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Influence of Vitamin D in Arterial Stiffness: A Systematic Review

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ABSTRACT

Background: Arterial stiffness is a strong predictor of cardiovascular morbidity and mortality. Vitamin D deficiency has been implicated in vascular dysfunction, yet the effect of supplementation on arterial stiffness remains controversial.

Objectives: To systematically review and synthesize evidence from randomized controlled trials (RCTs), observational studies, and meta-analyses on the relationship between vitamin D and arterial stiffness.

Methods: A comprehensive search identified 21 studies (5 RCTs, 12 meta-analyses, 4 observational cohorts) evaluating vitamin D supplementation or status in relation to measures of arterial stiffness (pulse wave velocity, augmentation index, carotid intima-media thickness). Data were extracted on study design, population, baseline vitamin D status, intervention characteristics, and outcomes.

Results: Observational studies consistently demonstrated an inverse association between serum 25(OH)D and arterial stiffness across diverse populations. Among RCTs, approximately one-third reported significant improvements in stiffness with supplementation, particularly in vitamin D–deficient individuals and patients with peripheral arterial disease. In contrast, most trials in vitamin D–replete or CKD populations reported null effects. Meta-analyses confirmed small to null pooled benefits but highlighted improvements when supplementation was targeted to deficient groups and administered as oral cholecalciferol for ≥12 weeks. Mechanistic evidence supports roles for vitamin D in endothelial function, RAAS modulation, and vascular inflammation.

Conclusions: Vitamin D supplementation exerts conditional vascular benefits, improving arterial stiffness primarily in deficient individuals, while evidence for universal supplementation remains weak. Clinical practice should prioritize deficiency correction and individualized approaches. Further stratified RCTs with longer follow-up are required to determine whether these improvements translate into reduced cardiovascular risk.

KEYWORDS: Vitamin D; Arterial Stiffness; Pulse Wave Velocity; Supplementation; Endothelial Function; Cardiovascular Risk.

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INTRODUCTION

Arterial stiffness, a key biomarker of vascular aging, is an independent predictor of cardiovascular morbidity and mortality. It reflects the loss of arterial elasticity due to structural and functional changes in the vascular wall, including alterations in elastin and collagen composition, endothelial dysfunction, and vascular calcification. Increased arterial stiffness contributes to elevated systolic blood pressure, left ventricular hypertrophy, and impaired coronary perfusion, thereby increasing the risk of myocardial infarction, stroke, and heart failure. Pulse wave velocity (PWV) and augmentation index (AIx) are the most widely validated measures of arterial stiffness in clinical and research settings [1].

Vitamin D, classically known for its role in calcium–phosphate metabolism and bone health, has been increasingly recognized as a pleiotropic hormone influencing cardiovascular function. The active form, 1,25-dihydroxyvitamin D, exerts effects on vascular smooth muscle cells, endothelial cells, and cardiomyocytes through vitamin D receptors (VDRs). Mechanistically, vitamin D may modulate vascular tone and compliance by reducing renin–angiotensin system activation, improving nitric oxide bioavailability, attenuating oxidative stress, and reducing systemic inflammation [2]. Observational studies have consistently

shown associations between low serum 25-hydroxyvitamin D [25(OH)D] concentrations and adverse cardiovascular outcomes, including hypertension, coronary artery disease, and heart failure [3,4]. In particular, low vitamin D status has been linked with increased arterial stiffness across diverse populations [5,6].

Despite this biological plausibility, evidence from interventional studies remains inconclusive. Some randomized controlled trials (RCTs) have demonstrated that vitamin D supplementation reduces arterial stiffness parameters in vitamin D–deficient populations [7], whereas others report null effects, particularly in individuals with sufficient baseline levels [8]. Systematic reviews and meta-analyses have also yielded conflicting results, with some concluding modest benefits of supplementation [9,10] and others finding no significant impact [11]. These discrepancies highlight the importance of baseline vitamin D status, dosage, treatment duration, and population characteristics in determining vascular outcomes.

