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Mechanisms of action and implications of vitamin D in–cardiovascular and diabetes diseases – A mini-review

Mecanismos de acción e implicaciones de la vitamina D en las enfermedades cardiovasculares y la diabetes: una mini-revisión

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ABSTRACT

Vitamin D (Vit D), traditionally recognised for its role in calcium-phosphate homeostasis and bone metabolism, is now understood to exert pleiotropic hormonal actions mediated through widespread expression of the Vit D receptor (VDR). Increasing evidence suggests that Vit D participates in the regulation of cardiovascular physiology, glucose metabolism, insulin sensitivity, and inflammatory pathways. This review summarises the principal molecular and cellular mechanisms through which Vit D may modulate cardiovascular diseases, diabetes, and metabolic syndrome, drawing on evidence from experimental, epidemiological, and clinical studies. A narrative synthesis of mechanistic data from basic science research was combined with findings from observational cohorts and randomised controlled trials evaluating vitamin D status or supplementation. Vit D influences cardiovascular health through multiple pathways, including enhancement of endothelial nitric oxide production, reduction of oxidative stress, inhibition of inflammatory adhesion molecules, modulation of immune responses, suppression of the renin-angiotensin-aldosterone system (RAAS), and prevention of vascular calcification. In glucose and lipid metabolism, Vit D exerts direct effects on pancreatic β-cell insulin secretion; improves peripheral insulin sensitivity via GLUT4 mobilisation and mitochondrial biogenesis; modulates adipokines such as adiponectin; and reduces chronic low-grade inflammation by inhibiting NF-κB signaling and promoting regulatory immune

phenotypes. Vit D also participates in RAAS regulation and epigenetic control of genes related to energy homeostasis. Maintaining sufficient Vit D levels may contribute to integrated prevention strategies for cardiovascular diseases, diabetes, and metabolic syndrome, although its role as a therapeutic agent remains uncertain.

Keywords: Vitamin D. Cardiovascular diseases. Diabetes. Metabolic syndrome.

RESUMEN

La vitamina D (Vit D), además de su papel en la homeostasis del calcio y el fosfato y en el metabolismo óseo, ejerce acciones hormonales pleiotrópicas mediadas por su receptor (VDR), ampliamente expresado en diferentes tejidos. La evidencia disponible sugiere que participa en la regulación de la función cardiovascular, el metabolismo de la glucosa, la sensibilidad a la insulina y las vías inflamatorias. Esta revisión analiza los principales mecanismos mediante los cuales la Vit D puede influir en las enfermedades cardiovasculares, la diabetes y el síndrome metabólico, integrando datos de estudios experimentales, observacionales y ensayos clínicos. En el sistema cardiovascular, la Vit D favorece la producción de óxido nítrico endotelial, reduce el estrés oxidativo y la inflamación, modula la respuesta inmunitaria, suprime el sistema renina-angiotensina-aldosterona (SRAA) y puede prevenir la calcificación vascular. En el metabolismo de la glucosa y los lípidos, favorece la secreción de insulina, mejora la sensibilidad periférica mediante la movilización de GLUT4 y la biogénesis mitocondrial, y modula adipocinas como la adiponectina. Asimismo, reduce la inflamación crónica de bajo grado mediante la inhibición de la señalización de NF-κB y participa en la regulación epigenética de genes relacionados con la homeostasis energética. Mantener niveles adecuados de Vit D podría contribuir a estrategias preventivas frente a las enfermedades cardiovasculares, la diabetes y el síndrome metabólico. Sin embargo, la evidencia actual no permite establecer con certeza su papel como agente terapéutico.

Palabras clave: Vitamina D. Enfermedades cardiovasculares. Diabetes. Síndrome metabólico.

