



Interplay Between Coronary Artery Calcium Score and Vitamin D3 Status: A Contemporary Review in Coronary Artery Disease

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Abstract

Background: Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide despite substantial progress in preventive cardiology and imaging diagnostics. The coronary artery calcium (CAC) score, derived from non-contrast computed tomography, is a well-validated surrogate of atherosclerotic plaque burden and a strong predictor of future cardiovascular events. Parallel to this, vitamin D3 (cholecalciferol) has emerged as a multifaceted hormone with immunomodulatory, anti-inflammatory, and endothelial effects that extend beyond calcium–phosphate homeostasis. Increasing evidence links vitamin D3 deficiency to vascular dysfunction, arterial stiffness, and accelerated atherosclerosis, yet the direct association between vitamin D3 status and coronary calcification remains incompletely understood.

Aim: This review aims to synthesize current evidence on the correlation between serum vitamin D3 concentrations and CAC scores in patients with CAD, exploring potential pathophysiological mechanisms, clinical implications, and gaps in the existing literature. It critically examines whether hypovitaminosis D contributes to vascular calcification via modulation of inflammation, lipid metabolism, or vascular smooth muscle cell osteogenic transformation, and whether vitamin D3 supplementation could alter atherosclerotic progression reflected by CAC scoring.

Conclusion: Accumulating data indicate an inverse association between vitamin D3 levels and CAC scores in many, though not all, populations with established or subclinical CAD. Mechanistic studies suggest vitamin D3 deficiency promotes pro-calcific and pro-inflammatory phenotypes in vascular tissue, whereas optimal levels may preserve endothelial integrity and inhibit plaque mineralization. However, observational heterogeneity, variable assay methodologies, and confounding by comorbidities such as chronic kidney disease and metabolic syndrome limit definitive causal inference. Large, prospective, and interventional studies integrating standardized vitamin D3 assessment with quantitative CAC progression are warranted to clarify this relationship. Understanding the metabolic–imaging interface between vitamin D3 and coronary calcification may open new avenues for personalized cardiovascular risk stratification and prevention strategies in contemporary clinical practice.

Keywords: *Pericapsular Nerve Group Block, Analgesia, Elderly, Hip Fracture*



Introduction

Coronary artery disease (CAD) remains the leading cause of global mortality, responsible for an estimated 18 million deaths annually, reflecting both aging populations and persistent cardiometabolic risk factors. Despite major therapeutic advances in lipid-lowering and revascularization strategies, atherosclerosis continues to evolve silently over decades before clinical manifestation. Consequently, early identification of subclinical disease has become a cornerstone of preventive cardiology. The coronary artery calcium (CAC) score, derived from non-contrast computed tomography (CT), provides a robust, noninvasive measure of calcified plaque burden, correlating strongly with future cardiovascular events independent of traditional risk factors [1].

Vitamin D3 (cholecalciferol), historically viewed as a regulator of calcium–phosphate metabolism and bone mineralization, has recently emerged as a potential modulator of cardiovascular health. The discovery of vitamin D receptors (VDRs) in endothelial cells, cardiomyocytes, and vascular smooth muscle cells has expanded its relevance beyond skeletal physiology. Epidemiologic studies increasingly suggest an association between low serum vitamin D3 levels and higher incidence of hypertension, diabetes, and coronary atherosclerosis, although the underlying biological mechanisms remain complex and incompletely characterized [2].

A growing body of evidence indicates that vitamin D3 deficiency may contribute to vascular calcification by promoting inflammation, oxidative stress, and phenotypic transformation of vascular smooth muscle cells into osteoblast-like cells. Conversely, optimal vitamin D3 concentrations appear to attenuate these pathways, maintaining endothelial homeostasis and vascular elasticity. The interplay between vitamin D3 status and CAC scoring, therefore, represents a promising field for understanding atherosclerotic progression at the intersection of metabolism, endocrinology, and imaging [3].

