary syndrome (ACS) or acute ischemic stroke (AIS). In this retrospective cohort study by Wu, et al. [14], 464 patients who used bisphosphonates were compared to 464 patients who did not create an association between bisphosphonates and all-cause mortality and major adverse cardiovascular events. Although the results were not statistically significant for risks of ACS and AIS between the two groups, there was a higher risk of hospitalization for atrial fibrillation in the bisphosphonates group than in the control group, with a hazard ratio of 1.76 [14]. Wu, et al. [14] concluded that patients with previous CVDs should be careful with bisphosphonate treatments due to the risk of atrial fibrillation.



Lastly, a study by Huang, et al. [15] examined which osteoporosis treatments had a higher risk of AMI in women with osteoporosis. The study compared 21,037 women using alendronate, a type of bisphosphonate, to 6,220 women using raloxifene, a type of SERM. The results showed that users of alendronate who had a history of cardiovascular events and had been on their medication for over a year faced a much higher risk of AMI compared to those taking raloxifene, with a hazard ratio of 2.24 [15]. This suggests that prolonged use of alendronate is not recommended for women with a history of cardiovascular incidents, as they face a heightened risk of experiencing an acute myocardial infarction.

These studies show that current treatments for musculoskeletal deficiencies need to look into the underlying connections between the vascular and skeletal systems. Bisphosphonates have been shown to have negative cardiovascular effects, so there is a need for new therapies that mitigate cardiovascular risks in the treatment of osteoporosis [7]. By understanding how both systems are affected, we can create better medications that prevent symptoms and address the underlying reasons for the disease.

Conclusion

Numerous studies have shown that there are similar pathophysiological mechanisms, like low-grade chronic inflammation, oxidative stress, and endothelial dysfunction, between the vascular and skeletal systems. Further,

empirical data shows that BMD is inversely related to CAC and MACEs. This indicates that CVDs may lead to musculoskeletal disease and vice versa. The evidence supports the idea that a key player in the development of CVDs and musculoskeletal deficiencies is disruptions to the bone vascular axis-where blood vessels assist in musculoskeletal functions. By understanding the interplay between bone and blood, we can create new effective therapies that address the underlying mechanisms between CVDs and bone musculoskeletal deficiencies.

Current treatments for musculoskeletal deficiencies, mainly bisphosphonates and raloxifene, are effective at mitigating bone loss and reducing fractures. However, they have other systemic effects on the cardiovascular system. Bisphosphonates, in particular, have been showed to lead to an increased risk of acute myocardial infarction and atrial fibrillation. If these medications result in CVDs, then the patient may have a high chance of developing other musculoskeletal deficiencies due to the link between bone and vascular health-an ineffective treatment. For this reason, medications for musculoskeletal diseases need to account for the interactions between the cardiovascular and musculoskeletal systems.

Using knowledge of the bone vascular axis, newer remedies can be developed to address musculoskeletal issues and mitigate cardiovascular risks. By combining therapies into addressing two systems rather than one, we may be able to detect biomarkers for bone and vascular issues earlier on. This would mean earlier interventions and reduce the probability of long-term drug usage of musculoskeletal treatments like bisphosphonates, which has been associated with acute myocardial infarction. By improving our understanding of the connections between vascular and bone health, we have the potential to create treatments that deal with the systemic causes of disorders rather than just treating their symptoms.

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