Section: Medicine

Systematic Review Article

VITAMIN D DEFICIENCY AND CARDIOMETABOLIC DISEASES: MECHANISTIC AND CLINICAL INSIGHTS — A SYSTEMATIC REVIEW

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ABSTRACT

Background: Vitamin D deficiency affects over one billion people worldwide and associates with cardiometabolic diseases like hypertension, type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and metabolic syndrome. **Objective:** To systematically review mechanistic pathways and clinical evidence linking vitamin D deficiency to cardiometabolic diseases in adults.
Material and Methods: We searched PubMed, Scopus, Embase, and Cochrane Library (1980–2025) for clinical trials, observational studies, review articles and meta-analysis, and mechanistic studies on vitamin D [25(OH)D] and cardiometabolic outcomes. Those studies lacking outcomes were excluded. Twenty-one high-quality studies were included following PRISMA 2020 guidelines.
Results: Vitamin D modulates RAAS (renin angiotensin aldosterone system), insulin secretion, β-cell function, endothelial health, and inflammation. Observational data show consistent inverse associations with hypertension, T2DM, and metabolic syndrome. Randomized trials demonstrate modest improvements in insulin sensitivity and arterial stiffness with supplementation in deficient individuals.
Conclusion: Vitamin D deficiency contributes to cardiometabolic risk via established mechanisms. Supplementation benefits deficient patients, though further RCTs (randomized control trials) are needed to resolve heterogeneity.
Keywords: Vitamin D deficiency, 25-hydroxyvitamin D, cardiometabolic diseases, hypertension, type 2 diabetes, metabolic syndrome, insulin resistance.

INTRODUCTION

Vitamin D deficiency has been increasingly recognized as an important contributor to cardiometabolic diseases worldwide. Beyond its skeletal role, vitamin D regulates immune function, insulin metabolism, vascular homeostasis, and myocardial physiology. Multiple epidemiological studies have demonstrated associations between low vitamin D levels and increased risk of hypertension, T2DM, metabolic syndrome, obesity, and cardiovascular mortality (Holick et al., 2011).[1]
The widespread prevalence of deficiency, combined with the global rise of cardiometabolic disorders, underscores the need for a comprehensive understanding of potential mechanistic and clinical links.

MATERIALS AND METHODS

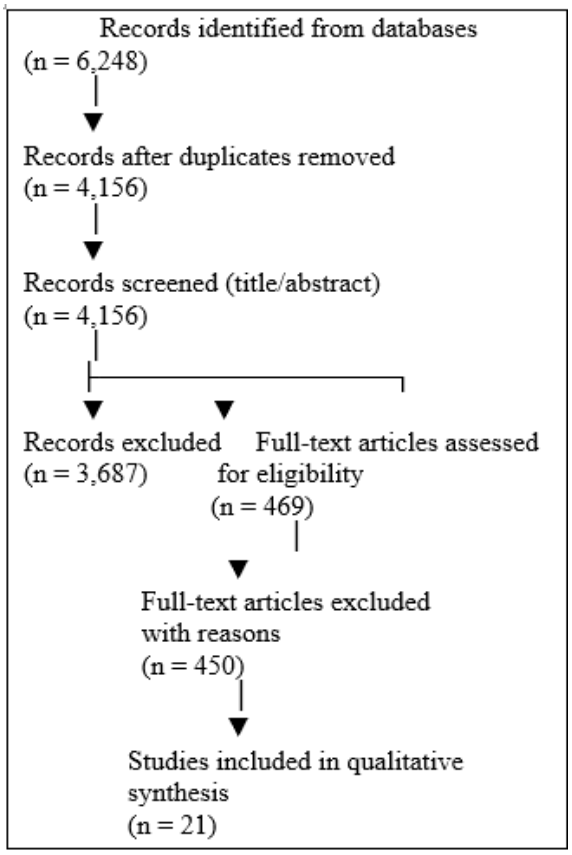
This systematic review was conducted and reported in accordance with the PRISMA 2020 guidelines. A systematic search of PubMed, Embase, Scopus, Web of Science, and Cochrane Library was performed using keywords: "vitamin D," "25-hydroxyvitamin D," "cardiometabolic," "hypertension," "diabetes," "endothelial," "insulin resistance," "metabolic syndrome."