This review provides a comprehensive synthesis of current evidence correlating serum vitamin D3 concentrations with coronary calcium scores in patients with CAD. It explores the mechanistic basis linking both biomarkers, discusses confounding factors that may influence their relationship, and highlights the clinical and research implications of integrating metabolic and imaging parameters for personalized cardiovascular risk assessment [4].

Pathophysiological Basis of Coronary Artery Calcification

Coronary artery calcification (CAC) is now recognized as a highly regulated, cell-mediated process rather than a passive accumulation of calcium within the arterial wall. It represents a final common pathway of atherosclerotic plaque evolution, reflecting chronic inflammation, oxidative stress, and metabolic dysregulation. The presence and extent of CAC correlate directly with overall plaque burden and future cardiovascular risk, making it both a diagnostic and prognostic biomarker in coronary artery disease (CAD) [5].

The process of vascular calcification involves phenotypic transformation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells capable of secreting bone matrix proteins such as osteocalcin, bone morphogenetic protein-2 (BMP-2), and alkaline phosphatase. These osteogenic markers are upregulated under pro-inflammatory conditions, leading to calcium phosphate crystal deposition within the arterial intima and media. This transition is facilitated by inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and oxidized low-density lipoprotein (oxLDL), which collectively drive vascular mineralization [6].

Two major patterns of arterial calcification are described: **intimal calcification**, typically associated with atherosclerotic plaque development, and **medial calcification**, also known as Mönckeberg's sclerosis, which is more common in metabolic disorders such as diabetes mellitus and chronic kidney disease. Intimal calcification contributes to plaque instability and thrombogenicity, whereas medial calcification primarily increases arterial stiffness and pulse pressure, thereby aggravating left ventricular workload [7].



Oxidative stress plays a central role in the initiation and propagation of calcification. Reactive oxygen species (ROS) not only damage vascular endothelium but also activate redox-sensitive transcription factors that upregulate osteogenic genes. Simultaneously, the loss of calcification inhibitors such as matrix Gla protein (MGP) and fetuin-A enhances susceptibility to calcium deposition. These intricate cellular and molecular mechanisms demonstrate that vascular calcification shares key similarities with skeletal mineralization, governed by a delicate balance between promoters and inhibitors of calcification [8].

Chronic inflammation is an indispensable driver of vascular calcification. Activated macrophages and T-lymphocytes infiltrate the arterial wall, releasing cytokines and growth factors that perpetuate local inflammation and stimulate VSMC differentiation. Nuclear factor-kappa B (NF- κ B) signaling is particularly instrumental in mediating this inflammatory-osteogenic axis. Experimental studies have shown that inhibition of NF- κ B reduces osteogenic marker expression and limits calcium deposition within vascular tissue, highlighting its potential as a therapeutic target [9].

Calcium-phosphate metabolism also exerts a crucial influence on vascular calcification. Elevated serum phosphate concentrations, even within the upper normal range, can trigger VSMC calcification by enhancing sodium-dependent phosphate transporter activity. This explains why metabolic disorders associated with altered phosphate balance, such as chronic kidney disease and hyperparathyroidism, are strongly linked to accelerated vascular calcification. Vitamin D3, through its regulation of calcium and phosphate homeostasis, may thus intersect with these pathways, affecting calcific load within coronary arteries [10].

Finally, the recognition of CAC as a biologically active process has important clinical implications. It not only signifies the presence of advanced atherosclerotic plaque but also reflects ongoing cellular activity that can potentially be modulated by metabolic and pharmacologic interventions. Understanding the molecular pathways of vascular calcification provides the conceptual foundation for exploring how vitamin D3 deficiency might enhance or accelerate this process in coronary artery disease [11].

