

Review Article

A conceptual model of a pathway from osteoporosis to atherosclerosis: A scoping review[☆]Gordon L. Klein^a, Joshua R. Lewis^b, Stephen J. Nicholls^c, Jothees Amuthavalli Thiagarajan^{d,*}, Peter R. Ebeling^e^a Department of Orthopaedic Surgery and Rehabilitation, University of Texas Medical Branch, Galveston, TX, USA^b Cardiometabolic Health, Edith Cowan University School of Medical and Health Sciences, Joondalup, WA, Australia^c Victorian Heart Institute, Monash University, Melbourne, Australia^d Department of Sexual, Reproductive, Maternal, Newborn, Child, Adolescent Health and Ageing (LHR), World Health Organization, Geneva, Switzerland^e Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia

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ABSTRACT

Objective: To address the evidence for shared biologic mechanisms between atherosclerotic cardiovascular disease and osteoporosis.**Method:** A scoping review was carried out that scanned 6285 manuscripts from 2025 to 1990 in five databases, yielding 742 relevant papers, from which 64 provided mechanistic evidence supporting the existence of a direct relationship. Papers that discussed other aspects of cardiovascular disease were not included.**Results:** From these papers, clinical, animal, and in vitro studies, we constructed a conceptual model determined by conditions resulting from osteoporosis ultimately resulting in atherosclerotic calcifications and the reverse. We describe how estrogen deficiency leads to hyperlipidemia, consequent inflammation and oxidative stress, liberation of calcium and phosphate from resorbing bone with trapping of both minerals in the circulation, reinforcement by calcium and phosphate of the inflammatory process, and the consequent effect on arteries. We also examine the effect of vascular calcification on subsequent bone loss and the clinical implications of this conceptual model both for the current definition of osteoporosis and for methods of screening and prevention of incipient cardiovascular disease in patients with osteoporosis and for screening and treatment of patients with atherosclerotic cardiovascular disease who may have subclinical osteoporosis.**Conclusion:** Evidence exists supporting biological pathways that can transition from osteoporotic bone loss to atherosclerotic vascular calcification. High bone resorption appears to be a factor in the development of atherosclerotic vascular calcification. These findings provide a conceptual framework to view both conditions. However, more work is needed to better define these pathways and their relative importance.

1. Introduction

This paper is in support of and in response to the Bone Health and Ageing Initiative of the World Health Organization (WHO). Cardiovascular disease, and atherosclerosis in particular, are well-described comorbidities of osteoporosis. In a systematic review and meta-analysis of the global prevalence of osteoporosis among the world's older adults, Salari et al. [1] found 40 studies, 31 from Asia, 5 from Europe, and 4 from America, with a total sample size of 79,127 older men and women.

The total prevalence was 35.3% (95% confidence interval 27.9–43.4%). Herrington et al. [2] examined the prevalence of angina from the United States National Health and Nutrition Survey Examination (NHANES) in men and women 65–74 years of age and found it to be 9% in men and 5% in women. Aronow [3] examined the prevalence of atherosclerotic vascular disease in women with osteoporosis, osteopenia, or neither, and reported a co-occurrence in 92 of 159 (60%) in osteoporosis, 63 of 179 (35%) women with osteopenia, and 148 of 667 (22%) with neither, $p < 0.001$ for osteoporosis versus osteopenia. Comorbidity is an

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epidemiologic term indicating the co-existence of two or more disease conditions without implying that one causes the other. One task of our WHO-sponsored Working Group was to review the existing literature covering osteoporosis and cardiovascular disease to identify potential evidence for a pathophysiologic relationship between these two conditions, either sub-clinically or clinically. The importance of this undertaking is that an understanding of disease mechanisms may lead to the development of strategies to detect, prevent, or treat these comorbid conditions. This paper is limited to the search for underlying mechanisms of pathogenesis of osteoporosis and atherosclerosis, or vice versa. A conceptual model will be proposed for this pathophysiology based on the evidence synthesis. A companion paper on the epidemiologic evidence for linkage and the shared risk factors is also in preparation. Asking the question as to whether there may be pathways that link these two conditions justifies a scoping review approach.

2. Methods

Key words in the search criteria were *osteoblast*, *osteoclast*, *calcium*, *calcium-sensing receptor*, *phosphate*, *cholesterol*, *osteoporosis*, *atherosclerosis*, *estrogen*, and *oxidative stress*. These terms were chosen as being components of biological pathways that may be pertinent to any existing physiologic links between the two conditions. We did not employ a pre-existing protocol and no protocol was registered

2.1. Search strategy

The literature search for this review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist, see Appendix 1. A comprehensive search strategy was developed by a reference librarian with feedback from the review team members. The search strategy was run on 20 December 2024, in multiple databases, including

Medline via Ovid, CINAHL via EBSCO Host, Cochrane Library, which includes both Cochrane Reviews and Cochrane Trials (CENTRAL), and Scopus via Elsevier. These searches included the years 2025–2012. As our library does not have access to Web of Science or Embase, an additional search of PubMed for the years 2012–1990 was carried out and Embase was picked up in the Cochrane Search that was conducted. The search consisted of variations and synonyms of MeSH and keywords for cardiovascular disease and osteoporosis and linkages to comorbidities. To view the full search strategy please see the supplementary information document, Appendix 2. No database limits or filters were applied to the search and adjacency, truncation, and Boolean search operators were used when necessary to ensure comprehensiveness of the search string for the review topic.