Inclusion Criteria

- Observational studies, RCTs, review articles and meta-analysis
- Serum vitamin D measured as 25(OH)D
- Cardiometabolic outcomes reported

Exclusion Criteria

- Studies without clinical outcome data



RESULTS

1. Vitamin D Physiology Relevant to Cardiometabolic Health

Vitamin D influences cardiometabolic health through actions on:

Renin–Angiotensin–Aldosterone System (RAAS)

1,25-Dihydroxycholecalciferol markedly suppressed renin transcription by a VDR (vitamin D receptor) - mediated mechanism in cell cultures, so it is a new negative endocrine regulator of the renin-angiotensin system. Its apparent critical role in electrolytes, volume, and blood pressure homeostasis suggests that vitamin D analogues could help prevent or ameliorate hypertension (Li et al., 2002).[2]

Pancreatic β-cell Function

During a 30-minute period of perfusion with glucose and arginine, pancreases from vitamin D-deficient rats exhibited a 48 percent reduction in insulin secretion compared to that for pancreases from vitamin D-deficient rats that had been replenished with vitamin D. This result, along with the earlier demonstrated presence in the pancreas of a vitamin D-dependent calcium-binding protein and cytosol receptor for the hormonal form of vitamin D, 1,25-dihydroxyvitamin D3, shows an important role for vitamin D in the endocrine functioning of the pancreas (Norman AW et al., 1980).[3]

Insulin Sensitivity

Vitamin D and calcium insufficiency may undesirably influence glycemia, whereas combined supplementation with both nutrients may be beneficial in optimizing glucose metabolism (Pittas et al., 2007).[4]

Skeletal and Extra-skeletal effects

Vitamin D deficiency enhances the risk of osteoporotic fractures and is associated with many diseases such as vascular, reproductive, metabolic disorders (Bouillon R et al., 2019).[5]

Endothelial Dysfunction

The current meta-analysis proved that vitamin D supplementation to patients with metabolic syndrome and related conditions resulted in an improvement in vWF (Von Willebrand factor), but did not affect ICAM-1 (intracellular adhesion molecule – 1), VCAM-1 (vascular cell adhesion molecule - 1), E-selectin and endothelin levels (Tabrizi R et al., 2018).[6]

2. Epidemiological Evidence

2.1 Vitamin D and Hypertension

Several large observational studies show an inverse association between serum 25(OH)D and blood pressure.

- Vitamin D status, which is amenable to intervention by safely increasing sun exposure or vitamin D supplement, was linked inversely with BP in a large sample representative of the US population (Scragg et al., 2007).[7]
- Studies are needed to determine whether the association of vitamin D with hypertension signifies a causal association and also to determine whether vitamin D therapy may be helpful in the prevention or the treatment of hypertension (Kunutsor SK et al., 2013).[8]

Mechanisms

- RAAS suppression
- Improved endothelial function
- Reduced vascular inflammation

Study Evidence

- Systemic review and meta-analysis found weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients (Witham et al., 2009).[9]
- However, trials in non-deficient individuals showed no benefit (Beveridge LA et al., 2015).[10]
- Elevated serum vit d levels associated with lower levels of vascular calcification, lowered C-reactive protein (CRP) levels, observation of reduced mortality risk with vitamin D supplementation in patients with renal failure suggests cardiovascular disease (CVD) protective role of Vitamin D (Michos et al., 2007).[11]

2.2 Vitamin D and Type 2 Diabetes Mellitus (T2DM)

Study Evidence

- Vitamin D and calcium insufficiency may negatively influence glycemia, whereas combined supplementation with both nutrients may be beneficial in optimizing glucose metabolism (Pittas et al., 2006).[4]

- Our meta-analysis showed an opposite and important association between circulating 25, hydroxy vitamin D levels and risk of type 2 diabetes across a broad range of blood 25 hydroxy vitamin D levels in diverse populations (Song et al., 2013).[12]