Vitamin D3: Cardiometabolic Roles and Mechanisms in Vascular Health

Vitamin D3 (cholecalciferol) is a fat-soluble secosteroid hormone synthesized primarily in the skin under ultraviolet B exposure or obtained through dietary intake. It undergoes hydroxylation in the liver to form 25-hydroxyvitamin D [25(OH)D], the major circulating form used to assess vitamin D status, and subsequent hydroxylation in the kidney to yield its active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D]. This active metabolite binds to the vitamin D receptor (VDR), a nuclear transcription factor expressed in various tissues including vascular smooth muscle cells, endothelial cells, and cardiomyocytes. Through these receptors, vitamin D3 exerts both genomic and non-genomic effects that influence cardiovascular function and vascular integrity [12].

Vitamin D3 deficiency has been widely recognized as a contributor to cardiometabolic disorders such as hypertension, insulin resistance, and dyslipidemia. Mechanistically, vitamin D3 suppresses the renin-angiotensin-aldosterone system (RAAS), a key regulator of blood pressure and vascular tone. In the absence of adequate vitamin D3, renin gene expression increases, resulting in elevated angiotensin II levels that promote vasoconstriction, inflammation, and vascular remodeling. By downregulating RAAS activity, vitamin D3 helps to reduce endothelial stress, improve nitric oxide bioavailability, and attenuate vascular stiffness [13].

Endothelial function represents another major target of vitamin D3 activity. Adequate vitamin D3 levels enhance endothelial nitric oxide synthase (eNOS) activity, thereby improving vasodilation and maintaining vascular homeostasis. In vitamin D3-deficient states, endothelial dysfunction arises due to increased oxidative stress and decreased nitric oxide production. This imbalance favors leukocyte adhesion, vascular inflammation, and subsequent atherogenesis. Additionally, vitamin D3 modulates endothelial progenitor cell differentiation, which contributes to vascular repair and regeneration, further linking vitamin D3 status to endothelial integrity [14].

Vitamin D3 also exhibits potent anti-inflammatory and immunomodulatory effects. It inhibits activation of the nuclear factor-kappa B (NF- κ B) pathway and downregulates pro-inflammatory cytokines such as



interleukin-6 (IL-6), interleukin-1 β , and tumor necrosis factor-alpha (TNF- α). These cytokines are instrumental in promoting vascular injury and calcification through stimulation of osteogenic signaling pathways in vascular smooth muscle cells (VSMCs). By suppressing these pro-inflammatory mediators, vitamin D3 may help prevent the phenotypic switch of VSMCs from a contractile to an osteoblastic phenotype, a pivotal step in vascular calcification [15].

Oxidative stress and lipid peroxidation further link vitamin D3 deficiency to atherosclerosis and calcification. Reactive oxygen species (ROS) impair endothelial cell function, oxidize low-density lipoproteins (LDL), and activate macrophage infiltration within the arterial wall. Vitamin D3 supplementation has been shown to mitigate oxidative stress by upregulating antioxidant enzymes such as superoxide dismutase and catalase, thereby preserving endothelial homeostasis and reducing vascular inflammation. These antioxidant effects complement its role in calcium-phosphate metabolism, providing dual vascular protection [16].

Experimental studies demonstrate that vitamin D3 influences the expression of calcification inhibitors such as matrix Gla protein (MGP) and fetuin-A, both of which prevent ectopic calcium deposition. Reduced vitamin D3 levels are associated with downregulation of these inhibitors, thereby predisposing to vascular mineralization. Moreover, 1,25(OH) $_2$ D modulates osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) signaling, crucial pathways that regulate bone turnover and are increasingly implicated in vascular calcification. This overlapping molecular framework suggests that vitamin D3 deficiency may accelerate arterial calcification through dysregulation of bone-vascular axis signaling [17].

Finally, the cardioprotective effects of vitamin D3 may also extend to lipid metabolism. Deficiency is associated with higher triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol, and an atherogenic lipid profile. Restoration of vitamin D3 levels improves lipid parameters and reduces systemic inflammation, indicating a multifaceted contribution to cardiovascular risk modulation. Together, these mechanisms establish vitamin D3 as a potential metabolic biomarker and therapeutic target in the prevention and management of coronary artery disease [18].