2.2. Eligibility criteria

Records were identified from five databases, including Ovid Medline, 2167, Scopus, 4170, Cochrane Reviews, 7, CINAHL, 0, and PubMed, 33. After removing 92 duplicates, 6285 records were screened, of which 5543 were initially excluded based on manuscript title, leaving 742 reports assessed for eligibility. Reports were included based on contents that provided evidence of biological pathways connecting osteoporosis to atherosclerosis or the reverse. Reports subsequently excluded concerned epidemiology, 109, cardiovascular pathology other than atherosclerosis, 26, no new information or insufficient information to define a specific biological role for factors discussed, 480, or other pathologies that could confound interpretation, such as renal disease, arthritis, or diabetes, 63. The reports initially included totaled 64. Identification of studies via other methods included a citation search in PubMed in response to questions raised by reviewers. A PRISMA flow diagram is provided as Fig. 1. Thirteen additional papers were identified in PubMed following specific comments from the manuscript reviewers.

When the conceptual model was completed, it was critically

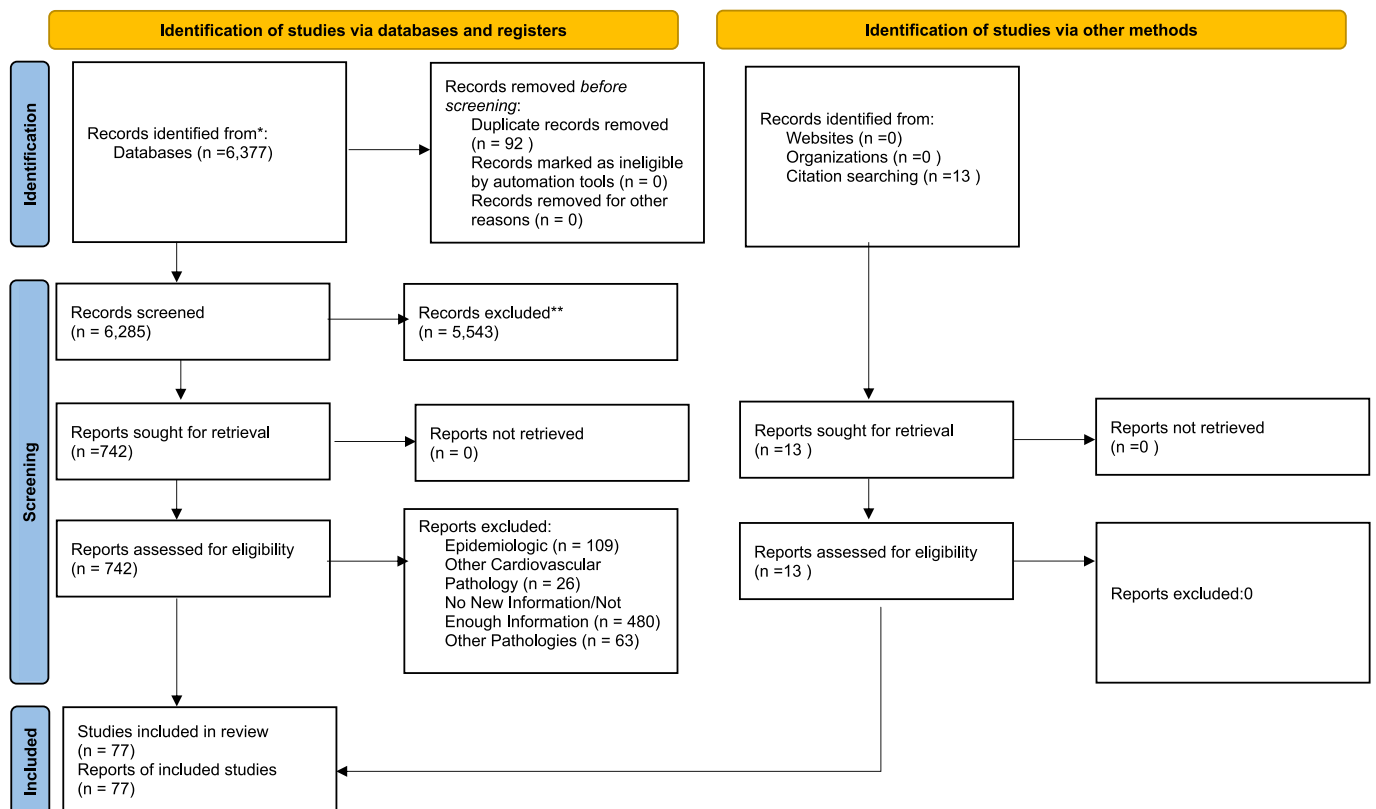


Fig. 1. PRISMA flow diagram as an outline of study method.

reviewed by experts in cardiology (SJN), osteoporosis (PRE, JRL), and public health (JRL, JAT).

3. Results

The conceptual model is presented for post-menopausal osteoporosis as this condition is the most studied. Studies included were taken from human, animal, and in vitro papers. Levels of evidence and study types provided by included papers are shown in a table provided as Appendix 3 [4]. Pathophysiology for osteoporosis-related cardiovascular disease in men and for those with secondary osteoporosis are more complex, but these latter two conditions may also utilize at least part of the pathophysiologic pathways created by post-menopausal osteoporosis. We began by first examining the roles of statins and nitrogen-containing bisphosphonates and their effects on cholesterol metabolism followed by a description of estrogen and cholesterol metabolism and the role of estrogen deficiency. Then the effects of cholesterol and related lipoproteins on osteoclasts and osteoblasts are discussed, as well as their effects on resorptive bone loss and subsequent calcium metabolism. These effects include novel insights into the role of the parathyroid calcium-sensing receptor (CaSR) and the parathyroid angiotensin-II AT1

receptor and their role in “trapping” in the circulation calcium from resorbing bone, combined with the reduction in renal Klotho production, resulting in phosphate accumulation in the circulation. Finally, the roles of extracellular calcium and cholesterol as “danger” signals resulting in the stimulation of the NLRP3 inflammasome will be discussed, and the role of excess calcium in the circulation and its effect on cholesterol metabolism will complete the review.