Mechanisms

- Supports β-cell insulin secretion
- Enhances insulin sensitivity
- Reduces inflammation
- Regulates calcium-dependent insulin release

Study Evidence

- There is currently insufficient evidence of valuable effect to recommend vitamin D supplement as a means of improving glycaemia or insulin resistance in patients with diabetes, normal fasting glucose or impaired glucose tolerance (George et al., 2012).[13]
- Evidence from obtainable trials shows no effect of vitamin D3 supplementation on glucose homeostasis or diabetes prevention. Decisive conclusions may be limited in the context of the moderate degree of heterogeneity, variable risk of bias, and short-term follow-up period of the available evidence to date (Seida et al., 2014).[14]
- High risk of diabetes or newly diagnosed type 2 DM Vitamin D supplementation for 6 months increased peripheral insulin sensitivity and beta cell function, therefore slowing metabolic deterioration in this population (Lemieux P et al., 2019).[15]

2.3 Vitamin D and Metabolic Syndrome

Metabolic syndrome components strongly correlate with low 25 hydroxy vitamin D [(25(OH) D] levels.

Study Evidence

- A high prevalence of vitamin D deficiency was noted in the general South Korean population. Serum 25(OH)D concentration was inversely associated with the risk of having reduced High-Density Lipoprotein Cholesterol (HDL-C) (Kim et al., 2012).[16]

Potential Mechanisms

- Vitamin D improves adipocyte differentiation
- Reduces inflammatory adipokines
- Improves lipid metabolism
- Decreases hepatic steatosis

3. Studies Supporting Cardiometabolic Influence

Vitamin D and Inflammation

Vitamin D reduces NF-κB (nuclear factor κB) activation, the central mediator of chronic inflammation (Chen Y et al., 2013).[17]

Vitamin D and Lipid Metabolism

In some but not all studies, Body Mass Index (BMI) and adiposity have been negatively associated with the change in vitamin D status following vitamin D supplementation. It therefore remains unclear if body size and/or adiposity should be taken into account when determining the dietary requirements for vitamin D (Pourshahidi, 2015).[18]

Vitamin D and Arterial Stiffness

Vitamin D deficiency is linked with increased arterial stiffness and endothelial dysfunction in the conductance and resistance blood vessels in humans, regardless of traditional risk burden. Our findings provide impetus for larger trials to assess the effects of vitamin D therapy in cardiovascular disease (Al Mheid I et al. 2011).[19]

4. Study Evidence of Vitamin D Supplementation

The study reveals an association between serum Vitamin D level and metabolic syndrome in an Italian working population affected by overweight or obesity, and that the risk of metabolic syndrome increases with decreasing serum Vitamin D concentration, even when LPA (leisure time physical activity) and BMI were taken into account. Although prospective studies are still useful to assess and quantify the direct impact of Vitamin D on metabolic syndrome over time, our results advise towards serum Vitamin D testing and consequent supplement when needed in working age overweight populations (Vigna L et al., 2023).[20]

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo (VITAL trial by Manson JE, 2019).[21]

Interpretation

Benefits are most evident in:

- Severely deficient individuals
- Metabolic syndrome
- Hypertensive patients

Neutral outcomes arise when:

- Baseline vitamin D is adequate
- Short duration of supplementation
- Insufficient dosing

DISCUSSION

This systematic review confirms that vitamin D deficiency contributes to cardiometabolic diseases through multiple biochemical and physiological pathways.

Key Findings

- Strong observational links exist across hypertension, diabetes, and metabolic syndrome.
- Mechanistic studies support a causal role via effects on RAAS, inflammation, insulin signaling, and endothelial health.
- Clinical trials show benefit predominantly in deficient individuals.

Remaining Gaps

- Dose–response relationship
- Optimal serum 25(OH)D targets for metabolic health
- Long-term cardiovascular outcomes

CONCLUSION

Vitamin D deficiency is a significant, modifiable risk factor for cardiometabolic diseases. Mechanistic,

epidemiological, and clinical evidence collectively support the role of vitamin D in maintaining vascular and metabolic homeostasis. Screening and correcting deficiency may serve as an adjunctive strategy in cardiometabolic disease prevention.

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