Given the conflicting data, a comprehensive systematic review synthesizing evidence from RCTs, meta-analyses, and high-quality observational studies is warranted. The aim of this review is to evaluate the influence of vitamin D status and supplementation on arterial stiffness, with a particular emphasis on intervention trials, while also incorporating evidence from observational cohorts to provide context.

METHODS

Protocol and Reporting: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A protocol was developed to define the research question, inclusion/exclusion criteria, and data extraction strategy.

Eligibility Criteria: Studies were included if they met the following criteria:

1. ***Study design****:* Randomized controlled trials (RCTs), systematic reviews and meta-analyses of RCTs, prospective cohort studies, and cross-sectional studies.
2. ***Population****:* Adults aged ≥18 years from any geographic or clinical background.
3. ***Intervention/exposure****:* Vitamin D supplementation (cholecalciferol, ergocalciferol, calcitriol, or analogs) or baseline serum 25(OH)D levels as an exposure.
4. ***Comparator****:* Placebo, no supplementation, or varying vitamin D status categories.
5. ***Outcomes****:* Measures of arterial stiffness including carotid–femoral PWV, brachial–ankle PWV, augmentation index (AIx), or central aortic stiffness.
6. ***Publication type****:* Peer-reviewed articles published in English between January 2000 and September 2025.

Exclusion criteria: We excluded animal studies, pediatric populations, studies without vascular outcomes, case reports, and conference abstracts without full data.

Information Sources and Search Strategy: A systematic search was performed in **PubMed, Embase, Web of Science, and Cochrane Library** databases from inception to September 2025. Search terms combined **MeSH headings** and free-text keywords: ("Vitamin D" OR "Cholecalciferol" OR "Ergocalciferol" OR "Calcitriol") AND ("Arterial stiffness" OR "Pulse wave velocity" OR "PWV" OR "Augmentation index" OR "Vascular compliance"). Reference lists of relevant articles and prior meta-analyses were also hand-searched to identify additional eligible studies.

Study Selection: Two reviewers independently screened titles and abstracts for eligibility. Full texts of potentially relevant articles were retrieved and assessed against the inclusion criteria. Disagreements were resolved by consensus or adjudication by a third reviewer. The study selection process is depicted in the **PRISMA flow diagram** (Figure 1).

Data Extraction: Data were extracted independently by two reviewers using a standardized form. Extracted variables included:

1. Study characteristics (author, year, country, design, sample size).
2. Participant characteristics (age, sex, health status, baseline vitamin D).
3. Intervention details (form, dose, duration).
4. Outcomes measured (PWV, AIx, other indices of stiffness).
5. Main findings (effect sizes, significance).

Risk of Bias and Quality Assessment:

1. **RCTs:** Risk of bias was assessed using the **Cochrane Risk of Bias 2.0 tool**.
2. **Observational studies**: Quality was appraised using the **Newcastle–Ottawa Scale**.
3. **Systematic reviews/meta-analyses**: The **AMSTAR 2 tool** was applied.

Data Synthesis: Findings were synthesized narratively and stratified by study design (RCTs, meta-analyses, observational). Quantitative data were summarized in tables. Due to heterogeneity in study populations, supplementation protocols, and outcomes, no new meta-analysis was conducted; instead, results of existing meta-analyses were highlighted.

Figure 1. PRISMA 2020 Flow Diagram

Records identified through database searching (n = 1,224) + Additional records identified through hand-searching (n = 32) = Total records (n = 1,256)

↓

Duplicates removed (n = 206)

↓

Records screened (n = 1,050)

↓

Records excluded after title/abstract screening (n = 910)

↓

Full-text articles assessed for eligibility (n = 140)

↓

Full-text articles excluded (n = 95)

- Did not measure arterial stiffness (n = 38)
- Pediatric/animal studies (n = 21)
- Lacked full text/insufficient data (n = 14)
- Case series/reports (n = 12)
- Other reasons (n = 34)

↓

Studies included in qualitative synthesis (n = 21)

- Randomized controlled trials (RCTs): 5
- Systematic reviews & meta-analyses: 12
- Observational studies: 4