3.1. Statins and bisphosphonates

An introduction to the interaction of osteoporosis with cardiovascular disease includes the resemblance of pharmacologic action between the two classes of drugs: statins, used to reduce hepatic cholesterol synthesis in patients with, or at high risk for, coronary artery disease, and nitrogen-containing bisphosphonates, used to decrease bone resorption in patients diagnosed with osteoporosis. The mode of action of statins is via inhibition of β -hydroxy, β -methylglutaryl co-enzyme A reductase (HMG CoA reductase) in the liver. This is a relatively early step in cholesterol biosynthesis, as shown in Fig. 2, as transformed from Kim et al. [5]. Of interest, even though its action is primarily in the liver, there have been reports of statins reducing bone resorption [6–8].

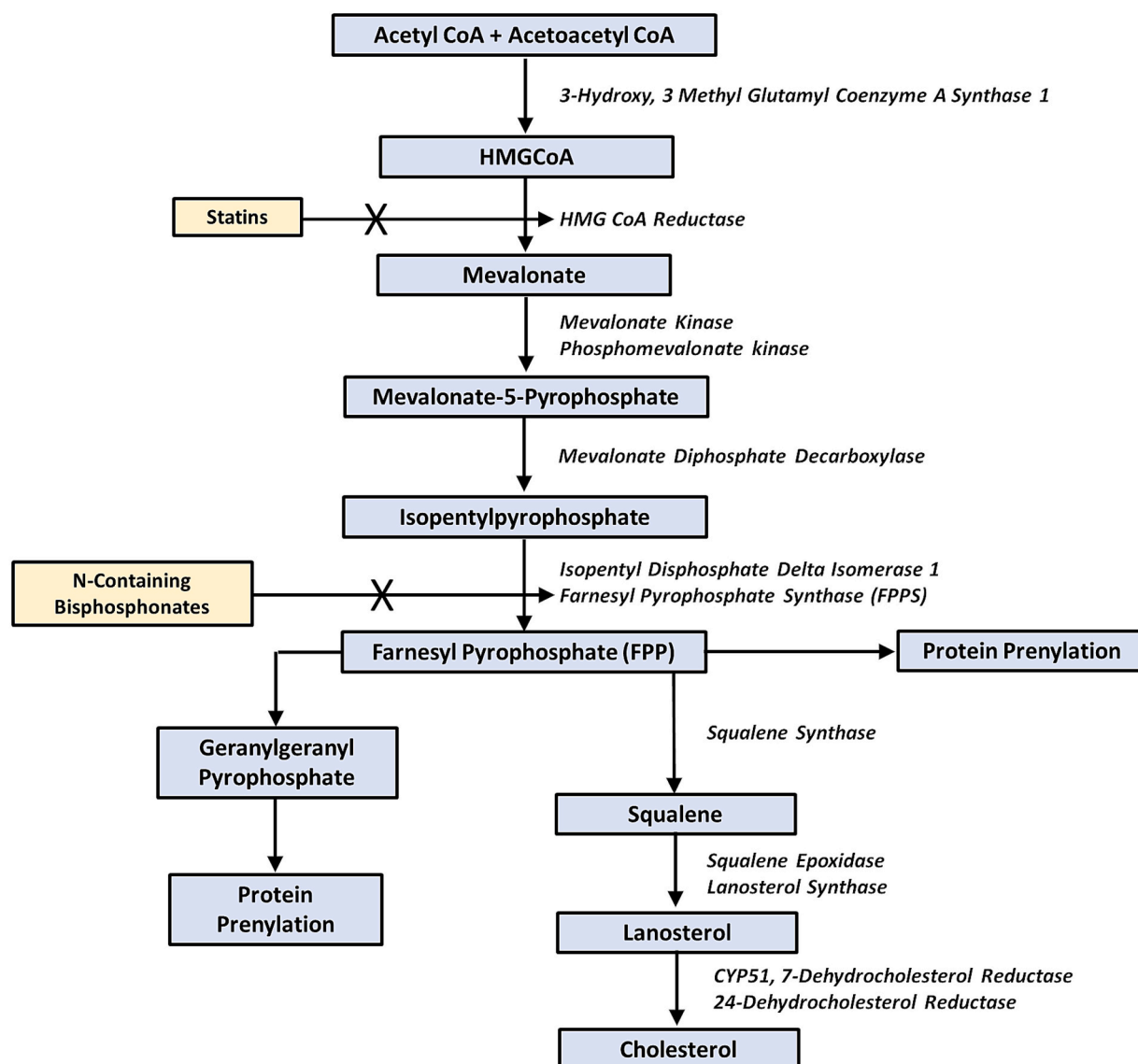


Fig. 2. Transformative chart based on Kim et al. [5] showing the steps in cholesterol biosynthesis but emphasizing the points of action of statins and nitrogen-containing bisphosphonates on cholesterol biosynthesis.

Nitrogen-containing bisphosphonates, while accumulating preferentially in the bone matrix, are ingested by osteoclasts and inhibit farnesyl pyrophosphate synthase (FPPS), ultimately damaging the osteoclast cell membrane, resulting in osteoclast apoptosis with consequent reduction in bone resorption [9]. FPPS action is involved in a cholesterol biosynthetic step shortly beyond the action of HMG CoA reductase, as illustrated in Fig. 2. While the reported effects of statin on bone are pleiotropic, it is not clear that they result from the spillover of the drug to non-hepatic tissues. However, the focus on cholesterol as a key factor in hepatic and bone metabolism became clear along with a growing epidemiologic literature suggesting that nitrogen-containing bisphosphonates may reduce mortality from cardiovascular disease [10,11]. These references are representative of the body of literature supporting these observations.

