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Review Article

Pharmacology for better Drug screening

Vitamin D Potential in Reducing Blood Pressure for Obese Geriatrics

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Abstract: Vitamin D deficiency and hypertension are significant global health concerns. Despite extensive research, the role of vitamin D in regulating blood pressure remains ambiguous. This raises questions about whether routine vitamin D testing and supplementation should be integrated into hypertension prevention and management strategies. Recent studies have explored the potential mechanisms linking vitamin D to blood pressure regulation, including its effects on vascular function and inflammation. This article reviews the latest evidence, focusing on research from the past two years, to provide insights into this ongoing scientific debate. Previous reviews on vitamin D and blood pressure have often overlooked the specific impact on older adults with obesity, a high-risk group for hypertension. This review addresses this gap by exploring the potential of vitamin D as an adjunct in managing hypertension in this population, emphasizing recent findings and clinical relevance. This article explores vitamin D's role in blood pressure regulation, focusing on biological mechanisms, including the renin-angiotensin-aldosterone system and endothelial impairment linked to reactive oxygen species. It reviews the studies where blood pressure was analyzed as a secondary result, emphasizing the processes of vitamin D in hypertension regulation. Our review also examines the impact of vitamin D supplementation on blood pressure, offering insights into its therapeutic potential. The review integrates recent findings, providing a comprehensive understanding of vitamin D's impact on hypertension management. This review addresses gaps in earlier studies by focusing specifically on older adults with obesity, a group often neglected in hypertension research. It integrates recent findings on vitamin D's mechanisms and supplementation effects, offering updated, targeted insights to guide current clinical strategies in managing hypertension amidst rising obesity prevalence.

Keywords: Vitamin D deficiency, Hypertension, Blood pressure regulation, Obesity, Renin–angiotensin–aldosterone system, Vitamin D supplementation

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1. INTRODUCTION

Vitamin D insufficiency is a widespread global health concern, affecting a significant portion of the population across diverse age groups and geographic regions. Its prevalence is higher in individuals with limited exposure to sunlight, particularly in areas with high latitudes or during winter months when ultraviolet B (UVB) radiation levels are insufficient for adequate vitamin D synthesis in the skin. Urbanization, increased indoor lifestyles, the use of sunscreens, and cultural practices that limit skin exposure further exacerbate the problem. A striking overlap exists between the geographical and seasonal patterns of vitamin D deficiency and the prevalence of cardiovascular disorders, suggesting a possible epidemiological and physiological connection. Decades ago, initial studies identified a potential link between vitamin D, blood pressure, and related hormonal pathways, sparking interest in the role of this vitamin beyond bone health. However, findings from subsequent research have yielded inconsistent results, with some studies reinforcing the association while others show weak or no significant correlation. This review aims to synthesize recent advancements in understanding the intricate relationship between vitamin D and blood pressure, particularly emphasizing findings from the past few years. Vitamin D, a group of fat-soluble steroids primarily recognized for its essential role in preventing rickets and osteomalacia, facilitates the absorption of critical minerals such as calcium and phosphate to maintain bone health[1]. Over the past decades, there has been a growing recognition of its extensive impact on various organ systems, including cardiovascular, endocrine, and immune functions. Receptors for the bioactive form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), have been identified in most human tissues, implying its systemic significance. Hypertension, a common and chronic condition often dubbed the "silent killer" due to its asymptomatic progression, has been strongly linked to vitamin D deficiency in numerous observational studies [2]. Elevated blood pressure is a leading risk factor for cardiovascular diseases, including heart attack, stroke, and heart failure, making the exploration of its modifiable risk factors, such as vitamin D status, of critical importance. While observational and animal studies suggest a robust correlation between vitamin D levels and cardiovascular health, including blood pressure regulation, interventional trials have produced mixed results. Differences influence variability in these findings in study design, sample size, population demographics, vitamin D dosage, and baseline deficiency levels. Moreover, factors such as aging, genetics, socioeconomic status, and lifestyle choices, including dietary habits, physical activity, and obesity, contribute to the multifactorial nature of hypertension. This review delves into the proposed physiological mechanisms by which vitamin D might influence blood pressure regulation, exploring pathways involving the renin-angiotensin-aldosterone system (RAAS), vascular endothelial function, and anti-inflammatory effects. It also examines the spectrum of evidence from prior studies conducted across diverse populations, highlighting gaps in knowledge and areas for future research.

