Advances in Obesity, Endocrinology, and Diabetes

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

Vascular Calcification: Understanding the Pathophysiology and Exploring Preventive Strategies- A Narrative Review

Maha A. Mohamed[1], Yalda Rahmani[2], Tooba Durrani[2], Shiza Ali[2], Hafsa Chhapra[2], Mohamed Hussein[1]

[1]Biomedical Sciences Department, Dubai Medical University, College of Medicine, Dubai, UAE

[2]Year 5 MBBCH students, Dubai Medical University, College of Medicine, Dubai, UAE

Corresponding Author: Dr. Maha A. Mohamed
Address: UAE. Dubai, Mirdif
Contact details: mayman@dmu.ae
Phone number: +971502551059

Abstract:

Background:

Cardiovascular calcification is defined as the deposition of calcium in vascular tissues. It represents a key aspect of cardiovascular disease pathology, and a serious medical problem associated with high morbidity and mortality.

Main body:

This review studies the intricate mechanisms underlying vascular calcification to elucidate its multifactorial etiology. Furthermore, it examines the contributory roles of traditional cardiovascular risk factors, genetic predispositions, and molecular pathways that influence the beginning and development of calcification in arterial walls. It also investigates emerging strategies for preventing and mitigating vascular calcification. Novel interventions, including pharmacological agents, lifestyle modifications, and targeted therapies, are examined in the context of their potential to counteract the calcification process.

Conclusions:

The findings hold promise for developing personalized preventive strategies that reduce the burden of cardiovascular disease worldwide.

Keywords:

Vascular Calcification, Cardiovascular Disease, Molecular Pathways, Pathophysiology, Prevention.

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

List of Abbreviations:

CKD (Chronic Kidney Diseases)

DOAJ (Directory of Open Access Journals)

CVD (Cardiovascular Disease)

Ca (Calcium) and P (Phosphorus)

FGF23 (fibroblast growth factor 23)

Vit D (Vitamin D)

VSMC(Vascular smooth muscle cells)

BMP-2, BMP4 (Bone morphogenetic proteins)

RUNX2 (Runt-related transcription factor 2)

Msx2 (Msh Homeobox 2)

CVCs (calcifying vascular cells)

HDL (High Density Lipoprotein)

p38-MAPK (Mammalian p38 mitogen-activated protein kinases)

LDL (Low Density Lipoprotein)

TNF-α (Tumour necrosis factor alpha)

PI3K/Akt (phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)

TNF-inhibitor (Tumour necrosis factor)

AGEs (Advanced Glycation End-Products)

Notch/Msx2 (Neurogenic locus notch homolog protein 1/Msh Homeobox Protein Coding gene)

mRNA (messenger Ribonucleic Acid)

RAGE/ AGE receptor (Advanced glycation end product receptor)

FGF (Fibroblast growth factor)

PTH (Parathormone)

TLR (toll-like receptor)

LPS (lipopolysaccharide)

MCP-1 (macrophage chemoattractant protein-1)

iNOS (inducible nitric oxide synthase)

UPR (unfolded protein response)

ER (endoplasmic reticulum)

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

PERK (PKR-like endoplasmic reticulum kinase)

IRE1 (inositol-requiring 1)

ATF6 (activating transcription factor 6)

eIF2-subunit (The eukaryotic initiation factor 2)

ATF4 (activating transcription factor 4)

SMC (smooth muscle cell)

CT (computed tomography)

OSM (Oncostatin M Receptor)

MGP (Matrix Gla Protein)

RANKL (receptor activator of nuclear factor kappa beta)

Introduction:

Vascular calcification, which is a prevalent pathology in the general population, is more common with increasing age and is a substantial risk factor for cardiovascular diseases, leading to increased related complications and death. [(1)] Conditions like diabetes and chronic kidney disease (CKD) exacerbate this problem. [(1)] Therefore, it is critical to explore potential therapeutic targets and drug development to delay or stop the development of vascular calcification. [(1)]

Arterial calcification is a predictor of future cardiovascular morbidities and mortality. [(2)] Various proteins actively control the process of calcification, mandating the search for effective prevention and treatment strategies. [(2)] Currently, the primary approach is focused on treating vascular calcification. [(2)] Several cardiovascular drugs have demonstrated positive therapeutic effects on vascular calcification in various preclinical and animal studies. [(2)] Additionally, plant foods, nutritional supplements, and bioactive compounds have shown promise as effective tools for inhibiting or decreasing calcification. [(2)]

Materials and Methods

To conduct this review, several databases were searched, including PubMed, Google Scholar, Scopus, Science Direct, and the Directory of Open Access Journals (DOAJ). Combinations of keywords and their equivalents were assigned, including vascular calculation, cardiovascular disease, etiology, risk factors, genetic factors, and molecular pathways. The research papers included in this study were published between 2000 and 2023.

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

Results

A comprehensive search of the electronic databases—including PubMed, Google Scholar, Scopus, Science Direct, and DOAJ—using combinations of keywords related to vascular calcification and cardiovascular disease (covering the period 2000 to 2023) initially yielded approximately 1,200 articles. After the removal of duplicate records (approximately 250 duplicates), 950 unique articles were subjected to a title and abstract screening.

During this initial screening, 600 articles were excluded because they failed to satisfy the quality and relevancy requirements. The full texts of the remaining 350 articles were then reviewed in detail. Based on predefined inclusion criteria—such as publication date, study design, relevance to the mechanisms and interventions of vascular calcification, and the availability of complete data—264 articles were excluded for reasons including insufficient information, lack of methodological rigor, or irrelevance to the topic.

Ultimately, 86 publications were included in the final review and analysis.

Discussion

Mechanisms of Vascular Calcification

Our study revealed that four theories have been proposed to explain the initiation of vascular calcification:

Loss of inhibition

Molecular research on humans and mice has revealed that blood vessels express inhibitors of mineralization, such as pyrophosphate and matrix Gla protein, and that the absence of these molecules leads to spontaneous vascular calcification and increased mortality. [(3)] Another study has connected reduced fetuin levels to increased CVD (cardiovascular disease) death rates among hemodialysis patients. In addition, fetuin/2-HS-glycoprotein is a vital inhibitor of blood apatite. [(4)]

Promotion of bone formation

The presence of bone proteins, such as osteopontin, osteocalcin, and BMP2, as well as matrix vesicles, and their role in the development of bone and cartilage suggest that osteogenic pathways may also be involved in the production of bone and cartilage in calcified vascular lesions. [(5)] Under various conditions, cells from the media of the arterial walls undergo phenotypic alterations and calcification, similar to those of bone and cartilage, in vivo. [(5)]

circulating nucleation complexes

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

This theory is best applied in postmenopausal women, where the relationship between arterial calcification and osteoporosis has been hypothesized to be explained by bone turnover that releases circulating nucleation complexes. [6]