4. Estrogen and cholesterol metabolism

The importance of this topic is underscored by an abstract reported by Bilezikian et al. [12] noting that the prevalence of hyperlipidemia in women with post-menopausal osteoporosis calculated from a review of the National Health and Nutrition Examination Survey (NHANES) III was as high as 63%. An earlier report by Stevenson et al. [13], who measured serum lipids in 542 healthy non-obese pre- and post-menopausal women, reported that compared with pre-menopausal women, post-menopausal women had significantly higher total and LDL cholesterol, and significantly lower HDL cholesterol. These differences persisted following regression analysis with adjustment for age and body mass index, although the calculations are not shown in the text.

Estrogen has several effects on cholesterol and lipid metabolism. Physiologic doses of estrogen up-regulate HMG CoA reductase and the G-Protein Coupled Estrogen Receptor (GPER), which stimulate the hepatic 7α hydroxylase enzyme, CYP7A1, which breaks down cholesterol into bile acids for excretion via the intestine. This increased catabolism helps lower circulating cholesterol [14,15]. A pharmacologic dose of estrogen, on the other hand, will up-regulate the number of hepatic low density lipoprotein receptors (LDLR), which will also lower circulating cholesterol [14]. In menopause, the absence of estrogen leads to the downregulation of GPER and CYP7A1, contributing to a reduction in cholesterol breakdown and an accumulation of circulating cholesterol and LDL cholesterol [14].

5. Effects of cholesterol and lipoproteins on osteoclasts and osteoblasts

Low density lipoproteins transport cholesterol to osteoclasts and their progenitor cells [16]. While cholesterol becomes part of the osteoclast cell membrane, it also plays a role in binding to the estrogen related receptor-alpha ($ERR\alpha$) to stimulate osteoclastogenesis, while deletion of the $ERR\alpha$ interferes with osteoclast differentiation and increases bone mass [17]. Increasing LDL cholesterol will increase cholesterol flow to the osteoclast with a resultant stimulation of osteoclast differentiation and function. Increasing high density lipoprotein (HDL) will transport cholesterol away from the osteoclast and back to the liver and other sites [18]. The cholesterol binding and activation of the $ERR\alpha$ in the osteoclast nucleus is facilitated by presence of the co-factor peroxisome proliferator activated receptor λ co-activator-1 β (PGC-1 β) [19]. The nucleus of the osteoclast contains cholesterol sensing receptors called Liver X Receptors (LXR) and Retinoid X Receptors (RXR), which can form heterodimers by binding to the LXR Response Element (LXRE) and can stimulate membrane transporters ATP-Binding Cassette Sub-Family G1 (ABCG1) and ABCA to carry cholesterol to HDL for transport from the osteoclast back to the liver [18]. Clinical studies of patients with hypercholesterolemia [20–22] have shown an increase in bone resorption markers and an increase in bone marrow adiposity along with reduced bone mineral density. For

example, a study by Zhou et al. [20] in 216 men matched for age and body mass index with either hypercholesterolemia or normal serum cholesterol measured median lower left forearm bone mineral density by dual energy x-ray absorptiometry and fasting lipids and bone turnover marker, β -CTX (C-telopeptide of type 1 collagen), a marker of resorption. Exclusion criteria included various hormone supplementations such as thyroid hormone and corticosteroids, as well as bone-active drugs. No mention of lipid lowering treatment was included in the subject description. They found that bone density of the hypercholesterolemic men averaged 0.505 ± 0.092 g/cm² compared to 0.536 ± 0.066 g/cm² in the controls with normal serum cholesterol, $p < 0.05$. Serum β -CTX in the hypercholesterolemic men averaged 0.5 ± 0.201 ng/ml compared to 0.437 ± 0.164 ng/ml, $p < 0.05$. Multiple regression analysis between bone mineral density, serum β -CTX, total and LDL cholesterol showed that total cholesterol was a significant independent predictor of bone mineral density and that β -CTX negatively correlated with bone mineral density and positively correlated with LDL cholesterol, $p < 0.05$.

Osteoblasts also receive cholesterol by means of LDL transport. The LDL cholesterol is taken up by the osteoblast cell membrane by LDL-receptor-mediated endocytosis. This complex combines with lysosomes to produce an enzyme called lysosomal acid lipase (LAL), which hydrolyzes the cholesterol esters and triglycerides to cholesterol and free fatty acids [23]. While small amounts of cholesterol can stimulate the expression of osteoblastic genes such as ALP and BMP, a high cholesterol diet and oxidized LDL will downregulate osteoblastic genes such as Bone Morphogenetic Protein Receptor-2 (BMPR)-2, Wnt 5, Transforming Growth Factor- β Receptor (TGF β R) and Smads –4 and –6, all of which take part in TGF- β and Wnt signaling pathways [24]. Also, as shown by Parhami et al. [25], the osteoblast, in contrast with the osteoclast, has the capacity of de novo synthesis of cholesterol via the mevalonate pathway. Thus, a certain amount of cholesterol is necessary to support osteoblast differentiation and function, as indicated by the action of the cholesterol synthetic pathway, but larger amounts, as in hypercholesterolemic diets, may result in suppression of osteoblast differentiation and function. In contrast, Bergstrom et al. [26] reported that osteoblasts have very little HMG CoA reductase, suggesting that cholesterol is more important for osteoclast function.