1.1 Biological Mechanisms

Vitamin D may influence blood pressure via multiple pathways, including its association with the renin-angiotensin-aldosterone system (RAAS), endothelial function, and vascular smooth muscle activity [3]. By modulating RAAS, vitamin D helps suppress renin expression, a critical factor in blood pressure regulation. V itamin D can also affect vascular smooth muscle activity, which is important for regulating the constriction and dilation of blood vessels. Overall, the various mechanisms through which vitamin D influences blood pressure highlight the importance of maintaining adequate levels of this essential nutrient for cardiovascular health. This modulation may prevent excessive vasoconstriction and fluid retention, both of which contribute to hypertension. Vitamin D enhances endothelial function by improving nitric oxide availability, promoting vasodilation, and reducing oxidative stress and inflammation [4]. These effects are essential for maintaining vascular health. In addition, vitamin D has been shown to inhibit the renin-angiotensin system, a key player in regulating blood pressure. By decreasing the production of angiotensin II, a potent vasoconstrictor, vitamin D helps to keep blood vessels relaxed and open, reducing the risk of high blood pressure. Overall, ensuring adequate levels of vitamin D through sunlight exposure, diet, or supplementation is crucial for cardiovascular health and the prevention of hypertension. Furthermore, vitamin D directly impacts vascular smooth muscle cells by inhibiting their proliferation and migration, processes that are often associated with vascular remodeling and hypertension development [5]. Collectively, these mechanisms support the potential role of vitamin D as a modulator of cardiovascular health, providing avenues for therapeutic interventions in blood pressure management. Obesity is linked to chronic inflammation, oxidative stress, and endothelial dysfunction, all of which contribute to high blood pressure[6]. Vitamin D reduces pro-inflammatory cytokines, improves nitric oxide availability, and combats oxidative stress. In obesity, vitamin D sequestration in adipose tissue lowers its bioavailability, exacerbating hypertension risk. Vitamin D enhances insulin sensitivity, countering insulin resistance commonly observed in obese individuals [7]. With age, reduced skin synthesis of vitamin D further necessitates supplementation. These effects collectively highlight vitamin D's potential as a therapeutic tool for hypertension management in this population.

1.2 Renin-angiotensin-aldosterone

Collaborative research in animal and human studies has furnished compelling evidence that vitamin D plays a significant role in diminishing the activity of the renin-angiotensin-aldosterone system (RAAS), a critical regulator of blood pressure and fluid balance[8]. Initial studies demonstrated that mice lacking vitamin D receptors exhibited elevated renin levels and hypertension, which were successfully alleviated using active vitamin D therapy [9]. These findings highlighted the integral role of vitamin D in maintaining cardiovascular homeostasis. Furthermore, inhibiting the RAAS axis through vitamin D therapy ameliorates cardiac structural alterations, notably left ventricular hypertrophy (LVH), a common consequence of prolonged hypertension [10]. Similarly, mice deficient in the enzyme necessary for converting vitamin D into active form demonstrated hypertension and LVH, underscoring the importance of active vitamin D in regulating cardiovascular and renal function [11]. At the molecular level, active vitamin D has been shown to directly interact with the promoter region of the renin gene in Mus musculus, effectively suppressing its expression and thereby reducing the overall activity of the RAAS axis [12]. This finding suggests that vitamin D plays a crucial role in regulating blood pressure and fluid balance by modulating the activity of the renin-angiotensin-aldosterone system. By inhibiting renin expression, active vitamin D helps prevent excessive vasoconstriction and

sodium retention, ultimately maintaining healthy blood pressure levels. Further research into the mechanisms underlying this interaction may provide new insights into the treatment and management of hypertension. This mechanistic insight is crucial in understanding vitamin D's antihypertensive effects. Recent research on renal arteries derived from patients with hypertension further indicated that calcitriol, the active form of vitamin D, diminishes the expression of angiotensin-1 receptors in endothelial cells, providing another layer of evidence for its role in modulating RAAS activity [13]. In addition to these biochemical and molecular findings, clinical observations have demonstrated that patients with lower vitamin D levels exhibit a weakened blood pressure response to angiotensin [14]. This suggests that vitamin D deficiency may impair the body's ability to regulate blood pressure effectively. Genetic studies have revealed that patients possessing a specific genetic variation in the gene encoding the vitamin D receptor show decreased plasma renin activity compared to individuals with alternative genetic profiles [15]. These findings emphasize the potential of vitamin D as a therapeutic target for managing hypertension and associated cardiovascular conditions, given its multifaceted role in regulating RAAS activity and maintaining vascular health. Emerging evidence highlights the role of vitamin D in addressing hypertension, particularly in obese older adults, who are at an appreciable risk due to chronic inflammation and increased RAAS activation. Vitamin D deficiency in this population is linked to impaired vascular function, insulin resistance, and elevated adiposity-related renin activity. Supplementation with vitamin D has been shown to improve endothelial function, reduce arterial stiffness, and lower systemic inflammation, which is crucial for blood pressure regulation. Vitamin D enhances nitric oxide bioavailability in vascular endothelium, counteracting the vaso-constrictive effects of obesity-related RAAS over activation, underscoring its therapeutic potential in this demographic [16].