INTRODUCTION

Vitamin D (Vit D), or more precisely ergosterol, was certainly one of the earliest biologically relevant molecules produced in primordial phytoplankton cells following exposure to sunlight. Over time, various higher animal species began to use Vit D to modulate essential physiological functions. However, it was only in relatively recent history, around 1822, that the hypothesis began to emerge that sunlight might influence a deforming bone disease typical of children, rickets (1). In the early 1900s, it was finally confirmed that exposure to sunlight could prevent or treat rickets (1).

It was around the 1930s that researchers discovered how irradiation of certain algae and yeasts could generate the first form of Vit D similar to that produced by phytoplankton (2): ergosterol, or Vit D_2, which began to be used to fortify certain foods. In contrast, vitamin D_3 (cholecalciferol), although described by Goldblatt and Soames in 1923 as being obtainable through the conversion of 7-dehydrocholesterol in the skin under ultraviolet exposure (3) was produced industrially only towards the late 1950s-early 1960s through the conversion of cholesterol—derived from lanolin in sheep's wool—into 7-dehydrocholesterol followed by irradiation. In the second half of the 1960s, the metabolism of vitamin D and the structure of calcitriol, the active hormonal form of vitamin D, were identified.

In subsequent decades, studies on the pharmacological effects of vitamin D increased exponentially, covering not only its role in bone structure and fracture prevention but also its actions on numerous organs expressing vitamin D receptors (VDR). Many investigations have specifically explored Vit D's influence on organ systems of major public health relevance such as the cardiovascular system, glucose metabolism—including diabetes—and the immune system.

The aim of this review is to succinctly illustrate the essential mechanisms of action that have justified the numerous clinical attempts to evaluate both the

activity and the limitations of Vit D in modulating important non-skeletal diseases affecting large segments of the population. The authors intend to present, in an almost schematic fashion, the aspects and properties through which Vit D may help prevent and/or treat specific pathological manifestations.

A literature search was performed using the databases PubMed, Scopus, and Web of Science. Articles published within the last 5 years were included, although selected landmark studies of historical relevance were also considered. The search strategy incorporated the following keywords: "*vitamin D, cardiovascular diseases, endothelial mechanisms, inflammation, RAAS (renin-angiotensin-aldosterone system), lipids, adipokines, insulin, β-cells, VCAM-1, ICAM-1,* and *E-selectin"*. Inclusion criteria encompassed studies providing evidence and novel insights that expanded upon existing knowledge. Studies that did not offer adequate or convincing evidence relevant to the research question were excluded.

MOLECULAR AND CELLULAR MECHANISMS IN CARDIOVASCULAR DISEASE

Vit D, traditionally considered a regulator of calcium–phosphate homeostasis and bone metabolism, is now recognised as a pleiotropic steroid hormone with systemic effects, including cardiovascular actions. The biologically active metabolite, 1,25-dihydroxyvitamin D_3 (calcitriol), exerts genomic and non-genomic effects through binding to the nuclear vitamin D receptor (VDR), which is expressed in numerous non-skeletal cells, including endothelial cells, cardiomyocytes, vascular smooth muscle cells, and immune cells. In recent years, a substantial body of epidemiological and experimental evidence has suggested a correlation between Vit D deficiency and increased risk of cardiovascular diseases (CVD), including atherosclerosis, arterial hypertension, and heart failure (4,5). Although the causal relationship remains debated, several molecular mechanisms have been identified that may support a pathophysiological role of vitamin D in the regulation of vascular function and in the prevention of arterial sclerosis (6).

Modulation of endothelial function

The mechanism underlying the effects on endothelial function is supported by the expression of VDR and the enzyme 1α-hydroxylase (CYP27B1) in endothelial cells, enabling local production of calcitriol. This favours autocrine and paracrine regulation of vascular function by increasing the expression of endothelial nitric oxide synthase (eNOS), with a consequent rise in nitric oxide (NO) production, a potent endothelium-dependent vasodilator (7,8). Moreover, the increased activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) reduces oxidative stress (9,10).