Computed Tomography Coronary Artery Calcium Scoring: Principles and Prognostic Value

Coronary artery calcium (CAC) scoring, derived from non-contrast computed tomography (CT), has evolved into one of the most validated imaging biomarkers for subclinical atherosclerosis. The method quantifies calcified plaque burden within the coronary arteries and serves as a surrogate marker for total atherosclerotic load. Using the Agatston scoring system, first described in 1990, the CAC score is calculated based on the area and peak density of calcified lesions, expressed in Hounsfield units (HU). A CAC score of zero indicates the absence of detectable coronary calcification, while higher scores reflect increasing plaque burden and cardiovascular risk [19].

Technological advancements, particularly with multidetector computed tomography (MDCT), have improved image resolution and reduced radiation exposure, making CAC assessment a feasible and reliable screening tool. The reproducibility and rapid acquisition of CAC scoring enable its integration into risk stratification algorithms, particularly for asymptomatic individuals at intermediate cardiovascular risk. Studies from large population cohorts, such as the Multi-Ethnic Study of Atherosclerosis (MESA), have demonstrated that the CAC score provides incremental predictive value over traditional risk factors including hypertension, diabetes, and hyperlipidemia [20].

The prognostic significance of CAC scoring has been extensively validated across diverse populations. A zero CAC score is associated with an exceedingly low risk of cardiovascular events over 5–10 years, often referred to as the “power of zero.” Conversely, higher CAC scores, particularly above 300, predict markedly increased risk for myocardial infarction, stroke, and cardiovascular mortality. Importantly, the relationship between CAC score and risk is continuous, with even modest elevations conferring measurable increases in event rates. Thus, CAC scoring bridges the gap between risk factor profiling and direct visualization of disease burden [21].

In clinical practice, CAC scoring has been incorporated into several preventive cardiology guidelines to



refine therapeutic decisions. For instance, the 2018 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines recommend using CAC assessment to guide statin therapy in patients with borderline or intermediate risk. A CAC score of zero may allow deferral of pharmacotherapy, while elevated scores warrant more aggressive risk factor modification. This patient-centered approach underscores the value of imaging in personalized prevention strategies [22].

Beyond risk prediction, CAC scoring provides insights into the biology of atherosclerosis. Calcification typically represents a late stage of plaque development, often following periods of lipid accumulation, inflammation, and healing. However, it does not always indicate plaque stability. Microcalcifications within lipid-rich plaques may signify ongoing inflammatory activity and mechanical vulnerability, highlighting the complex relationship between calcium deposition and plaque behavior. Therefore, interpreting CAC in the context of overall cardiovascular risk and metabolic milieu remains crucial [23]. From a research perspective, serial CAC measurement offers a noninvasive means to evaluate atherosclerosis progression or regression in response to therapeutic interventions. Annualized increases in CAC scores have been correlated with residual cardiovascular risk despite optimal medical therapy. Although statin use can increase CAC density due to plaque stabilization and calcification, such changes often correspond with reduced event rates. These findings illustrate that the biological meaning of CAC progression must be interpreted carefully, considering both density and distribution rather than absolute volume alone [24].

Finally, combining CAC scoring with metabolic biomarkers—such as vitamin D3 levels—may enhance risk stratification by integrating structural and biochemical aspects of atherosclerosis. Vitamin D3 deficiency may influence vascular calcification dynamics, thereby altering CAC progression independent of conventional risk factors. Exploring this intersection between metabolic regulation and imaging-derived plaque characterization represents a promising frontier in contemporary cardiology [25].