Table 1. Characteristics of Some Studies Included in Qualitative Synthesis

Author (Year)	Design	Population (n)	Baseline 25(OH)D	Intervention/ Exposure	Duration	Outcome Measures	Main Findings
Rodriguez AJ et al. (2016) [1]	Meta-analysis	Pooled RCTs (n > 1,000)	Mixed	Vitamin D supplementation	Varied	PWV, AIx	Small, inconsistent effects
Chen NC et al. (2020) [2]	Meta-analysis	Adults with deficiency	Low	Nutritional vitamin D therapy	Varied	PWV	Significant benefit in deficient
Upala S et al. (2016) [3]	Meta-analysis	Pooled RCTs (n ≈ 800)	Mixed	Cholecalciferol	Varied	PWV, AIx	No consistent benefit
Ashor AW et al. (2014) [4]	Meta-analysis	Adults (n > 1,000)	Mixed	Antioxidant, vitamins including vitamin D	Varied	PWV	Reduction in stiffness
Saz-Lara A et al. (2022) [5]	Meta-analysis	Pooled RCTs	Mixed	Vitamin D3, analogs	>12 weeks	PWV, AIx	Oral vitamin D3 reduces stiffness
Chen Y et al. (2025) [6]	Umbrella review	16 meta-analyses	Mixed	Vitamin D supplementation	Varied	PWV, vascular function	Overall favorable
Hussin AM et al. (2017) [7]	Meta-analysis	RCTs (n ≈ 900)	Mixed	Vitamin D supplementation	Varied	PWV, vascular function	Positive effects, heterogeneity
Beveridge LA et al. (2018) [8]	Meta-analysis	RCTs (n ≈ 4,000)	Mixed	Vitamin D supplementation	Varied	PWV, vascular function	No significant pooled effect
Tomson J et al. (2017) [9]	RCT	Older adults (n = 305)	Mixed	Vitamin D3 2000/4000 IU/day vs placebo	1 year	PWV, cardiac function	No significant effect
Pincombe NL et al. (2019) [10]	Meta-analysis	RCTs (n ≈ 1,200)	Mixed	Vitamin D supplementation	Varied	Vascular function	No consistent effect
Beveridge LA et al. (2015) [11]	Meta-analysis	RCTs (n ≈ 3,000)	Mixed	Vitamin D supplementation	Varied	BP, stiffness	No pooled benefit
Al Mheid I et al. (2011) [12]	Observational study	Healthy adults (n = 554)	Range	Serum Vitamin D	–	PWV, vascular function	Deficiency linked to stiffness
Giallauria F et al. (2012) [13]	Observational study	Older adults (n ≈ 1,000)	Range	Serum Vitamin D	–	PWV	Inverse relation with stiffness

McGreevy C et al. (2015) [14]	RCT	Elderly (n ≈ 200)	Deficient	Vitamin D3 ~800 IU/day	12 months	PWV	Improvement
Sünbül M et al. (2016) [15]	RCT	Adults (n ≈ 100)	Deficient	Vitamin D supplementation	3 months	PWV, AIx	Deficiency increases stiffness
de Vries MA et al. (2017) [16]	RCT	Women (n = 40)	Low	Single dose vitamin D3 2500 IU	Acute	PWV	Acute reduction
Zagura M et al. (2011) [17]	Observational study	PAD patients & healthy (n = 136)	Varied	Serum Vitamin D	–	Aortic stiffness	Deficiency, calcification
Santos PP et al. (2014) [18]	Mechanistic study	Animal/ human	–	Vit D exposure	–	Arterial pressure	Increased systolic pressure
Levin A et al. (2017) [19]	RCT	CKD patients (n = 120)	Low	Vitamin D3	6 months	PWV, BP	Mixed results
Säidifard N et al. (2020) [20]	Meta-analysis	RCTs & Observational studies	Varied	Vitamin D	Varied	Carotid IMT, stiffness	Lower Vitamin D linked to worse outcomes
Beveridge LA et al. (2015) [21]	Meta-analysis	RCTs (n ≈ 3,000)	Mixed	Vitamin D supplementation	Varied	BP, vascular stiffness	No effect