6. Effect of consequent bone loss on calcium and phosphate metabolism

6.1. The role of the parathyroid glands

Considering bone resorption, it is understood that calcium and phosphate are released from bone into the circulation. What should normally occur next is that calcium concentration in the blood increases following its release from bone. The calcium-sensing receptor (CaSR) on the membrane of the parathyroid chief cell should detect the increase in calcium concentration and send a message via the G-Protein-Coupled linkage to the nucleus to suppress PTH secretion with resultant functional hypoparathyroidism and increased urinary excretion of the excess calcium as shown in young sheep [27]. However, while this occurs in young children following metabolic stress, such as in acute burn injury, it does not occur in adults [28]. Acute burn injury is an important stressor, and its relevance for osteoporotic patients is that burn victims are usually healthy normal individuals who are subject to acute stress and inflammation and whose response is presumed to be that of a normal healthy individual. It is presently not clear at what age failure to suppress PTH secretion with bone resorption occurs as some adult astronauts exhibit CaSR up-regulation and excrete excess calcium in the urine [29]. However, in adults with burn injury or sepsis, PTH secretion is not inhibited and they continue to manifest PTH levels in blood that are either inappropriately normal or even increased [30]. The result is that calcium may be trapped in the circulation due to the inappropriately elevated serum PTH concentration. One hypothesis as to why this change occurs is put forth by Centeno et al. [31], who identified

phosphate binding sites within the CaSR. As phosphate is also elevated in the circulation following release from bone [28], it may be taken up by the CaSR phosphate binding sites with consequent distortion of the receptor, which is then unable to function to normally suppress PTH secretion [31,32]. Further, Klotho, the kidney produced factor that helps Fibroblast Growth Factor (FGF)-23 bind to its receptor to activate renal tubular phosphate excretory transporters is reduced with age and inflammation [33]. Thus, phosphate may also be trapped in the circulation. It has not been firmly established that this phenomenon occurs uniformly in aging adults. However, it remains a possibility that in situations with markedly increased bone loss, this situation may occur.

With calcium and phosphate thus trapped, several events occur. The first is that circulating calcium can interact with the vascular endothelial CaSR to increase vascular tone [34], which will retard blood flow in small arteries, such as the coronaries [35] and make precipitation more likely, especially as calcium and phosphate normally circulate at or near the solubility constant as noted by Kuro-o et al. [36]. Furthermore, there is additional phosphate in the circulation for the excess calcium to bind to, as previously mentioned. Inasmuch as circulating phosphate is thought to be a factor aiding in the de-differentiation of vascular smooth muscle cells and their replacement by osteoblast-like cells [32,37], the resulting matrix can take up excess calcium and phosphate to form hydroxyapatite [32,38,39]. Circulating calcium is also pro-inflammatory, and this, along with an additional receptor in the parathyroid glands, will be discussed in the next section, since chronic inflammation also contributes to the resulting vascular calcification.

6.2. Pathogenesis of chronic inflammation and its role in vascular calcification

Cholesterol crystals and extracellular calcium can both serve as “danger” signals for toll-like receptors (TLR) in the innate immune system, and both can up-regulate the NLRP3 inflammasome [40–42]. Each can stimulate the monocytes and macrophages of the innate immune system to produce interleukin (IL)-1. Furthermore, in vitro studies of cultured peripheral blood mononuclear cells have found that addition of calcium to the culture medium can increase immune cell production of certain chemokines, namely, Monocyte Inhibitory Protein (MIP)-1 α , or CCL3 and Regulated Upon Activation, Normal T Cell Expressed and Secreted (RANTES, or CCL5), and can suppress production of Monocyte Chemotactic Protein (MCP)-1, or CCL2, all in dose-dependent fashion [43].

Thus calcium, in addition to stimulating the NLRP3 inflammasome, can attract and direct immune cells to a site of existing inflammation. Cholesterol crystals, in addition to calcium, can cause or exacerbate inflammation in the arteries, especially at the site of lipid deposition, a consequence of hypercholesterolemia.

In addition, senescent cells in post-menopausal women can produce inflammatory cytokines and chemokines as a result of the senescence associated secretory phenotype, or SASP, which stimulates cytokine and chemokine production [44,45]. Calcium from resorbing bone can thus add to the intensity or duration of an inflammatory response [43,46]. Significantly, this scenario implies that at least some of the excess calcium and phosphate in the circulation precipitates in the vascular system. It is presently unclear what the rate or frequency of calcium phosphate precipitation might be. However, serum concentrations of calcium and phosphate only measure the concentration of these elements in solution at the time of sampling and do not reliably reflect the amount or frequency of calcium phosphate precipitation in blood vessels.

6.3. The role of the renin-angiotensin system and its relation to parathyroid function

To add an additional layer of complexity to this scenario, high circulating cholesterol levels can increase the density of angiotensin II

receptor-1 (AT1) in vascular smooth muscle [47,48], and both pro-inflammatory cytokines, such as IL-6, and vascular inflammation can increase hepatic angiotensinogen production [49], which converts to angiotensin-II. While angiotensin II can be stimulated by both cholesterol and chronic inflammatory changes, its relationship to calcium was not clear until Grant et al. [50] demonstrated a dose-dependent relationship between angiotensin II and circulating PTH when healthy humans were infused with exogenous angiotensin II. Brown et al. [51] confirmed this relationship and noted that the angiotensin converting enzyme (ACE) blocker captopril acutely lowered PTH concentration in addition to levels of angiotensin II and aldosterone. They also reported that both normal and adenomatous parathyroid glands express the AT1 receptor. These reports now force a reconsideration of events in the parathyroid gland in the face of hypercholesterolemia or inflammation. The question now posed is the functional relationship between the parathyroid CaSR and AT1 receptors. Is the primary reason for lack of PTH suppression in older adults related to a relative increase in angiotensin II production, an increase in AT1 receptor density, an overriding of the CaSR by the AT1 receptor, or a combination of all of these? At this point the answer is not clear. One recent development favoring the role of the AT1 receptor is a study by Fitzpatrick et al. [52] which examined a cohort from the TUDA study of osteoporosis patients at or above age 60 receiving either angiotensin receptor blockers, angiotensin converting enzyme inhibitors, or neither comparing bone density and bone turnover markers. Results from over 1500 participants showed that those taking angiotensin II receptor blockers had significantly higher bone mineral density at the femoral neck ($p = 0.005$), total hip ($p = 0.002$), and lumbar spine ($p < 0.001$) than non-users, and serum tartrate resistant acid phosphatase, a marker of osteoclast activity, significantly lower than in non-users ($p = 0.040$). In contrast, those taking angiotensin converting enzyme inhibitors showed no difference from non-users.