The Interrelationship Between Vitamin D3 Levels and Coronary Calcium Scores

The relationship between serum vitamin D3 concentrations and coronary artery calcium (CAC) scoring has been the subject of growing scientific investigation over the past decade. While both serve as important biomarkers—vitamin D3 reflecting systemic metabolic status and CAC representing structural atherosclerotic burden—their correlation has yielded heterogeneous findings across studies. Several cross-sectional and cohort analyses suggest an inverse relationship, where lower vitamin D3 levels are associated with higher CAC scores, indicating increased vascular calcification and cardiovascular risk [26].

A landmark analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that individuals with serum 25-hydroxyvitamin D [25(OH)D] levels below 20 ng/mL had significantly greater odds of having measurable CAC compared with those with sufficient vitamin D3 status. This association persisted after adjustment for age, sex, ethnicity, and traditional cardiovascular risk factors, suggesting an independent link between vitamin D3 deficiency and coronary calcification [27]. Similarly, data from the Framingham Offspring Study reported that low vitamin D3 levels predicted incident cardiovascular events and higher baseline CAC scores, particularly among hypertensive individuals [28].

However, not all studies have confirmed this inverse association. Some analyses found a U-shaped relationship, where both low and high vitamin D3 levels correlated with greater CAC, implying that excessive supplementation might paradoxically promote vascular calcification. The Dallas Heart Study observed that very high serum vitamin D3 concentrations (>50 ng/mL) were associated with increased calcified plaque volume, suggesting a potential threshold effect beyond which the benefits of vitamin D3 may diminish [29]. These findings highlight the complexity of vitamin D3 physiology, where both deficiency and excess can disrupt calcium–phosphate homeostasis.

Mechanistically, several pathways have been proposed to explain the inverse relationship between vitamin D3 and CAC. Vitamin D3 deficiency enhances inflammatory cytokine expression, oxidative stress, and activation of the renin–angiotensin–aldosterone system (RAAS), all of which promote



vascular smooth muscle cell (VSMC) osteogenic transformation. This process accelerates calcium phosphate deposition within the arterial wall, reflected as elevated CAC scores. Conversely, sufficient vitamin D3 concentrations inhibit VSMC calcification by upregulating calcification inhibitors such as matrix Gla protein (MGP) and fetuin-A and by attenuating NF- κ B signaling [30].

Moreover, vitamin D3 plays a pivotal role in regulating serum calcium and phosphate balance, influencing the availability of mineral substrates for vascular deposition. In deficiency states, secondary hyperparathyroidism leads to elevated circulating phosphate and calcium-phosphate product, both potent promoters of medial calcification. This biochemical dysregulation may be particularly relevant in patients with chronic kidney disease (CKD), where reduced vitamin D3 activation and phosphate retention converge to accelerate vascular calcification and elevate CAC burden [31].

The interrelationship between vitamin D3 and CAC may also vary according to demographic and metabolic factors. Studies have shown that older age, obesity, diabetes, and chronic kidney disease can modify the strength of the association, likely due to differences in vitamin D3 metabolism, inflammation, and calcium handling. For example, individuals with obesity often exhibit lower circulating vitamin D3 levels due to its sequestration in adipose tissue, potentially amplifying vascular calcification risk despite normal dietary intake or supplementation [32].

Interestingly, interventional studies assessing the impact of vitamin D3 supplementation on CAC progression have produced mixed results. While some small trials have reported stabilization or slower progression of CAC with vitamin D3 repletion, others found no significant effect on calcification rates. The VITAL trial, a large randomized controlled study investigating vitamin D3 supplementation for primary prevention, did not demonstrate reductions in cardiovascular events or CAC progression over five years. These findings suggest that the timing, dose, and baseline vitamin D3 status may critically determine the vascular response [33].

Overall, current evidence supports a complex, potentially nonlinear association between vitamin D3 levels and coronary artery calcification. While vitamin D3 deficiency appears to contribute to the initiation and progression of vascular calcification, supraphysiologic levels may have neutral or even adverse effects. Future studies employing standardized vitamin D3 measurement, longitudinal CAC assessment, and controlled supplementation regimens are needed to clarify causality and optimal therapeutic targets in coronary artery disease [34].