Cell death

Cell death can produce membranous debris rich in phospholipid material and apoptotic bodies that can nucleate apatite, particularly in conditions characterized by a combination of necrosis and apoptosis, such as atherosclerosis. [7] Increased Ca (Calcium) and P (Phosphorus) levels encourage apatite nucleation and crystal development through thermodynamic processes. [7]

Risk Factors Associated with Vascular Calcification

Our study revealed some factors that contribute to increased risk of vascular calcification, as outlined in Table (1):

Table (1): Risk factors for Vascular Calcification [8]

Traditional Risk Factors	Non-traditional Risk Factors
Hypertension	Inflammation
Diabetes	Oxidative stress
Dyslipidemia	Advanced Glycation End Product
Age	Abnormal mineral metabolism
Genetics	FGF23
Smoking	Vit D

Traditional Risk Factors

Hypertension:

Though hypertension has been correlated with arteriosclerosis and arterial remodeling, it is not frequently a cause of calcification. [8]

The renin-angiotensin system is the primary cause of VSMC (Vascular smooth muscle cells) mortality, proliferation, and differentiation, possibly promoting calcification. [8]

This was supported by one study, where rabbits were fed an atherogenic diet high in vitamin D to induce arterial calcification. [9] Overexpression of BMP-2 and a decrease in alpha-smooth muscle actin were observed, indicating a dedifferentiation of vascular smooth muscle cells into osteoblasts. [9] Angiotensin receptor blockers were successfully used to prevent the resulting calcification. [9]

In another study, increased calcium content and elevated levels of angiotensin II and aldosterone were observed in a rat model of arterial calcification induced by oral nicotine and

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

vitamin D. [10] The calcification was also prevented with the use of captopril or spironolactone medication. [10]

Diabetes:

Diabetic patients exhibited more calcification than non-diabetics, and the media of the arterial walls in diabetic patients expressed bone matrix proteins, including osteopontin, type I collagen, and alkaline phosphatase. [10] In another study, in vitro exposure of bovine VSMC to high concentrations of glucose led to increased production of the osteoblast transcription factors RUNX2, BMP-2, and osteocalcin. [10] This rise in the production of RUNX2 and bone matrix proteins caused by the high glucose levels was carried on via the protein kinase C signaling pathway. [10]

It was also found that high glucose causes myofibroblasts to exhibit osteogenic traits, which enhances the expression of the BMP2 and Msx2 genes. [11] In diabetic aortas, BMP2 and BMP4 were detected in several sites. [11] BMP4 was located in the endothelium, but BMP2 was spread through the arterial wall. [12] These findings suggest that vascular calcification is triggered by diabetes, at least in part, due to the direct effect of hyperglycemia on the VSMC, which modifies it to an osteoblast-like phenotype through different mechanisms. [12]

Dyslipidemia:

Lipids have been shown to play a role in vascular calcification during osteogenic growth, with calcifying vascular cells (CVCs) accumulating minerals and lipids, including triglycerides. [13] Inhibiting acetyl-CoA carboxylase or acyl-CoA synthetase was found to reduce the process of mineralization, and HDL suppresses osteogenic development, while stearate enhances mineralization in CVCs. [13]

The anti-CVC actions of n-3 unsaturated fatty acids depend on p38-MAPK and peroxisome proliferator-activated receptor gamma. [14] Oxidized lipids, such as oxysterols and oxidized phospholipids, have pro-calcific actions in vascular cells. [15]

Thus, dyslipidemia, rather than high LDL cholesterol levels, is a key risk factor for the development of arterial calcification.

Non-traditional Risk Factors:

Inflammation:

Inflammation, a risk factor for atherosclerosis and vascular diseases, is linked to increased deaths and coronary artery calcification in CKD patients. [16] In an experimental study, Macrophage infiltration and local inflammation were connected to osteogenesis in experimental mice with atherosclerosis. [17] In another in vitro study, the mixture of monocytes

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

with tumour necrosis factor alpha (TNF-α) was found to speed up the mineralization of calcifying vascular cells. [18]

The P3K/Akt pathway's inhibition of alkaline phosphatase and pyrophosphate in human VSMC prevents inflammation-induced calcification. [19] It was proposed that the inflammatory cytokine stimulation of VSMC alkaline phosphatase significantly contributes to diabetes-associated calcification. [19] This hypothesis was supported by a study that showed that the TNF-inhibitor infliximab reduces calcification in the middle layer and the osteogenic phenotype of VSMCs in diabetic rats without reducing obesity, hypercholesterolemia, or hyperglycemia. [20]

Herrmann and his colleagues conducted an in vivo study, in which they found an association between osteogenic activity and macrophage burden in the arteries of apolipoprotein E/mice. [21] In another study, Abdelbaky and his colleagues showed that in a total of 137 individuals who underwent computed tomography and positron-emission tomography at one to five years, the baseline inflammatory signal increased, accompanied by a matching increase in aortic wall vascular calcification. [22] According to the studies cited above, inflammation is a precursor to vascular calcification. [22]

Oxidative stress:

It has been demonstrated that Oxidized low-density lipoprotein advances the osteoblast differentiation in primary cultures of VSMCs by upregulating Osterix expression in an Msx2-dependent manner. [23] Additionally, oxidized lipids direct the osteoclast cytokines liberated by osteoblasts. [24] As a result, oxidative stress is suggested to be responsible for vascular calcification. [25] It could be the source of the amplified coronary artery calcification and osteoporosis that are observed in both people with CKD and the general population. [25]

Advanced Glycation End-Products (AGEs):

AGEs are created due to indirect protein alteration by reactive carbonyl compounds constructed by the auto-oxidation of lipids and carbohydrates. [26] In addition, the arterial and cardiac tissues of the patients on dialysis who have atherosclerotic lesions are reported to contain these AGEs. [26] They were also reported to have higher levels of circulating AGEs, such as pentosidine. [27] The co-localization of medial calcification and AGE-modified elastin in the aortic medium is mainly due to the binding of minerals to elastin. [27] AGEs can promote the creation of RUNX2 mRNA and alkaline phosphatase and accelerate the calcification of microvascular pericytes. [27] VSMCs are one type of cells that express the AGE receptor (RAGE). [28] Through the

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

stimulation of Notch/Msx2, RAGE activation controls the expression of VSMC phenotypic genes and promotes osteogenic differentiation. [29]

Abnormal mineral metabolism:

A new risk factor for vascular calcification that was detected in CKD patients is unusual mineral metabolism. [30]