7. Does extracellular calcium affect serum cholesterol concentration?

The answer appears to be yes. Li et al. [15] identified a pathway whereby calcium supplementation reduces cholesterol catabolism by increasing hepatocyte intracellular calcium, reducing intracellular cyclic AMP, and inhibiting the 7 α hydroxylase enzyme that breaks down cholesterol into bile acids for excretion in the gut. Additionally, Gallo et al. in humans [53] and Cousineau et al. in mice [54] found serum calcium to be associated with serum cholesterol and an independent predictor of serum cholesterol concentration.

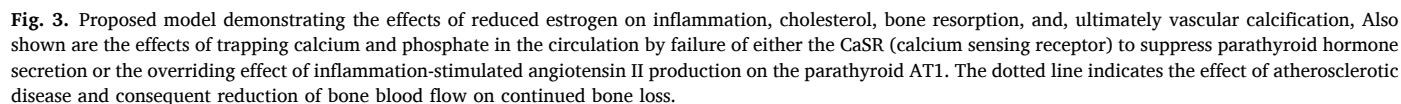
Thus, evidence suggests a loop that starts with estrogen deficiency contributing both to the inhibition of cholesterol catabolism and the depression of inflammation [30] results in the increase in serum cholesterol, increased inflammation through the activation of the NLRP3 inflammasome, increased chemokine production, and the stimulation of osteoclastogenic bone resorption. The calcium liberated from bone is trapped in the circulation as the parathyroid CaSR fails to suppress PTH secretion considering either or both decreased CaSR function or AT1 receptor activation. Renal Klotho production is also reduced due to inflammation and aging, allowing circulating phosphate to be retained. The hypercholesterolemia leads to lipid deposition in the arterial intima followed by cholesterol and calcium-induced inflammation and vascular smooth muscle de-differentiation and replacement by osteoblast-like cells. Finally, the excessive calcium in the circulation inhibits the CYP7A1 hydroxylase in the hepatocytes preventing cholesterol breakdown and completing the cycle. There is no evidence that elevated serum calcium concentration affects cholesterol biosynthesis or absorption.

Additionally, studies in rats by Mace et al. [55] demonstrated that transplantation of calcified aortas from nephrectomized rats into normal rats resulted in bone loss, suggesting that vascular calcification can further exacerbate bone loss. While the nephrectomy itself with

latter, while they serve to elucidate cellular mechanisms by design remove the cells from their environment and therefore remove environmental influences from the pathophysiologic processes affecting the cells in question. We have had to depend on the consistency of the in vitro studies with the in vivo animal and human studies. In addition, many papers mentioned changes in one factor or another, such as Matrix Metalloproteinase -9 (MMP-9) [57] and osteoprotegerin [58,59]. However, the interpretation of these findings is limited by not knowing their precise roles in the process of arterial calcification due to a lack of defining studies. As a result, these studies are not included in the current proposed conceptual model, lacking the basic context for their proposed function or dysfunction.

This conceptual framework is not meant to define the relative importance of the pathways described. In fact, it cannot do so with the amount of available information. The aim of the conceptual framework is to provide evidence of existence of pathways that can be set up once conditions of either osteoporosis or atherosclerotic cardiovascular

This conceptual framework is not meant to define the relative importance of the pathways described. In fact, it cannot do so with the amount of available information. The aim of the conceptual framework is to provide evidence of existence of pathways that can be set up once conditions of either osteoporosis or atherosclerotic cardiovascular



disease are established. Clearly, further studies are needed to elucidate the roles of many of the pathogenic factors partially described in the literature, such as insulin resistance, adiposity, smoking and alcohol consumption. And, as mentioned in the following paragraph, genetics and epigenetics may play key roles in determining which pathways are of primary importance in each individual. The idea behind this proposed conceptual framework is that there is evidence for the existence of pathways that can favor the development of other comorbidities. If one conceives of the health of the body of an organism, human or animal, as one in which inter-organ communication works optimally, then interruption of optimal communication by disease states can trigger the formation of compensatory pathways by each organ system. These may be the pathways that we are currently seeing described or partially described in the literature. Aging currently consists of a great many changes. What this study attempts to do is to identify biological pathways that are detected in an aging population, in other words, to try to begin to define the components of aging so that we can begin to address them.

Genetics and epigenetics are likewise important in this model. A bioinformatics analysis by Mo et al. [60] identified various genes in common to both osteoporosis and atherosclerosis. These include COL1A, IBSP, CTSD, RAC2, MAF, AND thbs-1. However, common genes need to be expressed, and the influence of DNA methylation, telomere length with age, micro RNAs and long noncoding RNAs [61,62] all combine to affect gene expression and therefore the ultimate phenotype expressed in the affected patient. In constructing this model, it is implied that patients with initial manifestations of coronary artery disease prior to osteoporosis may still be at risk for the development of osteoporosis by invoking the proposed model as shown in Fig. 3. However, gene expression may determine which of the two conditions develops first.