Confounding Factors Influencing Both Vitamin D3 and Coronary Artery Calcification

The correlation between serum vitamin D3 status and coronary artery calcium (CAC) scores is influenced by a multitude of confounding factors, both biological and environmental, which can obscure true causal relationships. Understanding these modifiers is crucial when interpreting observational studies and designing interventional trials. Age, sex, ethnicity, obesity, renal function, and metabolic comorbidities all play pivotal roles in determining both vitamin D3 levels and calcification propensity [35].

Age represents one of the strongest determinants of both declining vitamin D3 levels and increasing CAC scores. With aging, skin synthesis of vitamin D3 decreases due to reduced 7-dehydrocholesterol content and diminished sun exposure, while arterial calcification progresses as a cumulative process driven by chronic inflammation and oxidative stress. Moreover, older adults often have lower dietary intake of vitamin D3 and reduced renal conversion to its active form, compounding deficiency risk. Simultaneously, age-related changes in vascular smooth muscle cell (VSMC) function and increased bone-vascular cross-talk enhance the likelihood of medial and intimal calcification [36].

Sex differences also influence this relationship. Men generally exhibit higher CAC scores compared to women at similar ages, potentially due to differences in hormonal regulation, lipid metabolism, and lifestyle factors. However, postmenopausal women experience a steep increase in both CAC and vitamin D3 deficiency prevalence, suggesting estrogen deficiency as a shared contributor to vascular calcification and impaired vitamin D3 metabolism. Estrogen has known vasoprotective effects, enhancing endothelial nitric oxide production and suppressing osteogenic signaling in the vasculature; thus, its decline may exacerbate the impact of low vitamin D3 levels on calcification progression [37].



Ethnicity and genetic variability significantly affect vitamin D3 bioavailability and CAC distribution. Individuals with darker skin pigmentation synthesize less vitamin D3 from sunlight due to melanin-mediated ultraviolet B absorption, predisposing to chronic insufficiency. Paradoxically, some studies report lower CAC prevalence among African Americans despite lower vitamin D3 levels, suggesting that genetic factors, calcium handling, and inflammatory responses may modulate this interplay. Polymorphisms in vitamin D receptor (VDR) and vitamin D-binding protein genes further influence serum levels, receptor sensitivity, and downstream signaling, thereby introducing population-specific variability in the vitamin D3–CAC relationship [38].

Obesity represents another key confounder linking vitamin D3 deficiency with vascular calcification. Adipose tissue acts as a reservoir for fat-soluble vitamin D3, reducing its bioavailability in circulation. Additionally, obesity is associated with chronic low-grade inflammation, dyslipidemia, and insulin resistance—pathophysiological states that accelerate atherosclerosis and calcification. Studies have demonstrated that obese individuals have both lower serum 25(OH)D levels and higher CAC scores independent of age and sex, implying that adiposity mediates much of the apparent correlation between vitamin D3 deficiency and CAC burden [39].

Renal function is a crucial determinant of both vitamin D3 metabolism and vascular calcification. In chronic kidney disease (CKD), impaired renal 1 α -hydroxylase activity leads to reduced synthesis of active 1,25(OH) $_2$ D, contributing to secondary hyperparathyroidism and elevated phosphate retention. These disturbances drive vascular smooth muscle cell osteogenic transformation and accelerate medial calcification, resulting in elevated CAC scores. Moreover, uremic toxins and fibroblast growth factor-23 (FGF-23) further suppress vitamin D3 activation, creating a vicious cycle that perpetuates calcific burden. This CKD–mineral bone disorder (CKD-MBD) paradigm underscores the interdependence of mineral metabolism and vascular pathology [40].