Hyperphosphatemia:

In dialysis patients, hyperphosphatemia is associated with the incidence and development of calcification. In these patients, non-calcium-based phosphate binders decrease calcification and death. [31] High levels of phosphorus are associated with higher mortality from all causes, including cardiovascular disease. [32]

Phosphate increases calcification of VSMC in a dose-dependent manner, affecting smooth muscle markers like alkaline phosphatase and VSMC loss while increasing osteochondrogenic markers Runx2, osterix, and osteopontin expression. [33]

Hypercalcemia:

In the CKD population, elevated serum calcium is associated with vascular calcification, and calcium-containing phosphate binders enhance arterial calcification. [42,43] Human vascular smooth muscle cells (VSMCs) become more calcified when exposed to calcium alone, and they can become more mineralised when exposed to calcium plus phosphorus. [34] In an aorta ring culture model, raised calcium is more effective than phosphorus at inducing VSMC calcification. [35] Moreover, calcium causes the release of VSMC matrix vesicles, and vascular calcification results from abnormal mineral metabolism through numerous pathways. In CKD patients, calcium and phosphorus work synergistically to promote vascular calcification. [36]

Fibroblast growth factor (FGF) 23:

FGF23, an osteocyte-expressed hormone, is vital for sustaining mineral homeostasis because it causes hyperphosphaturia, stops the manufacture of calcitriol, and decreases PTH secretion. [37] Additionally, it works in the kidneys by interacting with the FGF receptor when the Klotho cofactor exists. [38] In CKD and dialysis patients, FGF23 is linked to the calcification of the coronary artery and the aorta. [39] When FGF23 or Klotho is deleted explicitly in mice, hyperphosphatemia and vascular calcification result. [40] It was found that phosphorus-mediated rise of FGF23 levels by phosphate affects vascular calcification. [41]

Unnecessary intake of Vit D:

In an experimental study done by us, injecting experimental mice with a vitamin D extra dose (250 microgram/20 g/day) induced cardiovascular calcification, as shown in Figure 1. [42]

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

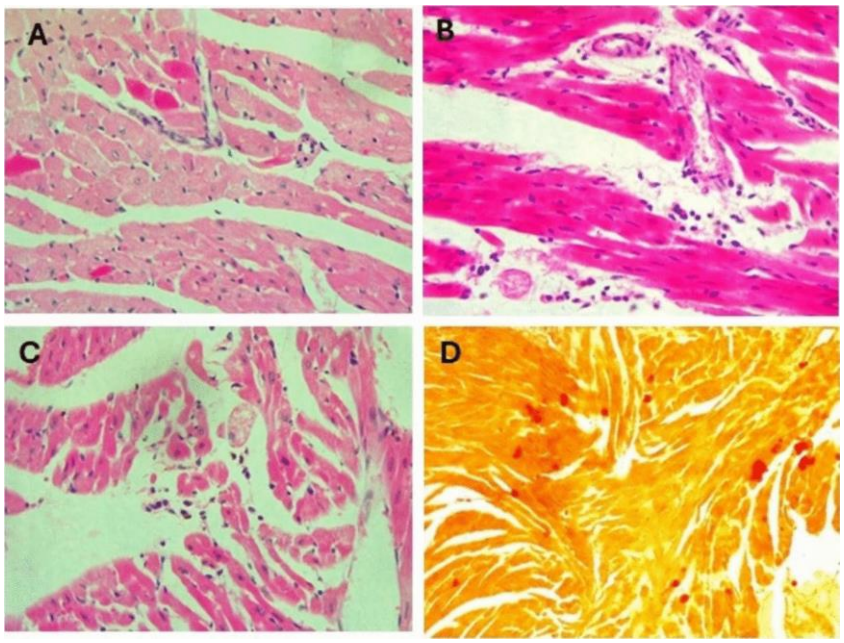

Figure (1): Histology of Vit D toxic dose treated mice heart, (A–C) H&E displays Apoptotic Myocytes, dilated and congested capillaries, inflammatory cell infiltrate, and damaged cardiac fibers, (D) Alizarin Red stain views orange red spots of calcification, Low Power (×10). [42]

Calcification in specific diseases:

Calcification in Atherosclerosis:

It has been demonstrated that arterial osteoblasts and osteoclasts contribute to the calcification of atherosclerotic plaques through inflammation-dependent pathways. [43]

Two distinct polarization states occur in macrophages: pro-inflammatory M1 phenotypes facilitate the advancement of inflammation, and anti-inflammatory M2 phenotypes promote regression. [44] Microcalcification occurs because VSMCs convert into early-phase osteoblasts, through vesicle-mediated mineralisation, and predominate M1 macrophages, promoting the initial calcium deposition within the necrotic core of the atherosclerotic lesions. [44]

Macrophages display remarkable flexibility, as they can adjust their phenotype in response to their functional needs and the surrounding environment, which is crucial for host defence, tissue homeostasis, and inflammation. [45]

The production of pro-inflammatory cytokines, reactive nitrogen and oxygen species, interferon, and toll-like receptor (TLR) ligands, such as lipopolysaccharide (LPS), enables macrophages to develop a prominent pro-inflammatory M1 phenotype. [46]

In an experimental study using a mouse model of regressing atherosclerotic plaques, the researchers observed decreased expression of M1 macrophage marker genes, including macrophage chemoattractant protein-1 (MCP-1), TNF, and inducible nitric oxide synthase

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

(iNOS). [47] This indicates that M1 macrophages predominate in the development of atherosclerotic plaque calcification and contribute to the inflammatory state. [47]

Inside plaque lesions, macrophages, endothelial cells, and VSMCs regularly activate the unfolded protein response (UPR), a stress pathway inside the endoplasmic reticulum (ER). [48] Oxidative stress, oxysterols, elevated cholesterol, and saturated fatty acids within the cells are among the elements present in these lesions that might result in continuous activation of the UPR. [48] Plaque necrosis is caused by the apoptosis (cell death) of macrophages and VSMCs due to the expanded ER stress. The ER stress-induced apoptosis in vascular cells may contribute to the initiation of plaque calcification. [48]

Additionally, ER stress can induce VSMCs to differentiate into osteoblasts, which may contribute to the development of calcified plaques. [49] There are three primary transducers involved in the unfolded protein response (UPR) signal transduction process: PERK (PKR-like endoplasmic reticulum kinase), IRE1 (inositol-requiring 1), and ATF6 (activating transcription factor 6). [49] The eukaryotic initiation factor 2 (eIF2-subunit) is phosphorylated due to PERK activation, which prevents the construction of the 80S ribosome and protein synthesis. [49] Particularly, phosphorylated eIF2 promotes the translation of activating transcription factor 4 (ATF4), which is a crucial transcription factor for osteoblast development and bone production. [49] The PERK-eIF2–ATF4 signaling pathway is activated by ER stress, which also occurs during osteoblast differentiation, and this stimulates the production of genes necessary for bone formation, including osteocalcin and bone sialoprotein. The stimulation of the PERK-eIF2-ATF4 signaling pathway also contributes to the TNF-induced differentiation of VSMCs into osteoblasts in an in vitro model of vascular calcification. [49] In light of this, ER stress may encourage plaque calcification by encouraging VSMCs to change into osteoblasts. [49]