It is well established that under pathogenic conditions, oxidative stress caused by excessive production of reactive oxygen species (ROS) promotes NO degradation and suppresses NO synthesis, thereby reducing NO bioavailability.

In addition to these protective mechanisms, vitamin D inhibits the expression of endothelial adhesion molecules (VCAM-1, ICAM-1, E-selectin), limiting monocyte recruitment into the vascular wall. These effects help preserve endothelial function and counteract early atherogenic processes. Experimental studies show that vitamin D_3 inhibits platelet adhesion and the expression of VCAM-1 and MT1-MMP in human endothelial cells and may have early therapeutic relevance in atherosclerotic disease (11,12).

Anti-inflammatory and immunomodulatory effects

Chronic inflammation is a key element in atherosclerotic progression; clinical trials have demonstrated that innate and adaptive immune responses can either promote or regulate atherosclerosis. Modulating inflammatory processes may therefore provide an effective therapeutic approach against atherosclerotic disease, and calcitriol modulates immune responses by acting on several cell lineages (13).

Several studies indicate that vitamin D regulates vascular tone, prevents fibrosis, and modulates vascular hypertrophy via inhibition of the NF-κB transcription factor, thereby suppressing the production of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), while instead stimulating the synthesis of anti-inflammatory cytokines (IL-10) (14). Various studies show that vitamin D inhibits monocyte and

macrophage recruitment, cholesterol uptake and esterification. It also induces autophagy of lipid droplets in macrophages, promotes cholesterol efflux, and regulates macrophage polarisation.

Some research shows that vitamin D has a direct inhibitory effect on the formation, adhesion, and migration of lipid-loaded monocytes, thus exerting anti-atherosclerotic effects.

Inflammatory processes are further influenced through modulation of T-cell polarisation, reducing Th1 and Th17 phenotypes in favour of regulatory T cells (Treg), leading to substantial attenuation of vascular inflammation and endothelial injury (15,16).

Interaction with the renin-angiotensin-aldosterone system (RAAS)

The potential regulatory action of vitamin D on blood pressure arises from its role as an endocrine regulator of the renin-angiotensin system (RAAS). Clinical studies have shown that low vitamin D levels are associated with elevated plasma renin activity, higher levels of angiotensin II, and increased RAAS activity within vascular tissues (17). Calcitriol acts as a transcriptional suppressor of the renin gene, reducing angiotensin II concentrations and RAAS activation. The resulting decrease in vasoconstriction and adrenergic overactivation leads to improved blood pressure control, reduced oxidative stress and vascular inflammation, and protection against myocardial hypertrophy and fibrosis. This mechanism contributes to the prevention of arterial hypertension and its cardiovascular complications (18,19).

Regulation of mineral metabolism and vascular calcification

The main physiological role of vitamin D is to stimulate adequate intestinal calcium absorption. Vitamin D is essential for maintaining healthy mineral and bone metabolism. It stimulates intestinal calcium and phosphate absorption, regulates bone turnover, and suppresses PTH secretion through the endocrine action of calcitriol.

Vitamin D therefore influences calcium-phosphate homeostasis and, consequently, vascular calcification processes. In cases of significant vitamin D deficiency, especially in the presence of renal failure or secondary hyperparathyroidism, alterations in calcium and phosphorus metabolism may occur. In fact, vitamin D deficiency leads to increased PTH secretion and secondary hyperparathyroidism, with elevations in circulating calcium and phosphate and subsequent deposition in arterial walls (20,21). Although this may occur to some degree, not all patients with sustained hyperphosphataemia develop vascular calcification.

Epidemiological studies show that vitamin D deficiency is associated with arterial stiffness, hypertension, and endothelial dysfunction in individuals with chronic kidney disease as well as in healthy subjects. Experimental evidence has also shown that vascular smooth muscle cells can undergo osteoblast-like phenotypic transformation.