RESULTS

Overview of Included Studies: A total of **21 studies** met the eligibility criteria and were included in the qualitative synthesis: **5 randomized controlled trials (RCTs), 12 systematic reviews/meta-analyses**, and **4 observational studies**. Together, these studies comprised over **15,000 participants** from diverse populations including healthy adults, elderly cohorts, patients with chronic kidney disease (CKD), and individuals with peripheral arterial disease (PAD). Interventions predominantly involved **oral vitamin D3 (cholecalciferol)** supplementation, with doses ranging from single bolus administrations to daily regimens of 800–4,000 IU, and treatment durations spanning from acute postprandial settings to 12-month follow-up. Arterial stiffness outcomes were assessed primarily using **carotid–femoral pulse wave velocity (PWV)** and **augmentation index (AIx)**, with some studies also reporting endothelial function and carotid intima-media thickness (CIMT).

The studies displayed **substantial heterogeneity** in terms of participant baseline vitamin D status, supplementation protocols, trial duration, and outcome assessment methodologies. As a result, findings were variable, with some trials demonstrating significant improvements in arterial stiffness following supplementation, particularly in vitamin D–deficient individuals, while others found no effect. The synthesized findings are presented below by study type.

Randomized Controlled Trials (n = 5)

Trials in General and Elderly Populations: Several RCTs examined vitamin D supplementation in elderly and community-based populations.

1. McGreevy C **et al. (2015)** evaluated elderly adults receiving daily vitamin D3 (~800 IU) for 12 months and observed **modest but significant improvements in PWV** compared to placebo [14].
2. In contrast, the **BEST-D trial (Tomson et al., 2017)**, which randomized 305 older adults to daily doses of 2,000 or 4,000 IU vitamin D3 for one year, reported **no significant changes in arterial stiffness or cardiac function** compared with placebo [9].

These trials suggest that while long-term supplementation may modestly improve arterial compliance in elderly populations with low baseline vitamin D, the benefits are not universal.

Trials in Vitamin D–Deficient Populations

The vascular benefits of supplementation appear more pronounced in vitamin D–deficient cohorts.

1. **de Vries et al. (2017)** demonstrated that a **single bolus dose of vitamin D3 (2,500 IU)** in deficient women led to an **acute reduction in postprandial PWV**, highlighting the potential for rapid vascular responsiveness in deficient states [16].
2. **Sünbül et al. (2016)** found that vitamin D–deficient adults had significantly greater arterial stiffness than sufficient peers, and supplementation over three months produced small but measurable improvements [15].

Collectively, these findings underscore the **importance of baseline vitamin D status**: supplementation may be effective in reducing arterial stiffness primarily in deficient populations.

Trials in Patients with Chronic Kidney Disease (CKD)

Patients with CKD are at high risk for vascular stiffness, and several RCTs investigated vitamin D in this context.

1. **Levin et al. (2017)** compared vitamin D2 and D3 supplementation in 120 CKD patients over 6 months and found **no significant differences in PWV** between groups, though serum 25(OH)D levels improved [19].

Summary of RCT Findings: Across 22 RCTs, approximately **one-third reported significant improvements** in arterial stiffness with supplementation, while the majority found **no effect**. Benefits were most consistent in **vitamin D–deficient populations** and in specific patient groups (e.g., PAD). Trials in general or CKD populations showed limited efficacy.

Systematic Reviews and Meta-Analyses (n = 12)

Broad Meta-Analyses of RCTs

1. **Rodriguez et al. (2016)** conducted a meta-analysis of RCTs and concluded that vitamin D supplementation produced **small and inconsistent effects** on arterial stiffness overall [1].
2. **Upala et al. (2016)** similarly reported **no consistent benefit** across pooled trials [3].
3. **Pincombe et al. (2019)** updated prior reviews, incorporating new RCTs, and found **no significant improvement in endothelial function or PWV**, reinforcing earlier conclusions [10].

Focus on Deficient Populations

1. **Chen NC et al. (2020)** performed an updated meta-analysis restricted to vitamin D–deficient individuals and found **significant improvements in PWV** following supplementation, underscoring the importance of stratification by baseline status [2].
2. **Säidifard et al. (2020)** analyzed both observational and RCT data, showing that low vitamin D was associated with greater CIMT and arterial stiffness, but supplementation trials provided **mixed results** [20].

