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Impact of vitamin D therapy on vascular consistency

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Abstract
The impact of vitamin D on vascular health is dualistic, with protective effects at physiological levels—such as enhanced endothelial function and reduced oxidative stress—alongside potential harmful effects at excessive doses or in disease states, such as vascular calcification and smooth muscle cell dysfunction. Targeting vitamin D receptor (VDR) signaling pathways may offer therapeutic strategies for cardiovascular diseases; however, dosage and patient-specific factors, such as chronic kidney disease and vitamin D status, should be carefully considered.

Keywords: Vitamin D, Endothelial cells, Vascular, Reactive oxygen species, Chronic kidney disease
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Introduction

Vitamin D influences vascular function and structure through genomic and nongenomic pathways mediated by vitamin D receptors (VDRs) in endothelial cells and vascular smooth muscle cells (VSMCs)(1). These mechanisms comprise modulation of calcium handling, oxidative stress, cell proliferation/migration, and calcification, with outcomes dependent on dosage, cell type, and disease context (2). This vitamin diminishes calcium influx into endothelial cells, lowering endothelium-derived contracting factors and improving vasodilation, VDR activation in endothelial cells decreases reactive oxygen species (ROS) generation, across with protecting against endothelial dysfunction and hypertension (1). This vitamin also strengthens endothelial progenitor cell function and promotes vascular repair by vascular endothelial growth factor (VEGF) upregulation (3). Previous studies also, physiological level of vitamin D inhibits VSMC proliferation by suppressing cyclin-dependent kinase 2 and ERK1/2 phosphorylation (4). In nongenomic pathway, it was shown that, high-dose $1,25(OH)_2D_3$ induces VSMC migration through kinase activation, contributing to the neointima formation (5). Earlier studies on genomic pathway found that, physiological doses inhibit migration by downregulating β_1-integrin receptors (6). Furthermore, vitamin D promotes VSMC differentiation into osteoblast-like cells under calcifying conditions, mediated by VDR and BMP-2. Meanwhile, high-dose vitamin D upregulates osteogenic genes like osteopontin, BMP-2 and suppresses calcification inhibitors such as fetuin-A (7). In chronic kidney disease also, VDR deletion in VSMCs reduces medial calcification, implicating VDR in pathological calcification (8,9). Similarly, physiological vitamin D improves elastin synthesis and matrix metalloproteinase activity, stabilizing vascular structure (10). Numerous vitamin D inhibits renin–angiotensin system, reducing vascular resistance and inflammation (11). On the other hand, vitamin D stimulates Fibroblast growth factor 23 and klotho, which protect against ectopic calcification by regulating phosphate metabolism (12). It should be noted that, at physiological levels, vitamin D improves endothelial function, reduces oxidative stress, and stabilizes the phenotype of VSMCs (13). However, excessive vitamin D like in CKD, promotes VSMC osteogenic transition and calcification by VDR-dependent pathway (14,15).

Search strategy

For this study, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords including; vitamin D, endothelial cells, vascular, reactive oxygen species and chronic kidney disease

Autocrine and paracrine actions of vitamin D

Vitamin D acts through classic endocrine pathways by autocrine and paracrine mechanisms within vascular tissues (16,17). These local actions are mediated through the conversion of circulating 25-hydroxyvitamin D to the active form, 1,25-dihydroxyvitamin D, through the enzyme

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Implication for health policy/practice/research/ medical education

Vitamin D influences vascular function and structure through genomic and nongenomic pathways mediated by vitamin D receptors (VDRs) in endothelial cells and vascular smooth muscle cells (VSMCs). These mechanisms include modulation of calcium handling, oxidative stress, cell proliferation/migration, and calcification, with outcomes dependent on dosage, cell type, and disease context.

CYP27B1, which is expressed in vascular endothelial cells, VSMCs and pericytes (2,18). The presence of VDRs in these cells allows for direct modulation of vascular structure and function (19). Additionally, endothelial cells express both VDR and CYP27B1, enabling them to locally produce and respond to $1,25(OH)_2D$ (20). This condition supports an autocrine/paracrine loop that modulates endothelial function (2). Besides, vitamin D stimulates nitric oxide creation through endothelial nitric oxide synthase, improving vasodilation and reducing oxidative stress (21,22). This vitamin decreases endothelial activation and inflammation, protecting against early thermogenesis and vascular injury (16). Besides, autocrine/paracrine vitamin D signaling enhances endothelial repair and regeneration, partly by upregulating VEGF (23). VSMCs also express VDR and CYP27B1, allowing for local conversion of vitamin D and autocrine/paracrine signaling (24). Since, vitamin D inhibits VSMC proliferation and migration, key processes in pathological vascular remodeling in conditions like atherosclerosis and restenosis (25). Imperatively, this compound, suppresses endothelin-induced activation of cell cycle kinases, reducing VSMC-driven neointima formation (26). At physiological levels, vitamin D promotes a quiescent, contractile VSMC phenotype, while high doses or pathological conditions may promote osteogenic differentiation and vascular calcification (27). More recent studies demonstrated that pericytes present VDR and react to local vitamin D signaling by reducing proliferation and migration, increasing VEGF production, and promoting vessel maturation and stabilization (16). Finally, vitamin D triggers anti-inflammatory responses in pericytes, which may protect against microvascular injury (28).

Vitamin D and vascular function

Vitamin D impacts both microvascular and large vessel function, however the magnitude and significance of its effects differ somewhat between these vascular beds (29). The deficiency of this vitamin is strongly associated with microvascular damage, as evidenced by retinal microvascular abnormalities, including signs of retinopathy, wider venular calibers, and narrower arterioles (30). The microvascular changes correlate with cardiovascular risk, indicating that vitamin D influences microvascular integrity and function through endothelial activation and nitric oxide production (31). Recently, it was detected a modest but significant improvement in microvascular function, measured by reactive hyperemia index, after vitamin D normalization in deficient individuals (29,32). Vitamin D levels similarly correlate with large vessel endothelial function and arterial stiffness (33). Lower serum 25-hydroxy vitamin D is independently associated with impaired flow-mediated dilation of the brachial artery, increased pulse wave velocity, and augmentation index, all markers of large artery stiffness and endothelial dysfunction (29,34). Furthermore, vitamin D supplementation tends to yield a more consistent and modest improvement in microvascular function compared to large vessel function (35). In addition, the improvements in microvascular vasodilation and arterial stiffness following vitamin D normalization were statistically significant but modest in magnitude (33,36). However, effects on large vessel endothelial function and stiffness markers like flow-mediated dilation and pulse-wave velocity are also present although account for smaller variability and sometimes show less robust changes in the short term (37).

Conclusion

The effect of vitamin D supplementation on vascular consistency, often measured through markers like endothelial function, arterial stiffness, and related cardiovascular indicators. Vitamin D receptors are present in vascular smooth muscle and endothelial cells, suggesting a biological basis for potential effects. Vitamin D may modulate inflammation, reduce vascular resistance, and influence the renin–angiotensin system, which could theoretically benefit vascular health.

Authors' contribution

Conceptualization: Kamran Shirbache.
Investigation: Kamran Shirbache, Ali Shirbacheh.
Resources: Ali Shirbacheh.
Supervision: Kamran Shirbache.
Validation: Kamran Shirbache.
Writing–original draft: Kamran Shirbache.
Writing–review and editing: Kamran Shirbache, Ali Shirbacheh.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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