When apoptotic bodies and matrix vesicles are produced during the death of macrophages and VSMCs, the first step of calcification, known as microcalcification, occurs in developing plaque lesions with a necrotic core, and the crystallization of calcium phosphate happens within these vesicles. [50] Microscopic examination showed tiny calcium deposits indicative of early calcification inside lipid pools, most likely resulting from SMC apoptosis or matrix vesicles. [50] The only way to see these deposits, typically less than 1 mm in size, is with a light microscope, as non-invasive imaging methods like computed tomography (CT) cannot identify them. [50] Plaque vulnerability and a higher likelihood of rupture are thought to be linked to microcalcification. [50]

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

Furthermore, microcalcification can exacerbate plaque inflammation and lead to plaque rupture by triggering a pro-inflammatory response in macrophages. [51] At the end, these microcalcifications combine to form larger masses, including the necrotic core and the collagen-rich extracellular matrix, resulting in speckled and fragmented calcification. [51] Calcified lesions may advance by converting VSMCs into osteogenic cells under the influence of pro-inflammatory cytokines like TNF- and OSM, which are generated by macrophages with an M1 phenotype. [51] These cytokines induce the expression of Runx2 and alkaline phosphatase, promoting further mineralization within plaque lesions. [51]

Calcification in Chronic Kidney Disease:

Chronic kidney disease (CKD) is defined as abnormal kidney structure and function that lasts for more than three months. [52] CKD patients frequently have vascular calcification, providing a crucial link between CKD and increased cardiovascular risk. [53] Vascular calcification is a process actively mediated by cells. [53] Angiogenesis is hampered by CKD-induced mineral dysregulation, which also has a detrimental effect on endothelial survival. [54] The activation of an osteoblast-like phenotypic transition in VSMCs is a significant event. [55] The dysfunction of inhibitory mechanisms such as fetuin-A and vitamin K-dependent proteins also causes mineralization and vascular calcification. [55]

Furthermore, Klotho deficiency, which was initially reported as an ageing suppressor, is a feature of chronic kidney disease. [56] Studies demonstrate that klotho improves phosphate metabolism by causing phosphaturia, which lowers serum phosphate levels and prevents the hardening of blood vessels. [57] Therefore, treating vascular calcification in people with chronic renal disease using klotho replacement may be a promising therapeutic strategy. [57] Magnesium, on the other hand, may prevent vascular calcification. [58] Clinical evidence indicates that in CKD patients, serum magnesium levels are inversely correlated with the manifestation of vascular calcification. [59] When vascular smooth muscle cells were exposed to higher magnesium concentrations, the production of hydroxyapatite was reduced. [60] Additionally, it prevents the transition of vascular smooth muscle cells by lowering the expression of osteogenic transcription factors. [61] In conclusion, magnesium supplementation is a viable therapeutic strategy to prevent vascular calcification; however, more clinical research and trials are required. [62]

Preventing Vascular Calcification: Insights from Translational Research and Clinical Trials

Nutritional supplements:

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

Vitamin K:

As a cofactor in activating several extracellular matrix proteins like Matrix Gla Protein [MGP], which inhibits calcification, vitamin K keeps the vascular system healthy. [63] According to several human investigations, vitamins K2 and K1 may reduce arterial stiffness and coronary artery calcification. [63]

Electrolyte Supplementation or Restriction:

While some data demonstrate the benefits of dietary phosphate restriction, dietary calcium does not affect vascular calcification. [64] Magnesium supplementation may help prevent the hardening of the coronary arteries, according to small-scale intervention trials. [65]

Magnesium and selected polyphenols:

Calcium phosphate deposits that accumulate on the inside of arteries are what cause arterial calcification. [66] Cardiovascular disorders are caused by the obstruction of blood flow by calcification. [66] Vascular smooth muscle cells change into bone-like cells and deposit calcium as hydroxyapatite, which causes vascular calcification. [66]

A study was conducted in vitro on rat vascular smooth muscle cells to evaluate the efficacy of the natural bioactive compounds (Q, C, and R) and magnesium present in OptiCel. [67]

Calcification was induced in the high-phosphate culture medium. The results demonstrated a synergistic effect of Mg and natural bioactive compounds in suppressing vascular calcification, with a 92.88% reduction in calcium deposition. [67] Therefore, regular consumption of bioactive compounds and magnesium may significantly slow the onset of cardiovascular diseases. [67]

A randomized, double-blind, placebo-controlled parallel-group clinical experiment was conducted to investigate the relationship between oral magnesium supplement consumption and the development of vascular calcification in chronic renal disease. [68] Compared to two fatalities and no cardiovascular events in the placebo group, the magnesium group experienced five deaths and six cardiovascular events. Consequently, magnesium did not pause the development of vascular calcification in CKD. [68]

Etidronate:

In a clinical study, the effect of Etidronate on arterial calcification was investigated in patients with pseudoxanthoma elasticum, and it significantly stopped the calcification process in all arterial beds except for the coronary arteries. [69]

Antioxidants:

The only study that tested the effect of antioxidants on vascular calcification in humans included a one-year, randomized, placebo-controlled study of treatment with aged garlic

combined with vitamin supplements, which dramatically decreased coronary calcification. It should be highlighted that each subject took statins and followed a low-cholesterol diet. [70] [71]

Plant-food bioactive derivatives:

According to some epidemiological studies, the consumption of fruits, vegetables, legumes, whole grains, and olive oil has cardioprotective effects on human health. [72]

Vegetables have less saturated fat and have a low glycemic index. [72] Legumes are also excellent sources of potassium, plant-based protein, and fiber. [72] They lessen the risk of hypertension and CV disease. [72]

Foods rich in polyphenols, particularly anthocyanins, can improve plasma lipid profiles and endothelial function, reduce inflammation, stop improper platelet aggregation, and protect from oxidative stress. [73]

A single-blind trial in hypertensive males observed that pomegranate juice shows immediate hypotensive effects. [73]