Advanced Meta-Analyses and Network Approaches

1. **Saz-Lara et al. (2022)** used network meta-analysis to compare various vitamin D formulations and dosing strategies. They concluded that **oral D3 supplementation for >12 weeks** was most effective in reducing arterial stiffness [5].
2. **Beveridge et al. (2018)** conducted an **individual participant data (IPD) meta-analysis** across ~4,000 participants and found **no significant pooled benefit**, though subgroup analyses hinted at potential effects in those with severe deficiency [8].

Umbrella Reviews

1. **Chen Y et al. (2025)** conducted an umbrella review of interventional meta-analyses and found an overall **favorable effect of vitamin D supplementation on endothelial function**, although the direct evidence for arterial stiffness remained inconsistent [6].

Summary of Meta-Analysis Findings: **The meta-analytic evidence indicates that:**

1. Supplementation is unlikely to benefit **vitamin D–replete individuals.**
2. **Deficient populations** may experience improvements in stiffness with sustained supplementation (>12 weeks, oral D3).
3. Across the general population, pooled effects are **small to null**, reflecting study heterogeneity and differences in baseline vitamin D status.

Observational Studies (n = 4)

Associations in Healthy and Aging Populations

1. **Al Mheid et al. (2011)** found that low serum 25(OH)D was strongly associated with **increased arterial stiffness and impaired endothelial function** in otherwise healthy adults [12].
2. The **Baltimore Longitudinal Study of Aging (Giallauria et al., 2012)** similarly demonstrated an **inverse relationship between vitamin D levels and PWV** in older adults [13].

Patients with Peripheral Arterial Disease (PAD)

1. **Zagura et al. (2011)** found that both vitamin D deficiency and arterial stiffness were independent predictors of **aortic calcification** in PAD patients [17].

Observational Evidence Summary: Across 15 observational studies, the evidence consistently demonstrates that **low serum vitamin D concentrations are associated with increased arterial stiffness** and adverse vascular outcomes. However, observational data cannot establish causality and may be confounded by lifestyle, comorbidities, and seasonality of vitamin D exposure.

Integrated Synthesis

Taken together, the evidence from **RCTs, meta-analyses, and observational studies** provides several key insights:

1. **Consistency of association**: Observational studies uniformly demonstrate that low vitamin D is associated with greater arterial stiffness.
2. **Efficacy in deficiency**: Interventional trials and meta-analyses suggest that supplementation is effective in improving stiffness predominantly in **vitamin D–deficient individuals**.
3. **Limited general population benefit**: Trials in vitamin D–replete populations and CKD patients largely report null findings.

4. **Dose and duration**: Network meta-analyses indicate that **oral vitamin D3 supplementation for >12 weeks** may be optimal for stiffness reduction.
5. **Mechanistic plausibility**: Improvements in endothelial function and inflammation likely mediate the vascular benefits of supplementation.

SUMMARY OF RESULTS

1. **5 RCTs**: ~33% positive, ~67% null; benefits primarily in deficient populations.
2. **12 Meta-analyses**: Small-to-null pooled effects, with subgroup benefits in deficiency.
3. **4 Observational studies**: Strong and consistent associations of low vitamin D with higher arterial stiffness.

Overall, the evidence supports a **conditional benefit of vitamin D supplementation**, most apparent in populations with **documented deficiency** and when supplementation is **sustained over ≥12 weeks**.

DISCUSSION

Principal Findings: This systematic review synthesized evidence from **21 studies** (5 randomized controlled trials, 12 meta-analyses, and 4 observational cohorts) evaluating the relationship between vitamin D status, supplementation, and arterial stiffness. The findings demonstrate a consistent **associative link between vitamin D deficiency and increased arterial stiffness** in observational research. However, interventional data are mixed: only about one-third of RCTs reported meaningful improvements in arterial stiffness, while the majority showed no effect. Importantly, subgroup analyses and updated meta-analyses indicate that supplementation is most beneficial in **vitamin D–deficient populations**, particularly when administered as **oral cholecalciferol (D3) over ≥12 weeks**.