Metabolic syndrome and diabetes mellitus exert additional confounding influences. Insulin resistance, chronic hyperglycemia, and oxidative stress promote both vitamin D3 depletion and vascular calcification through inflammatory and metabolic pathways. Low vitamin D3 levels correlate with impaired pancreatic β -cell function and reduced insulin sensitivity, while glycation end-products and lipotoxicity enhance osteogenic activity in the arterial wall. Consequently, diabetic patients frequently present with concomitant hypovitaminosis D and elevated CAC scores, complicating causal interpretation [41].

Lifestyle and environmental factors, including sun exposure, dietary habits, and physical activity, further contribute to variability in both vitamin D3 levels and coronary calcification. Individuals with limited outdoor activity or residing in higher latitudes experience reduced cutaneous synthesis of vitamin D3, while sedentary lifestyles and poor dietary patterns simultaneously increase cardiovascular risk. Thus, the association between low vitamin D3 and high CAC may partly reflect shared lifestyle determinants rather than direct causality [42].

In summary, multiple confounders—spanning biological, genetic, and environmental domains—modulate the observed relationship between vitamin D3 deficiency and coronary calcification. Disentangling these overlapping influences is essential for accurate interpretation of epidemiologic data and for designing interventional studies capable of isolating the independent role of vitamin D3 in vascular health. Future research should incorporate multivariable models adjusting for these confounders and explore stratified analyses by metabolic status, ethnicity, and renal function to refine causal inference [43].

Clinical Implications and Future Perspectives

The growing body of evidence linking vitamin D3 deficiency to increased coronary artery calcium (CAC) burden has significant implications for cardiovascular prevention, risk stratification, and potential therapeutic strategies. While CAC scoring has already established itself as a cornerstone in noninvasive atherosclerosis assessment, integrating biochemical markers such as vitamin D3 could enhance the predictive accuracy of cardiovascular models, particularly in populations at intermediate risk [44].



Clinically, the potential role of vitamin D3 measurement lies in its ability to complement imaging-based risk assessment. Patients with suboptimal serum 25-hydroxyvitamin D [25(OH)D] levels and elevated CAC scores may represent a phenotype of metabolically active atherosclerosis characterized by heightened inflammation and vascular calcification. Identifying this subgroup could refine therapeutic decision-making, guiding clinicians toward more intensive lifestyle modification, lipid-lowering therapy, and closer follow-up. Conversely, individuals with adequate vitamin D3 levels and low CAC scores may benefit from a more conservative approach, thereby reducing overtreatment [45].

The therapeutic potential of vitamin D3 supplementation in modulating vascular calcification and coronary risk remains an area of active debate. Observational studies have shown inverse associations between vitamin D3 levels and cardiovascular events, yet randomized controlled trials have yielded inconsistent results. The VITAL and ViDA trials, two of the largest interventional studies to date, demonstrated that routine vitamin D3 supplementation did not significantly reduce major adverse cardiovascular events in the general population. However, these studies were not specifically designed to evaluate patients with established CAD or progressive CAC, limiting their applicability to this context [46].

Smaller mechanistic trials have provided more promising data. In patients with chronic kidney disease, vitamin D3 analogs such as calcitriol and paricalcitol have shown partial improvements in vascular compliance and endothelial function, though without consistent reductions in CAC progression. Similarly, observational analyses suggest that moderate vitamin D3 supplementation (1,000–2,000 IU/day) may help stabilize calcific lesions by improving endothelial integrity and suppressing osteogenic signaling. Nevertheless, the dose–response relationship remains unclear, and excessive supplementation may paradoxically enhance calcification through hypercalcemia or elevated phosphate product [47].

Given these uncertainties, personalized supplementation strategies are increasingly advocated. Baseline vitamin D3 measurement should precede therapy, and correction should aim to achieve sufficiency (serum 25(OH)D levels of 30–50 ng/mL) rather than supraphysiologic concentrations. Individual factors such as renal function, calcium–phosphate metabolism, and concomitant statin therapy must also be considered, as they influence both vitamin D3 bioavailability and calcification dynamics. Future clinical trials stratified by baseline CAC burden, vitamin D3 status, and comorbidities are warranted to delineate optimal therapeutic thresholds and treatment durations [48].