What about inhibitors of vascular calcification, such as fetuin A, calciproteins, Matrix Gla Protein, and Pyrophosphate? In the above-mentioned review by Kuro-o [36], blood is supersaturated with calcium and phosphate ions. Thus any addition of ions from resorbing bone could trigger precipitation of calcium phosphate in amorphous form. However, the serum protein, fetuin-A, can bind limited amounts of amorphous calcium phosphate to form calciproteins, or CPP. This amorphous CPP prevents premature precipitation of additional calcium phosphate. This type of CPP transitions to a crystalline phase to become secondary CPP, which can be extravasated through the liver sinusoids and bone marrow to undergo phagocytosis by reticuloendothelial cells and be redeposited to bone. However, secondary CPP is also capable of activating NFkB signaling in vascular smooth muscle cells to induce de-differentiation and replacement by osteoblast producing cells, thus providing an extracellular scaffolding for calcium phosphate precipitation.

Matrix GLA Protein (MGP) is a vitamin K-dependent protein secreted by vascular smooth muscle cells and expressed in endothelial cells, from where it ends up in the circulation. In a systematic review, Barrett et al. [63] consider the different modified forms of MGP, which is thought to be an inhibitor of vascular calcification. The authors concluded that different underlying molecular mechanisms can accelerate local disease progression in the affected blood vessels and specific fractions of circulating MGP may be influenced differently. So, whether the MGP fractions are glycosylated, carboxylated, or otherwise chemically altered may affect their function under different circumstances, and more research is called for.

Regarding pyrophosphate, another potent inhibitor of vascular calcification, Villa-Bellosta [64] notes that extracellular pyrophosphate, or PPI is a major endogenous physicochemical inhibitor of calcium phosphate crystal formation and growth, both in vivo and in vitro by binding to hydroxyapatite and can inhibit crystal formation in micromolar concentrations. The enzyme ectonucleotide pyrophosphatase/phosphodiesterase, or ENPP, hydrolyzes ATP to form PPI. Tissue non-specific alkaline phosphatase can break down PPI into phosphate. This process is generally under strict enzymatic control, and, so far, only

genetic mutations, such as in ENPP deficiency, can lead to PPI insufficiency and diffuse vascular calcifications. However, as can be seen from these reports, the precise way in which these inhibitors are affected by specific conditions such as osteoporosis or cardiovascular disease have not been adequately studied. We can speculate that the body's physiologic means to inhibit excess calcium phosphate crystal formation may be overwhelmed in cases of severe bone loss or sudden rapid bone loss, as might be seen in osteoporosis.

While this conceptual model was built on the loss of estrogen, there is also evidence that follicle stimulating hormone, FSH, also contributes to the pathogenesis of atherosclerotic cardiovascular disease. Wang et al. [65] performed a population study of FSH in relation to the 10-year risk of developing atherosclerotic cardiovascular disease in 2658 postmenopausal women in China. They found that with increasing FSH quartiles, the mean 10-year risk for atherosclerotic cardiovascular disease decreased from 4.9 to 3.3% ($p < 0.05$). In regression analyses, one standard deviation increment in the natural log of FSH was negatively associated with the 10-year risk for atherosclerotic cardiovascular disease ($p < 0.05$), and that these associations existed with or without medication, obesity, diabetes, hypertension, or dyslipidemia.

How can this model address clinical intervention? Knowing that cardiovascular disease with osteoporosis is more than a coincident occurrence, physicians can screen patients for cardiovascular disease. This will be discussed in more detail in our companion publication in preparation. However, since osteoporosis patients are now seen in specialty clinics such as Bone Health and Fracture Liaison Services, systematic and periodic evaluation of fasting serum lipids, including cholesterol, would be valuable in picking up first signs of cardiovascular disease, as would performance of lateral spine dual energy x-ray absorptiometry (DXA) to detect abdominal aortic calcification as well as occult vertebral fractures.

Additionally, since bone is a likely source of vascular calcification, earlier introduction of anti-resorptive agents rather than waiting for the accepted criteria for clinical diagnosis of osteoporosis, a DXA T-score of ≤ -2.5 , may prevent some vascular calcium accumulation if calcification is detected at an earlier stage of bone loss, such as osteopenia. While it is true that large randomized controlled trials of anti-resorptive agents have not shown significant effect in prevention of vascular calcification, it is also true that the criteria for initiation of treatment with anti-resorptives is currently a bone density T score of -2.5 (or a fracture). Therefore, it is possible that initiation of therapy occurs too late to prevent the development significant vascular calcium phosphate accumulation. A cost-benefit analysis may provide additional justification for such a study. Furthermore, patients diagnosed with atherosclerotic coronary artery disease may benefit from diagnostic investigation for osteoporosis as they may be at increased risk for fragility fractures. This can also be inferred from the model shown in Fig. 3. However, one caveat to consider is the extent to which patients with cardiovascular disease may have any undetected osteoporosis masked by the pleiotropic effect of statins they may be taking. Care providers should be aware that osteoporosis is a disease not limited to the skeleton but can involve at least the cardiovascular system. One can speculate that other diseases of aging, other comorbidities, may be pathophysiologically linked, although clearly more investigation would be required to determine this.

9. Osteoporosis in males and secondary osteoporosis

The conceptual model above was developed using the relatively straightforward example of postmenopausal osteoporosis. The analogous situation in males is less clear. Whether this form of osteoporosis is primary or secondary is open to question as aging, diabetes and dyslipidemia may be present before any osteoporosis is detected, and each of these pre-existing conditions can result in chronic inflammation and oxidative stress which appear to be common denominators in the model of cardiovascular disease with osteoporosis. We will therefore limit our

comments to the potentially analogous situation in aging males involving reduction of testosterone or estrogen concentrations, and the pathogenesis of dyslipidemia and chronic inflammation (“inflammaging”) and how they may fit into the above model (Fig. 3).