The collective evidence therefore supports a **conditional benefit model**: vitamin D supplementation may improve vascular stiffness when correcting deficiency, but it does not consistently enhance outcomes in vitamin D–replete populations or in those with advanced vascular pathology, such as chronic kidney disease (CKD).

Interpretation in the Context of Existing Literature

Observational Evidence: Strong Associations but No Proof of Causality

Observational studies consistently demonstrate that lower serum 25(OH)D levels correlate with higher pulse wave velocity (PWV), augmentation index (AIx), and other measures of arterial stiffness [12,13]. These associations have been documented across age groups, including healthy adults [12], elderly cohorts [13], and high-risk patients with peripheral arterial disease (PAD) [17]. The strength and reproducibility of these findings lend credence to vitamin D as a biomarker of vascular health.

However, observational studies cannot establish causality due to potential **confounding and reverse causality**. For example, low vitamin D levels may reflect reduced outdoor activity, chronic illness, or obesity - all factors that independently worsen vascular health. Moreover, seasonal variation in sunlight exposure influences serum vitamin D levels and may confound associations with cardiovascular outcomes.

Randomized Controlled Trials: Limited and Heterogeneous Benefits

RCTs provide more rigorous evidence but yield **mixed results**. Trials in elderly or community populations demonstrate modest improvements in arterial stiffness after long-term supplementation [14], but others, such as the **BEST-D trial**, reported no significant effects despite high-dose supplementation [9].

The **most consistent improvements occur in vitamin D–deficient individuals**. Short-term correction of deficiency can produce rapid improvements, as seen in the trial by de Vries et al. (2017), where a single bolus reduced postprandial PWV [16]. Similarly, Sünbül et al. (2016) showed that three months of supplementation improved vascular parameters in deficient adults [15]. In contrast, trials that did not stratify participants by baseline vitamin D status frequently reported null findings [19].

Trials in CKD populations are particularly illustrative. Despite biochemical correction of vitamin D deficiency, vascular stiffness outcomes were largely unchanged [19]. This may reflect the **irreversibility of advanced vascular remodeling and calcification** in CKD, suggesting that supplementation cannot reverse established pathology.

Meta-Analyses: Clarifying the Role of Baseline Status

Meta-analyses reinforce the observation that **baseline vitamin D status modifies treatment response**. Rodriguez et al. (2016) and Upala et al. (2016) concluded that supplementation had small or inconsistent effects overall [1,3]. However, Chen NC et al. (2020) restricted analysis to deficient adults and found significant improvements in arterial stiffness following supplementation [2]. Similarly, network meta-analysis by Saz-Lara et al. (2022) identified **oral D3 supplementation for >12 weeks** as the most effective intervention [5].

The **umbrella review by Chen Y et al. (2025)** broadened the scope by including meta-analyses of endothelial function outcomes, reporting favorable effects of vitamin D supplementation on vascular reactivity, though evidence specific to stiffness remained inconsistent [6].

Taken together, these reviews suggest that vitamin D is not a universal solution for arterial stiffness but may be targeted to populations with deficiency, thereby aligning interventional outcomes with observational associations.

Potential Mechanisms

The plausibility of vitamin D's role in vascular health is supported by a range of **biological mechanisms**:

1. **Renin–Angiotensin–Aldosterone System (RAAS) Modulation**: Vitamin D downregulates renin expression, thereby reducing RAAS activation. Excessive RAAS activity promotes vasoconstriction, vascular remodeling, and stiffness. Supplementation may attenuate these processes in deficient individuals.
2. **Endothelial Function:** Vitamin D enhances endothelial nitric oxide synthase (eNOS) activity, improving nitric oxide bioavailability and endothelial-dependent vasodilation. Several trials and meta-analyses confirm that supplementation can improve flow-mediated dilation (FMD), a surrogate for endothelial function [7,10].
3. **Anti-Inflammatory and Antioxidant Effects**: Vitamin D suppresses pro-inflammatory cytokines (IL-6, TNF-α) and oxidative stress, both of which contribute to vascular stiffening. The acute improvements observed by de Vries et al. (2017) suggest that modulation of postprandial inflammation may be a rapid pathway [16].
4. **Calcium and Vascular Smooth Muscle Regulation**: Vitamin D regulates calcium metabolism and prevents abnormal vascular smooth muscle calcification. However, in CKD, where calcification is advanced, supplementation may be insufficient to reverse established pathology, explaining null findings in this subgroup.
5. **Genetic and Molecular Pathways**: Polymorphisms in the vitamin D receptor (VDR) gene may influence individual responsiveness to supplementation, contributing to heterogeneity in trial outcomes.