In a placebo-controlled crossover study, drinking cranberry juice negatively influenced the carotid-femoral pulse wave velocity, which gauges arterial stiffness. [74] Rich in polyphenols, virgin olive oil lowers systolic blood pressure but has a minimal effect on diastolic blood pressure. [74] Nuts reduce blood cholesterol because they have unsaturated fatty acids and dietary fiber. [74] Although a healthy diet can lower the overall risk of coronary artery disease, there is insufficient evidence to suggest that it can also reduce vascular calcification. [74]

Lifestyle modification:

Quitting smoking is one of the lifestyle changes that need to be addressed. Smoking considerably raises the risk of calcification of the abdominal aorta. [75]

Pharmacological treatment:

Calcium channel blockers:

Calcium channel blockers prevent the voltage-dependent calcium channels in the plasma membrane from functioning, thereby lowering the amount of calcium inside the cell. [76] This decreases the calcium content of vascular smooth muscle cells' extracellular vesicles. [76] Vascular calcification decreases as a result, but there is not much clinical data available in this area. [76]

Renin-angiotensin system inhibitors:

Angiotensin II promotes the formation of calcium deposits in aortic vascular smooth muscle cells in vitro, by switching these cells into phenotypic osteoblast-like vascular smooth muscle cells via kappa B ligand [RANKL]. [77] So the Renin-angiotensin system inhibitors hinder the

Volume 2 Issue 2 (July-December 2025) | ISSN: 3049-0715

proliferation and migration of vascular smooth muscle cells, and they stop the extracellular matrix from changing. [77]

Statins:

Statins mitigate certain factors that contribute to the transition of vascular smooth muscle cells to resemble phenotypic osteoblasts by lowering LDL cholesterol and reducing arterial wall inflammation. [78] However, several clinical studies have shown conflicting results regarding the effects of statins on vascular calcification. [78]

Bisphosphonates and Denosumab:

Most human trials using bisphosphonates in vascular illness have limited sample sizes. [79] Despite their established inhibitory effect on atherosclerosis, the effect of Bisphosphonates is varied and weak. [79]

A humanized monoclonal antibody called denosumab binds to RANKL and prevents calcium buildup was reported. [80] Nevertheless, its effects are only seen in experimental animals, and there is no proof that it significantly impacts vascular calcification in humans. [80]

Emerging Therapeutic Targets for Inhibiting Vascular Calcification

A study was conducted on endogenous calcification-inhibitory proteins, including fetuin-A, Klotho, and vitamin-K-dependent matrix Gla protein. [81] Patients with chronic renal disease usually have a deficiency of vitamin K. [81] This could result from anticoagulant treatments with vitamin K antagonists or dietary limitations causing malnutrition. [81] The bioavailability of the vitamin K-dependent proteins, which are inhibitors of tissue calcification, is lowered by vitamin K deficiency, resulting in calcification both in vivo and in a test tube. [82] Patients with CKD who took oral vitamin K2 replacement exhibited no improvement. [82] Fortunately, vascular calcification in CKD patients was positively influenced by vitamin K1 treatment. [82] In conclusion, reducing the progression or development of vascular calcification may be possible by raising the matrix Gla Protein activity in the arteries. [83]

Furthermore, increasing vascular calcification is associated with a decline in fetuin-A levels, as fetuin-A acts as an inhibitor of calcification by forming stable fetuin-mineral complexes, known as calciprotein particles, thereby reducing hydroxyapatite production. [84] Consequently, the delivery of fetuin-A may likewise represent a possible therapeutic target. [84]

Another cutting-edge therapeutic target is autophagy, which is essential for maintaining calcium homeostasis, vascular smooth muscle cell phenotypic switching, and endothelial cell homeostasis in normal vascular function. [85] According to some studies, autophagy can effectively guard against vascular calcification. [85] Ultimately, research into pharmacological

modulation of autophagy may provide a potential method for treating vascular calcification. [85] If mitochondria function normally, calcium homeostasis is controlled. [86] When mitochondria consume too much calcium, cytochrome C is released, which leads to cell death. [86] Vascular calcification may be treated by pharmacologically modulating autophagy with medicines like spermidine. [86] Due to the lack of expertise and information, it would be interesting to determine whether medications may activate specific autophagy to recycle excess calcium, phosphate, or hydroxyapatite. [86]

Conclusions & Recommendations

Through a comprehensive review of existing literature and critical analysis of current research, this study aimed to enhance our understanding of vascular calcification, ultimately paving the way for innovative approaches to prevent its occurrence and ameliorate its impact on cardiovascular health. The findings hold promise for developing personalized preventive strategies that reduce the burden of cardiovascular disease worldwide. It is highly recommended to investigate further the therapeutic effectiveness of substances such as Klotho, Magnesium, and Fetuin-A in the prevention and/or treatment of vascular calcification, as previous studies have been insufficient.

Acknowledgment

We acknowledge the support provided by Prof. Ahmed Hassan Fahal and Dr. Hiba Mohamed in revising the article.

References:

1. Palit, S., & Kendrick, J. (2014). Vascular calcification in chronic kidney disease: role of disordered mineral metabolism. Current pharmaceutical design, 20(37), 5829–5833.
2. Rennenberg, R. J., Schurgers, L. J., Kroon, A. A., & Stehouwer, C. D. (2010). Arterial calcifications. Journal of cellular and molecular medicine, 14(9), 2203–2210.
3. Shen, J., Zhao, M., Zhang, C., & Sun, X. (2021). IL-1β in atherosclerotic vascular calcification: From bench to bedside. International journal of biological sciences, 17(15), 4353–4364.
4. Rudloff, S., Jahnen-Dechent, W., & Huynh-Do, U. (2022). Tissue chaperoning expanded functions of fetuin-A beyond inhibition of systemic calcification. Pflugers Archiv : European journal of physiology, 474(8), 949–962.
5. Lee, S. J., Lee, I. K., & Jeon, J. H. (2020). Vascular Calcification-New Insights Into Its Mechanism. International journal of molecular sciences, 21(8), 2685.
6. Cannata-Andia, J. B., Roman-Garcia, P., & Hruska, K. (2011). The connections between vascular calcification and bone health. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association, 26(11), 3429–3436.