9.1. Cardiovascular disease and testosterone in men with osteoporosis

Chronic inflammation, obesity, and insulin resistance are known to reduce circulating testosterone [66]. Testosterone signaling is complex, as it can act through the androgen receptor, or it can be converted to a more potent dihydrotestosterone, or it can be aromatized to 17 β -estradiol activating the estrogen receptor [67]. We know that sex hormone receptors and testosterone converting enzymes are present in the arterial wall and in cultured vascular cells [68]. Low testosterone levels have been linked to oxidative stress and reduced blood flow [69]. IL-1 β , IL-6 and Tumor Necrosis Factor (TNF)- α are inversely related to serum testosterone concentration in patients with coronary artery disease [70–72]. Potentially, these inflammatory cytokines could create an inflammatory pathway that could enter the inflammatory component of the conceptual model shown in Fig. 3. Additionally, one could speculate that with a reduction in testosterone, there is reduced aromatization to estrogen, and, depending on the role of aromatized testosterone, some aspects of estrogen deficiency in relation to lipid metabolism could also be active, as seen in Fig. 3. However, it is not clear that osteoporosis in aging men contributes to cardiovascular disease without development of hyperlipidemia and inflammation. The importance of low testosterone alone in the development of cardiovascular disease has not been conclusively demonstrated.

9.2. Secondary osteoporosis

The number of conditions in which osteoporosis is a secondary development is significant with highly variable underlying pathology. The pertinent questions raised by this complexity include: a) whether cardiovascular comorbidities arise because of the secondary osteoporosis or due to the primary underlying pathology, and b) whether primary pathology exacerbates or mitigates the risk of cardiovascular comorbidities and, how can we sort these out? Among the varied primary conditions that can develop a secondary osteoporosis are a) chronic kidney disease, b) rheumatic disease, c) spinal cord injury, and d) burn injury. In each case can we relate cardiovascular comorbidity to the conceptual model we have developed? Each of these four conditions have in common chronic inflammation and oxidative stress. Therefore, these conditions are clearly capable of contributing to the pathogenesis of either cardiovascular disease or osteoporosis.

An example of how secondary osteoporosis may contribute to vascular calcification is given by Lv et al. [73]. In a cross-sectional study of 221 Chinese patients with end-stage renal disease awaiting transplantation, the investigators measured bone mineral density by dual energy x-ray absorptiometry, vascular calcification by lateral abdominal radiography and echocardiography, and fasting serum for intact parathyroid hormone and β -CTX, a bone resorption biomarker. Intact PTH (iPTH) was significantly higher in patients with osteoporosis compared to those with no osteoporosis, 1087 (range 755–1908) pg/ml versus 676 (299–1320) pg/ml, $p < 0.001$ and patients with vascular calcification had significantly higher levels of iPTH than those without vascular calcification, 1263(797–1709) pg/ml versus 463 (238–873) pg/ml, $p < 0.01$. The resorptive marker, β -CTX was significantly higher in patients with osteoporosis, 6000 (4432–6007) pg/ml, compared to patients with no osteoporosis, 3959 (2780–5923) pg/ml respectively, $p < 0.01$. B-CTX was higher in patients with vascular calcification, 5985 (4492–6009) pg/ml compared to those without vascular calcification, 3959 (2780–5923), $p < 0.001$. Thus end stage renal disease, as a result of high bone turnover, results in osteoporotic bone loss and accumulation of calcium and phosphate in the blood vessels. However, it may be difficult to interpret high serum concentrations of β -CTX inasmuch as fragments

of the molecule are present in end stage kidney disease and are also detected in the assay. Similar scenarios are reported in rheumatoid conditions [74], burns and spinal cord injury as documented in a systematic review by Rahmani et al. [75] and cohort studies by Orakzai et al. [76] and Duke et al. [77]. Each of these conditions have atherosclerotic cardiovascular disease reported as a prominent complication of the primary disease process. The extent to which secondary osteoporosis by itself contributes to the pathogenesis of atherosclerotic cardiovascular disease has not been sufficiently teased out. However, the breakdown of bone and consequent release of calcium and phosphate into the circulation may contribute to the atherosclerotic condition as may the inflammation. To be sure, the pathophysiology of these diseases is complex, and in the case of the study by Lv et al. [73], the evidence is noted to be level 3, which does not imply causation.

10. Conclusion

In this manuscript, we propose a way to understand how a patient with post-menopausal osteoporosis may develop atherosclerotic calcifications based on documented evidence of biological processes initiated by hormonal changes and resultant bone loss, involving the development of dyslipidemia and inflammation. We suggest that patients with secondary osteoporosis and men with osteoporosis may manifest many changes that could also fit at least part of the proposed pathway. Further, we suggest that patients with atherosclerotic cardiovascular disease may also be at risk for subclinical osteoporosis by means of the proposed pathway. This conceptual model would indicate that osteoporosis is not a condition confined to the musculoskeletal system but may extend to the cardiovascular system. Other diseases of aging should be studied in relation to osteoporosis to determine whether they are pathophysiologically linked as well. This scoping review is designed to be objective, and yet to suggest the possibility of existing biological mechanisms linking osteoporosis with atherosclerotic cardiovascular disease. This paper does not definitively demonstrate the existence of a shared mechanism. However, it provides supporting evidence from existing studies and provides a conceptual framework for more definitive studies in the future.

CRedit authorship contribution statement

Gordon L. Klein: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Joshua R. Lewis:** Writing – review & editing, Validation, Investigation. **Stephen J. Nicholls:** Writing – review & editing, Validation. **Jothees Amuthavalli Thiyagarajan:** Writing – review & editing, Validation, Resources, Conceptualization. **Peter R. Ebeling:** Writing – review & editing, Validation, Resources.

Declaration of competing interest

The authors state they have no financial conflicts of interest. PRE currently serves as Editor-in-Chief of Bone.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bone.2027.118097>.

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