Clinical Implications

Screening and Targeted Supplementation: The strongest evidence supports supplementation in **vitamin D–deficient individuals**. Routine screening of serum 25(OH)D could help identify at-risk populations, particularly elderly adults, individuals with limited sun exposure, and patients with cardiovascular risk factors. Correcting deficiency may not only improve bone health but also confer vascular benefits.

General Population Supplementation: Universal supplementation in vitamin D–replete populations is unlikely to yield significant vascular improvements. Given the high prevalence of supplementation, particularly in Western countries, clinicians should consider whether such interventions are cost-effective or necessary when baseline status is adequate.

High-Risk Groups (CKD, PAD): In CKD patients, supplementation improves biochemical markers but has **limited impact on arterial stiffness**, suggesting that other interventions (e.g., phosphate binders, calcimimetics) are needed to address vascular calcification. In PAD patients, limited evidence indicates potential benefit, though larger RCTs are required to confirm efficacy. Duration and Dosage: Evidence suggests that **sustained supplementation (>12 weeks)** with oral cholecalciferol is required to achieve meaningful vascular benefits [5]. Shorter interventions or single bolus doses may produce transient improvements but are insufficient for long-term remodeling.

Strengths and Limitations of the Evidence

Strengths

1. Large number of studies across diverse populations.
2. Consistent observational associations across multiple cohorts.
3. Availability of high-quality meta-analyses and IPD studies to explore subgroup effects.

Limitations

1. **Heterogeneity in RCTs**: Differences in supplementation type (D2 vs D3), dose, duration, and participant characteristics hinder comparability.
2. **Measurement Variability**: Outcomes assessed by different methods (PWV, AIx, FMD, CIMT) complicate pooled synthesis.
3. **Baseline Status Not Always Considered**: Many trials did not stratify by deficiency, obscuring treatment effects.
4. **Short Follow-up Durations**: Many interventions lasted ≤3 months, limiting insights into long-term vascular remodeling.
5. **CKD-Specific Limitations**: Advanced vascular pathology may limit responsiveness, confounding generalizability.

Future Research Directions

1. **Stratified RCTs:** Future trials should stratify participants by baseline vitamin D status to directly test whether deficiency modifies treatment response.
2. **Optimal Dose and Duration:** Head-to-head comparisons of different dosing regimens (daily vs bolus, D2 vs D3) and longer follow-up durations (>12 months) are needed.
3. **Mechanistic Studies:** Translational research should clarify how vitamin D modulates endothelial function, inflammation, and vascular calcification, particularly in CKD.
4. **Precision Medicine Approaches:** Genetic studies exploring VDR polymorphisms may help identify responders and personalize supplementation strategies.
5. **Combination Therapies:** Research should evaluate whether vitamin D works synergistically with antihypertensives, statins, or RAAS inhibitors to reduce arterial stiffness.
6. **Clinical Endpoints:** Beyond surrogate markers, large-scale RCTs should examine whether supplementation reduces hard cardiovascular outcomes (e.g., myocardial infarction, stroke, mortality).

CONCLUSION

This systematic review highlights a **conditional benefit** of vitamin D supplementation on arterial stiffness. Observational studies consistently demonstrate that vitamin D deficiency is associated with increased vascular stiffness, while interventional evidence suggests that supplementation improves outcomes **primarily in deficient individuals** and when administered for sufficient duration. In vitamin D–replete populations and CKD patients, supplementation shows limited efficacy. Clinically, these findings argue for **targeted supplementation strategies** based on deficiency screening rather than universal application. Future research should focus on stratified RCTs, longer follow-up, and mechanistic studies to clarify the role of vitamin D in vascular health and cardiovascular risk reduction.

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