7. Yahagi, K., Kolodgie, F. D., Lutter, C., Mori, H., Romero, M. E., Finn, A. V., & Virmani, R. (2017). Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes Mellitus. Arteriosclerosis, thrombosis, and vascular biology, 37(2), 191–204.
8. Jaminon, A., Reesink, K., Kroon, A., & Schurgers, L. (2019). The Role of Vascular Smooth Muscle Cells in Arterial Remodeling: Focus on Calcification-Related Processes. International journal of molecular sciences, 20(22), 5694.
9. Greenberg, H. Z. E., Zhao, G., Shah, A. M., & Zhang, M. (2022). Role of oxidative stress in calcific aortic valve disease and its therapeutic implications. Cardiovascular research, 118(6), 1433–1451.
10. Chen, N. X., & Moe, S. M. (2012). Vascular calcification: pathophysiology and risk factors. Current hypertension reports, 14(3), 228–237.
11. Stabley, J. N., & Towler, D. A. (2017). Arterial Calcification in Diabetes Mellitus: Preclinical Models and Translational Implications. Arteriosclerosis, thrombosis, and vascular biology, 37(2), 205–217.
12. Yang, P., Troncone, L., Augur, Z. M., Kim, S. S. J., McNeil, M. E., & Yu, P. B. (2020). The role of bone morphogenetic protein signaling in vascular calcification. Bone, 141, 115542.
13. Zhu, D., Mackenzie, N. C., Farquharson, C., & Macrae, V. E. (2012). Mechanisms and clinical consequences of vascular calcification. Frontiers in endocrinology, 3, 95.
14. Abedin, M., Lim, J., Tang, T. B., Park, D., Demer, L. L., & Tintut, Y. (2006). N-3 fatty acids inhibit vascular calcification via the p38-mitogen-activated protein kinase and peroxisome proliferator-activated receptor-gamma pathways. Circulation research, 98(6), 727–729.
15. Demer, L., & Tintut, Y. (2011). The roles of lipid oxidation products and receptor activator of nuclear factor-κB signaling in atherosclerotic calcification. Circulation research, 108(12), 1482–1493.
16. Poznyak, A. V., Sadykhov, N. K., Kartuesov, A. G., Borisov, E. E., Sukhorukov, V. N., & Orekhov, A. N. (2022). Atherosclerosis Specific Features in Chronic Kidney Disease (CKD). Biomedicines, 10(9), 2094.
17. Lin, P., Ji, H. H., Li, Y. J., & Guo, S. D. (2021). Macrophage Plasticity and Atherosclerosis Therapy. Frontiers in molecular biosciences, 8, 679797.
18. Tintut, Y., Patel, J., Parhami, F., & Demer, L. L. (2000). Tumor necrosis factor-alpha promotes in vitro calcification of vascular cells via the cAMP pathway. Circulation, 102(21), 2636–2642.
19. Okazaki, H., Shioi, A., Hirowatari, K., Koyama, H., Fukumoto, S., Ishimura, E., & Nishizawa, Y. (2009). Phosphatidylinositol 3-kinase/Akt pathway regulates inflammatory mediators-induced calcification of human vascular smooth muscle cells. Osaka city medical journal, 55(2), 71–80.

20. Sinha, A., & Vyavahare, N. R. (2013). High-glucose levels and elastin degradation products accelerate osteogenesis in vascular smooth muscle cells. Diabetes & vascular disease research, 10(5), 410–419.
21. Herrmann, J., Gummi, M. R., Xia, M., van der Giet, M., Tölle, M., & Schuchardt, M. (2021). Vascular Calcification in Rodent Models-Keeping Track with an Extended Method Assortment. Biology, 10(6), 459.
22. Abdelbaky, A., Corsini, E., Figueroa, A. L., Fontanez, S., Subramanian, S., Ferencik, M., Brady, T. J., Hoffmann, U., & Tawakol, A. (2013). Focal arterial inflammation precedes subsequent calcification in the same location: a longitudinal FDG-PET/CT study. Circulation. Cardiovascular imaging, 6(5), 747–754.
23. Taylor, J., Butcher, M., Zeadin, M., Politano, A., & Shaughnessy, S. G. (2011). Oxidized low-density lipoprotein promotes osteoblast differentiation in primary cultures of vascular smooth muscle cells by up-regulating Osterix expression in an Msx2-dependent manner. Journal of cellular biochemistry, 112(2), 581–588.
24. Tseng, W., Lu, J., Bishop, G. A., Watson, A. D., Sage, A. P., Demer, L., & Tintut, Y. (2010). Regulation of interleukin-6 expression in osteoblasts by oxidized phospholipids. Journal of lipid research, 51(5), 1010–1016.
25. Dube, P., DeRiso, A., Patel, M., Battepati, D., Khatib-Shahidi, B., Sharma, H., Gupta, R., Malhotra, D., Dworkin, L., Haller, S., & Kennedy, D. (2021). Vascular Calcification in Chronic Kidney Disease: Diversity in the Vessel Wall. Biomedicines, 9(4), 404.
26. Oleniuc, M., Secara, I., Onofriescu, M., Hogas, S., Voroneanu, L., Siriopol, D., & Covic, A. (2011). Consequences of Advanced Glycation End Products Accumulation in Chronic Kidney Disease and Clinical Usefulness of Their Assessment Using a Non-invasive Technique - Skin Autofluorescence. Maedica, 6(4), 298–307.
27. Mallipattu, S. K., He, J. C., & Uribarri, J. (2012). Role of advanced glycation endproducts and potential therapeutic interventions in dialysis patients. Seminars in dialysis, 25(5), 529–538.
28. Bardeesi, A. S. A., Gao, J., Zhang, K., et al. (2017). A novel role of cellular interactions in vascular calcification. Journal of Translational Medicine, 15, 95.
29. Cao, G., Xuan, X., Hu, J., Zhang, R., Jin, H., & Dong, H. (2022). How vascular smooth muscle cell phenotype switching contributes to vascular disease. Cell communication and signaling: CCS, 20(1), 180.
30. Dai, Z., & Zhang, X. (2023). Pathophysiology and Clinical Impacts of Chronic Kidney Disease on Coronary Artery Calcification. Journal of cardiovascular development and disease, 10(5), 207.
31. Spaia S. (2011). Phosphate binders: Sevelamer in the prevention and treatment of hyperphosphataemia in chronic renal failure. Hippokratia, 15(Suppl 1), 22–26.