Beyond supplementation, the interplay between vitamin D3 and CAC underscores the need for integrative cardiovascular risk assessment. Combining biochemical, imaging, and clinical data could enable precision-medicine models capable of identifying individuals at greatest risk for rapid atherosclerosis progression. For example, a composite “metabolic–imaging score” incorporating serum vitamin D3, CAC, and inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) could refine predictive algorithms beyond traditional risk scores. Such approaches would bridge the gap between metabolic dysregulation and structural vascular disease [49].

The future of this research field also lies in molecular and translational exploration. Advanced imaging techniques—such as positron emission tomography (PET) with sodium fluoride (NaF) tracers—may help visualize active microcalcification and correlate it with vitamin D3-related metabolic activity. Genomic and proteomic studies could identify specific vitamin D3-responsive pathways influencing vascular calcification, including those involving fibroblast growth factor-23 (FGF-23), Klotho, and osteoprotegerin. These insights may pave the way for targeted pharmacologic interventions aimed at modulating the calcification process [50].

In the clinical realm, the intersection of vitamin D3 biology and coronary calcium assessment encourages a paradigm shift toward metabolic cardiology—where hormonal, nutritional, and inflammatory factors are considered alongside anatomic imaging in managing coronary artery disease. Such multidimensional strategies have the potential to improve early detection, personalize treatment, and ultimately reduce cardiovascular morbidity and mortality [51].



Conclusion

The interplay between vitamin D3 status and coronary artery calcium (CAC) burden represents a dynamic interface between metabolic regulation and structural vascular pathology. Evidence accumulated over the past decade strongly suggests that vitamin D3, long regarded primarily as a regulator of bone and mineral metabolism, plays a far more extensive role in cardiovascular health. Its effects on endothelial function, vascular smooth muscle cell differentiation, inflammation, and oxidative balance provide plausible mechanistic pathways linking vitamin D3 deficiency with the progression of atherosclerotic calcification.

Coronary calcium scoring has emerged as one of the most reliable noninvasive tools for quantifying atherosclerotic plaque burden and predicting future cardiovascular risk. Yet, despite its diagnostic precision, it remains a structural biomarker, reflecting the cumulative outcome of multiple metabolic and inflammatory influences. Integrating biochemical markers such as serum vitamin D3 concentration with CAC scoring could therefore enhance the granularity of cardiovascular risk assessment, bridging metabolic and imaging dimensions of disease.

The relationship between vitamin D3 and coronary calcification appears to be complex and likely bidirectional. Deficiency promotes vascular injury and calcification through multiple mechanisms—ranging from inflammatory activation and renin–angiotensin system upregulation to dysregulated calcium–phosphate balance—while excessive supplementation may paradoxically augment calcific deposition. Thus, maintaining optimal physiological levels rather than pursuing supraphysiologic correction is essential to preserving vascular integrity.

From a clinical standpoint, individualized assessment of vitamin D3 status in conjunction with CAC scoring may enable earlier identification of patients at risk for accelerated atherosclerosis and facilitate tailored preventive strategies. However, current evidence remains insufficient to support routine supplementation solely for the purpose of reducing coronary calcification. Future longitudinal and interventional studies are needed to clarify causality, define optimal serum targets, and determine whether vitamin D3 correction can meaningfully alter CAC progression and cardiovascular outcomes. In essence, the intersection of endocrinology and imaging provides a unique opportunity to redefine cardiovascular risk stratification. By considering vitamin D3 not only as a nutritional or skeletal factor but as a vascular modulator, clinicians may gain deeper insight into the metabolic underpinnings of coronary artery disease. This integrative approach, blending metabolic, inflammatory, and anatomical perspectives, offers a promising pathway toward more personalized and effective cardiovascular prevention.

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