Conversely, calcitriol regulates the expression of anti-calcifying proteins such as matrix Gla protein (MGP) and osteopontin, and inhibits ectopic mineralisation processes, with an overall effect of reducing arterial stiffness and the progression of arteriosclerosis (22-24).

Indirect metabolic effects

Vitamin D also influences metabolic parameters associated with cardiovascular risk. Experimental data report that reduced plasma vitamin D levels may contribute to excessive white adipose tissue, insulin resistance (IR), and dyslipidaemia (25). In contrast, vitamin D improves insulin sensitivity through increased expression of insulin receptors and enhanced intracellular signaling, in addition to reducing adipose tissue inflammation and the release of pro-atherogenic adipokines.

An association between low vitamin D levels and adverse lipid profiles has been identified in children, adolescents, and adults, whereas adequate vitamin D intake may improve lipid parameters by reducing triglycerides and increasing HDL

cholesterol. These effects indirectly contribute to a reduction in overall cardiovascular risk.

Recent experimental and clinical evidence

Animal models lacking VDR or enzymes involved in vitamin D synthesis develop left ventricular hypertrophy, increased renin levels, and vascular calcifications, supporting a direct pathophysiological role (26). Observational studies in large cohorts have shown that serum 25(OH)D levels below 20 ng/mL are associated with a significantly increased risk of major cardiovascular events (27,28). However, randomised controlled trials (e.g., VITAL, ViDA, DO-HEALTH) have not demonstrated a significant reduction in cardiovascular mortality with supplementation, although marginal benefits emerge in subjects with severe deficiency (< 15 ng/mL) or in specific subgroups (29-32).

In particular, the VITAL Trial (VITamin D and OmegA-3 TriaL), a randomized, double-blind clinical trial, enrolled approximately 25,000 participants aged over 50 years who received 2,000 IU of vitamin D daily for 5 years. Most participants had adequate baseline vitamin D levels. As reported by Zhu et al., the study did not provide conclusive evidence regarding the prevention of cancer or fragility fractures.

The ViDA Study enrolled more than 5,000 participants aged 50-84 years who received 100,000 IU of vitamin D monthly for over three years. No significant effects were observed on cardiovascular events, respiratory infections, non-vertebral fractures, falls, or cancer incidence. However, among participants with low baseline vitamin D concentrations (≤ 30 nmol/L), improvements in bone mineral density (BMD) and arterial function were reported by Robert Scragg et al.

Finally, a post hoc analysis of the DO-HEALTH Trial included 777 participants who received 2,000 IU of vitamin D daily for 3 years. Participants who also received omega-3 supplementation and engaged in a structured exercise program showed a modest slowing of biological aging, as assessed using the PhenoAge methodology, according to Heike Bischoff-Ferrari et al.

Thus, vitamin D appears to act more as a modulatory factor than a direct therapeutic intervention, and maintaining serum 25OHD levels sufficient to ensure adequate synthesis of 1α,25(OH)$_2$D seems the most rational strategy within integrated cardiovascular prevention (33).

CELLULAR MECHANISMS IN GLYCAEMIC AND INSULIN METABOLISM

The wide distribution of vitamin D receptors in organs and tissues involved in glucose metabolism with effects on insulin resistance, diabetes, and metabolic syndrome has made it plausible that adequate circulating vitamin D levels may influence the onset or progression of these conditions. This assumption is well supported by the presence of calcitriol binding to the nuclear vitamin D receptor (VDR) expressed in pancreatic β-cells, hepatocytes, adipocytes, skeletal muscle cells, and immune cells. The calcitriol-VDR complex heterodimerises with the retinoid X receptor (RXR), regulating the expression of hundreds of genes involved in metabolism, inflammation, and insulin sensitivity.