32. Chang, A. R., Lazo, M., Appel, L. J., Gutiérrez, O. M., & Grams, M. E. (2014). High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. The American journal of clinical nutrition, 99(2), 320–327.
33. Lau, W. L., Pai, A., Moe, S. M., & Giachelli, C. M. (2011). Direct effects of phosphate on vascular cell function. Advances in chronic kidney disease, 18(2), 105–112.
34. Shanahan, C. M., Crouthamel, M. H., Kapustin, A., & Giachelli, C. M. (2011). Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circulation research, 109(6), 697–711.
35. Paloian, N. J., & Giachelli, C. M. (2014). A current understanding of vascular calcification in CKD. American journal of physiology. Renal physiology, 307(8), F891–F900.
36. Durham, A. L., Speer, M. Y., Scatena, M., Giachelli, C. M., & Shanahan, C. M. (2018). Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovascular Research, 114(4), 590–600.
37. Martin, A., David, V., & Quarles, L. D. (2012). Regulation and function of the FGF23/klotho endocrine pathways. Physiological reviews, 92(1), 131–155.
38. Kurosu, H., Ogawa, Y., Miyoshi, M., Yamamoto, M., Nandi, A., Rosenblatt, K. P., Baum, M. G., Schiavi, S., Hu, M. C., Moe, O. W., & Kuro-o, M. (2006). Regulation of fibroblast growth factor-23 signaling by klotho. The Journal of biological chemistry, 281(10), 6120–6123.
39. Muzasti, R. A., & Lubis, N. D. (2021). Diagnostic value of fibroblast growth factor 23 for abdominal aortic calcification in Indonesian hemodialysis patients. Tzu Chi Medical Journal, 33(2), 154–159.
40. Hum, J. M., O'Bryan, L. M., Tatiparthi, A. K., Cass, T. A., Clinkenbeard, E. L., Cramer, M. S., Bhaskaran, M., Johnson, R. L., Wilson, J. M., Smith, R. C., & White, K. E. (2017). Chronic Hyperphosphatemia and Vascular Calcification Are Reduced by Stable Delivery of Soluble Klotho. Journal of the American Society of Nephrology : JASN, 28(4), 1162–1174.
41. Cozzolino, M., Ciceri, P., Galassi, A., Mangano, M., Carugo, S., Capelli, I., & Cianciolo, G. (2019). The Key Role of Phosphate on Vascular Calcification. Toxins, 11(4), 213.
42. Mohamed, M. A., Hussein, M., Moustafa, S., & et al. (2025). Histopathological effects of hypervitaminosis D and the protective role of fetuin-A in renal, hepatic, and cardiac tissues in a murine model. *Scientific Reports*, *15*(1), 1078. https://doi.org/10.1038/s41598-025-85200-1
43. Doherty, T. M., Asotra, K., Fitzpatrick, L. A., Qiao, J. H., Wilkin, D. J., Detrano, R. C., Dunstan, C. R., Shah, P. K., & Rajavashisth, T. B. (2003). Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. Proceedings of the National Academy of Sciences of the United States of America, 100(20), 11201–11206.
44. Shioi, A., & Ikari, Y. (2018). Plaque Calcification During Atherosclerosis Progression and Regression. Journal of atherosclerosis and thrombosis, 25(4), 294–303.

45. Wynn, T. A., Chawla, A., & Pollard, J. W. (2013). Macrophage biology in development, homeostasis and disease. Nature, 496(7446), 445–455.
46. Marrocco, A., & Ortiz, L. A. (2022). Role of metabolic reprogramming in pro-inflammatory cytokine secretion from LPS or silica-activated macrophages. Frontiers in immunology, 13, 936167.
47. Barrett T. J. (2020). Macrophages in Atherosclerosis Regression. Arteriosclerosis, thrombosis, and vascular biology, 40(1), 20–33.
48. Tabas I. (2010). The role of endoplasmic reticulum stress in the progression of atherosclerosis. Circulation research, 107(7), 839–850.
49. Rao, Z., Zheng, Y., Xu, L., Wang, Z., Zhou, Y., Chen, M., Dong, N., Cai, Z., & Li, F. (2022). Endoplasmic Reticulum Stress and Pathogenesis of Vascular Calcification. Frontiers in cardiovascular medicine, 9, 918056.
50. Chistiakov, D. A., Myasoedova, V. A., Melnichenko, A. A., Grechko, A. V., & Orekhov, A. N. (2017). Calcifying Matrix Vesicles and Atherosclerosis. BioMed research international, 2017, 7463590.
51. Barrett, H. E., Van der Heiden, K., Farrell, E., Gijsen, F. J. H., & Akyildiz, A. C. (2019). Calcifications in atherosclerotic plaques and impact on plaque biomechanics. Journal of Biomechanics, 87, 1-12.
52. Chapter 1: Definition and classification of CKD. (2013). Kidney international supplements, 3(1), 19–62.
53. Jono, S., Shioi, A., Ikari, Y., & Nishizawa, Y. (2006). Vascular calcification in chronic kidney disease. Journal of bone and mineral metabolism, 24(2), 176–181.
54. Zununi Vahed, S., Mostafavi, S., Hosseiniyan Khatibi, S. M., Shoja, M. M., & Ardalan, M. (2020). Vascular Calcification: An Important Understanding in Nephrology. Vascular health and risk management, 16, 167–180.
55. Leopold J. A. (2015). Vascular calcification: Mechanisms of vascular smooth muscle cell calcification. Trends in cardiovascular medicine, 25(4), 267–274.
56. Zou, D., Wu, W., He, Y., Ma, S., & Gao, J. (2018). The role of klotho in chronic kidney disease. BMC nephrology, 19(1), 285.
57. Hu, M. C., Shi, M., Zhang, J., Quiñones, H., Griffith, C., Kuro-o, M., & Moe, O. W. (2011). Klotho deficiency causes vascular calcification in chronic kidney disease. Journal of the American Society of Nephrology: JASN, 22(1), 124–136.
58. Bressendorff, I., Hansen, D., Schou, M., Kragelund, C., & Brandi, L. (2017). The effect of magnesium supplementation on vascular calcification in chronic kidney disease-a randomized clinical trial (MAGiCAL-CKD): essential study design and rationale. BMJ open, 7(6), e016795.

59. Massy, Z. A., & Drüeke, T. B. (2012). Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. Clinical kidney journal, 5(Suppl 1), i52–i61.
60. Ter Braake, A. D., Tinnemans, P. T., Shanahan, C. M., Hoenderop, J. G. J., & de Baaij, J. H. F. (2018). Magnesium prevents vascular calcification in vitro by inhibition of hydroxyapatite crystal formation. Scientific reports, 8(1), 2069.
61. Jiang, Y., & Qian, H. Y. (2023). Transcription factors: key regulatory targets of vascular smooth muscle cell in atherosclerosis. Molecular medicine (Cambridge, Mass.), 29(1), 2.
62. Bressendorff, I., Hansen, D., Schou, M., Kragelund, C., Svensson, M., Hashemi, B., Kristensen, T., Vrist, M. H., Borg, R., Tougaard, B., Borg, K., Hjortkjær, H. Ø., Kristiansen, C. H., Carlson, N., Nasiri, M., Ashraf, H., Pasch, A., & Brandi, L. (2023). The Effect of Magnesium Supplementation on Vascular Calcification in CKD: A Randomized Clinical Trial (MAGiCAL-CKD). Journal of the American Society of Nephrology : JASN, 34(5), 886–894.
63. Shioi, A., Morioka, T., Shoji, T., & Emoto, M. (2020). The Inhibitory Roles of Vitamin K in Progression of Vascular Calcification. Nutrients, 12(2), 583.
64. Vossen, L. M., Kroon, A. A., Schurgers, L. J., & de Leeuw, P. W. (2019). Pharmacological and Nutritional Modulation of Vascular Calcification. Nutrients, 12(1), 100.
65. DiNicolantonio, J. J., Liu, J., & O'Keefe, J. H. (2018). Magnesium for the prevention and treatment of cardiovascular disease. Open heart, 5(2), e000775.
66. Giachelli C. M. (2009). The emerging role of phosphate in vascular calcification. Kidney international, 75(9), 890–897.
67. Mehansho, H., Majeti, S., & Tzeghai, G. (2021). Prevention of Vascular Calcification by Magnesium and Selected Polyphenols. Advances in preventive medicine, 2021, 6686597.
68. Bressendorff, I., Hansen, D., Schou, M., Silver, B., Pasch, A., Bouchelouche, P., Pedersen, L., Rasmussen, L. M., & Brandi, L. (2016). Oral Magnesium Supplementation in Chronic Kidney Disease Stages 3 and 4: Efficacy, Safety, and Effect on Serum Calcification Propensity-A Prospective Randomized Double-Blinded Placebo-Controlled Clinical Trial. Kidney international reports, 2(3), 380–389.
69. Bartstra, J. W., de Jong, P. A., Kranenburg, G., Wolterink, J. M., Isgum, I., Wijsman, A., Wolf, B., den Harder, A. M., Mali, W. P. T. M., & Spiering, W. (2020). Etidronate halts systemic arterial calcification in pseudoxanthoma elasticum. Atherosclerosis, 292, 37–41.
70. Li, M., Yun, W., Wang, G., Li, A., Gao, J., & He, Q. (2022). Roles and mechanisms of garlic and its extracts on atherosclerosis: A review. Frontiers in pharmacology, 13, 954938.
71. Budoff, M. J., Takasu, J., Flores, F. R., Niihara, Y., Lu, B., Lau, B. H., Rosen, R. T., & Amagase, H. (2004). Inhibiting progression of coronary calcification using Aged Garlic Extract in patients receiving statin therapy: a preliminary study. Preventive medicine, 39(5), 985–991.

72. Anand, S. S., Hawkes, C., de Souza, R. J., Mente, A., Dehghan, M., Nugent, R., Zulyniak, M. A., Weis, T., Bernstein, A. M., Krauss, R. M., Kromhout, D., Jenkins, D. J. A., Malik, V., Martinez-Gonzalez, M. A., Mozaffarian, D., Yusuf, S., Willett, W. C., & Popkin, B. M. (2015). Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the Workshop Convened by the World Heart Federation. Journal of the American College of Cardiology, 66(14), 1590–1614.
73. Mozos, I., Flangea, C., Vlad, D. C., Gug, C., Mozos, C., Stoian, D., Luca, C. T., Horbańczuk, J. O., Horbańczuk, O. K., & Atanasov, A. G. (2021). Effects of Anthocyanins on Vascular Health. Biomolecules, 11(6), 811.
74. Dohadwala, M. M., Holbrook, M., Hamburg, N. M., Shenouda, S. M., Chung, W. B., Titas, M., Kluge, M. A., Wang, N., Palmisano, J., Milbury, P. E., Blumberg, J. B., & Vita, J. A. (2011). Effects of cranberry juice consumption on vascular function in patients with coronary artery disease. The American journal of clinical nutrition, 93(5), 934–940.
75. Jung, J. G., Wu, L. T., Kim, J. S., Kim, E. D., & Yoon, S. J. (2019). Relationship between Smoking and Abdominal Aorta Calcification on Computed Tomography. Korean journal of family medicine, 40(4), 248–253.
76. Calcium Channel Blockers. (2017). In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases.
77. Tyson, J., Bundy, K., Roach, C., Douglas, H., Ventura, V., Segars, M. F., Schwartz, O., & Simpson, C. L. (2020). Mechanisms of the Osteogenic Switch of Smooth Muscle Cells in Vascular Calcification: WNT Signaling, BMPs, Mechanotransduction, and EndMT. Bioengineering (Basel, Switzerland), 7(3), 88.
78. Demer, L. L., & Tintut, Y. (2008). Vascular calcification: pathobiology of a multifaceted disease. Circulation, 117(22), 2938–2948.
79. Santos, L. L., Cavalcanti, T. B., & Bandeira, F. A. (2012). Vascular effects of bisphosphonates-a systematic review. Clinical medicine insights. Endocrinology and diabetes, 5, 47–54.
80. Lewiecki E. M. (2009). Denosumab in postmenopausal osteoporosis: what the clinician needs to know. Therapeutic advances in musculoskeletal disease, 1(1), 13–26.
81. Bäck, M., Aranyi, T., Cancela, M. L., Carracedo, M., Conceição, N., Leftheriotis, G., Macrae, V., Martin, L., Nitschke, Y., Pasch, A., Quaglino, D., Rutsch, F., Shanahan, C., Sorribas, V., Szeri, F., Valdivielso, P., Vanakker, O., & Kempf, H. (2019). Endogenous Calcification Inhibitors in the Prevention of Vascular Calcification: A Consensus Statement From the COST Action EuroSoftCalcNet. Frontiers in cardiovascular medicine, 5, 196.
82. Cozzolino, M., Mangano, M., Galassi, A., Ciceri, P., Messa, P., & Nigwekar, S. (2019). Vitamin K in Chronic Kidney Disease. Nutrients, 11(1), 168.

83. Lin, Y. L., & Hsu, B. G. (2022). Vitamin K and vascular calcification in chronic kidney disease: An update of current evidence. Tzu chi medical journal, 35(1), 44–50.
84. Chekol Abebe, E., Tilahun Muche, Z., Behaile T/Mariam, A., Mengie Ayele, T., Mekonnen Agidew, M., Teshome Azezew, M., Abebe Zewde, E., Asmamaw Dejenie, T., & Asmamaw Mengstie, M. (2022). The structure, biosynthesis, and biological roles of fetuin-A: A review. Frontiers in cell and developmental biology, 10, 945287.
85. Phadwal, K., Feng, D., Zhu, D., & MacRae, V. E. (2020). Autophagy as a novel therapeutic target in vascular calcification. Pharmacology & therapeutics, 206, 107430.
86. Wang, P., Zhang, N., Wu, B., Wu, S., Zhang, Y., & Sun, Y. (2020). The Role of Mitochondria in Vascular Calcification. Journal of translational internal medicine, 8(2), 80–90.