Direct effects on pancreatic β-cells

The abundant expression of VDR in β-cells has suggested that vitamin D may directly regulate their function. Some studies have shown that insufficient vitamin D results in closure of calcium channels and reduced insulin synthesis and secretion, as well as increased insulin resistance (34,35). The suspicion that Vit D deficiency contributes to insulin resistance is also supported by evidence that polymorphisms in both the VDR gene and the DBP (Vit D binding protein) gene are associated with insulin resistance (36). β-cells not only express VDR but also 1α-hydroxylase (CYP27B1), enabling local activation of 25OHD and subsequent nuclear actions of calcitriol that enhance transcription of the insulin gene (INS), favouring glucose-induced insulin secretion. Calcitriol also stabilises intracellular Ca^{2+} essential for insulin granule exocytosis nd protects β-cells from oxidative stress and apoptosis induced by inflammatory cytokines (IL-1β, TNF-α, IFN-γ).

Effects on peripheral insulin sensitivity

Skeletal muscle and adipose tissue are VDR targets, and calcitriol regulates GLUT4 translocation to the cell membrane, improving glucose uptake (37).

Multiple studies report that excessive fat accumulation strongly contributes to skeletal muscle mitochondrial dysfunction and metabolic complications (4,38). Vitamin D can reduce lipid accumulation, increase mitochondrial DNA (mtDNA) content, enhance ATP levels, and upregulate genes involved in mitochondrial biogenesis (PGC-1α, NRF1, Tfam) and β-oxidation. Overall, vitamin D may mitigate lipid accumulation and mitochondrial dysfunction, improving oxidation and mitochondrial biogenesis, as shown in both cell models and animal models (39).

Vitamin D deficiency in obese mice increases lipogenesis (PPARγ, SREBP1c, FAS expression) and reduces markers of β-oxidation (PPARα), worsening hepatic steatosis. This suggests that adequate vitamin D status may support hepatic fatty acid oxidation. Another study (40) reports that adequate vitamin D concentrations lead to reduced oxidative stress and improved mitochondrial and endocrine functions, lowering the risk of autoimmunity, infections, metabolic disorders, and impaired DNA repair. Vitamin D is also a potent antioxidant that helps maintain balanced mitochondrial activity, preventing protein oxidation, lipid peroxidation, and DNA damage (41).

However, although many results are promising, much evidence derives from cellular or animal models, and not all studies directly assessed the entire pathway from gene expression to mitochondrial function and reduced lipotoxicity. Tissue-specific and context-specific differences (diet, degree of deficiency, etc.) also exist. Nonetheless, several data support the hypothesis that vitamin D positively influences β-oxidation gene expression and mitochondrial biogenesis, promoting improved lipid metabolism and reducing oxidative stress (42).

Despite some inconsistent findings, large studies show that vitamin D's favourable effects on glycaemic and lipid parameters are mediated by adiponectin. A major review on vitamin D supplementation found that increases in adiponectin were generally significant, especially in patients with diabetes, and more pronounced when vitamin D was administered daily (43). Vitamin D may

also modulate leptin and resistin—both linked to insulin resistance—and reduce hepaticinsulin resistance and local inflammation sustained by cytokines (4,44-46).

Immunomodulatory and anti-inflammatory mechanisms

Chronic low-grade inflammation is a key feature of both type 2 diabetes and metabolic syndrome. It is well established that vitamin D (calcitriol) inhibits the NF-κB pathway, reducing production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) by dendritic cells and macrophages, while promoting macrophage polarisation towards the anti-inflammatory M2 phenotype. These effects are reinforced by reduced differentiation of pro-inflammatory Th1 and Th17 lymphocytes and increased Treg differentiation (47,48). Such mechanisms are particularly relevant in type 1 diabetes, where autoimmune destruction of β-cells may be attenuated by adequate vitamin D availability.

Integrated endocrine-metabolic mechanisms

Numerous studies have demonstrated a positive correlation between TNF-α levels, obesity, and circulating TNF-α in subjects with obesity or type 2 diabetes *mellitus* (49). Elevated TNF-α expression in adipose tissue has also been linked to insulin resistance in both humans and animal models. TNF-α can regulate angiotensinogen (ANT) expression in hepatocytes, suggesting a potential mechanism through which insulin may increase ANT and subsequent angiotensin II production (50). This provides a mechanistic explanation for obesity-associated hypertension.

Calcitriol, by inhibiting renin gene expression, reduces systemic and tissue RAS activation, thereby attenuating adipocyte hypertrophy, inflammation, and insulin resistance associated with excess angiotensin II. The VDR/RXR complex binds to thousands of genomic sites (vitamin D response elements, VDREs), modulating genes involved in glucose homeostasis, inflammation, mitochondrial biogenesis, and lipid oxidation (51-53).

Limitations

This mini-review took into consideration in vitro studies, animal models, observational studies, RCTs (randomized controlled trials), and genetic and molecular studies, which present different levels of evidence (Table I).

Table I

Evidence	**Main results**	**Limitations**
In vitro	VDRE, GLUT4, PGC-1α	Limited clinical transferibility
Animal models	Metabolic and cardio-vascular effects	Species-specific differences
Observational studies	Association hypovitaminosis D and cardio-vascular diseases	Residual confounding
RCT	Limited or inconsistent benefits	Heterogenous populations

Furthermore, compared with randomized controlled trials (RCTs), observational studies often include participants who are not vitamin D deficient. In addition, follow-up periods may be insufficient, clinical endpoints may occur too late to be adequately captured, and, in some cases, vitamin D supplementation has been administered at suboptimal doses. Finally, although several biologically plausible mechanisms have been proposed, their existence alone is insufficient to establish a causal relationship or to demonstrate a clinically relevant benefit**.**

DISCUSSION

Vitamin D, through its hormonal action mediated by VDR, exerts vascular, immunomodulatory, and metabolic effects that may contribute to cardiovascular protection by improving endothelial function, modulating the RAAS, preventing arterial calcification, and optimising metabolic homeostasis. However, despite strong pathophysiological rationale, clinical results remain variable and

inconclusive. Vitamin D is likely to act as a permissive factor for normal cardiovascular function rather than a direct therapeutic agent. Correction of vitamin D deficiency nevertheless remains a relevant goal in cardiovascular prevention, particularly in high-risk or deficient individuals.

The scientific literature indicates that vitamin D, in its active form calcitriol, acts as a pleiotropic modulator of glucose and lipid metabolism through direct effects on β-cells and insulin-sensitive tissues, as well as indirect effects via immune, inflammatory, RAAS, and epigenetic regulation of energy homeostasis genes. Adequate vitamin D status helps preserve β-cell function, insulin sensitivity, a low inflammatory profile, and balanced lipid metabolism, making vitamin D a potential protective or adjunctive factor in preventing or managing diabetes and metabolic syndrome.

Although several observational studies have shown an association between low vitamin D intake or low serum 25(OH)D and incident type 2 diabetes, randomised controlled trials have yielded inconsistent results (54). More recent population-based studies (55) provide evidence for an association between vitamin D concentrations and lower risk of insulin resistance. Nevertheless, many studies report contradictory conclusions, prompting consideration of factors such as differences in population characteristics, age, adiposity levels—especially hepatic fat—oxidative stress, PTH concentrations, and immune system status. These variables may influence outcomes and calcitriol availability.

In conclusion, experimental and clinical evidence suggests that vitamin D may play a predominantly preventive rather than therapeutic role in diabetes and metabolic syndromes, with potentially stronger effects in predisposed individuals and those with low baseline vitamin D levels.

Given that the dosages generally used are derived from experiences with bone metabolism, it is plausible to hypothesize that, where one wishes to use vitamin D in the prevention/treatment of extra-skeletal conditions, higher doses may be required. It is nevertheless our opinion that the risk of overdose is unlikely, as the formation of calcitriol in the kidneys is subject to various controls (PTH, FGF23, and \(1,25(OH)_2D\) itself) that regulate its synthesis (56).

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