1.3 Endothelial dysfunction and reactive oxygen species

Prolonged administration of active vitamin D compounds has significantly affected vascular tone and cardiovascular health. In animal studies involving Rattus norvegicus, such administration was observed to decrease blood pressure and cyclooxygenase-1 levels, both of which are critical markers of vascular health [17]. Simultaneously, this intervention was associated with increased endothelial dysfunction and reactive oxygen species (ROS) production, highlighting the complex interplay between vitamin D and vascular homeostasis [18]. Conversely, a contrasting scenario was observed in rats with pronounced vitamin D deficiency, which resulted in significantly elevated blood pressure levels compared to their vitamin D-sufficient counterparts [19]. This increase in blood pressure was further linked to a marked reduction in endothelium-derived nitric oxide-mediated vasodilation, a critical factor for maintaining vascular relaxation and preventing hypertension. These findings underline the dual role of vitamin D in vascular function depending on its levels. Complementing these preclinical insights, a minor clinical trial involving patients with type 2 diabetes and low 25(OH)D levels offered additional evidence of vitamin D's therapeutic potential. Participants in the trial were randomly assigned to receive either a single high dosage of vitamin D2 or a placebo. The results demonstrated that vitamin D supplementation significantly improved endothelial function, as evidenced by enhanced vasodilatory responses, and led to a notable reduction in systolic blood pressure compared to the placebo group [20]. These findings suggest that addressing vitamin D deficiency might be a viable strategy to mitigate cardiovascular risks, particularly in populations with co-existing conditions like diabetes. However, further extensive clinical trials are needed to validate these results and elucidate the mechanisms by which vitamin D modulates vascular health. Vitamin D deficiency correlates with increased arterial stiffness, reduced endothelial nitric oxide synthase (eNOS) activity, and heightened renin-angiotensin-aldosterone system (RAAS) activation. In obese older adults, diminished cutaneous synthesis of vitamin D and altered metabolism contribute to lower serum 25(OH)D levels, intensifying cardiovascular risks. Clinical evidence indicates that restoring vitamin D levels improves endothelial function, enhances vasodilation, and reduces systolic blood pressure. Targeted vitamin D supplementation in this demographic may provide a cost-effective strategy to alleviate hypertension and associated vascular complications.

1.4 Blood pressure as a secondary outcome measure

Numerous randomized trials have not established blood pressure as the primary endpoint. Overweight or obese individuals were randomly allocated to receive cholecalciferol or a placebo for one year to evaluate cardiovascular outcomes. Both vitamin D groups had comparable 25(OH)D levels at baseline, whereas the placebo group presented a distinct baseline. The trial revealed no impact on systolic or diastolic blood pressure. Previous studies have examined the impact of vitamin D on blood pressure; nevertheless, the majority have determined that 25(OH)D exerts no meaningful effect on blood pressure [21]. The most extensive research in this domain, the Women's Health Initiative, the Calcium/Vitamin D Trial, included postmenopausal women randomly allocated to receive either cholecalciferol or a placebo daily for seven years. The main outcome was the occurrence of hip fractures, with no significant changes observed in either systolic or diastolic blood pressure [22]. This study's strengths comprised its substantial sample size and prolonged follow-up duration. The increased occurrence of vitamin D supplementation unrelated to the study in the placebo group may have diminished the disparity between the groups. Two recent trials utilizing active vitamin D compounds, which are markedly more efficacious than dietary forms of 25(OH)D, evaluated the effect of paricalcitol on proteinuria over a 24-week compared to a placebo in individuals. The study revealed a dose-dependent decrease in SBP in the paricalcitol cohort vs. the placebo group [23]. The majority of individuals exhibited hypertension at baseline, and, akin to other studies, the dosage of antihypertensive medication was omitted from the analysis, perhaps presenting a bias against finding a meaningful outcome. The Paricalcitol Capsule Benefits trial examined patients with chronic renal disease and left ventricular hypertrophy, who were randomly assigned to receive either paricalcitol or a placebo for 48 weeks. No differences were observed in primary outcomes or systolic and diastolic blood pressure. This study had limitations, including the absence of a requirement for vitamin D deficiency in patients, all participants undergoing advanced blood pressure control, and a lack of data on antihypertensive medication dosages. Due to the insufficient and ambiguous evidence, Additional randomized trials focusing on blood pressure as the major outcome while rigorously assessing antihypertensive drug utilization in individuals with substantial vitamin D deficiency are necessary.

1.5 The Function of Vitamin D in Blood Pressure Regulation

The vitamin D receptor (VDR) is found in various organs, with several containing 1α-hydroxylase alongside the renal proximal tubule. The data indicate that vitamin D is crucial for the biological functioning of cells in various tissues. Various mechanisms influence hypertension; the inappropriate stimulation of the renin-angiotensin-aldosterone system (RAAS) is a major factor. Renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and mineralocorticoid receptor antagonists are essential in treating hypertension as inhibitors of the RAAS. Vitamin D, also known as the "sunshine hormone," has demonstrated an impact on the RAAS at clinical, pathophysiological, and molecular levels in animal and human studies. Preliminary epidemiological data indicated an inverse link between vitamin D and renin, a correlation corroborated by recent research. Individuals exhibiting low vitamin D levels demonstrated increased angiotensin II concentrations and impaired renal responses to angiotensin II infusion, signifying RAAS activation amid diminished vitamin D. Furthermore, studies on mice deficient in vitamin D signaling demonstrated elevated Renin gene expression and plasma angiotensin II levels lead to elevated blood pressure, heart hypertrophy, and increased fluid consumption. The influence of vitamin D on renin suppression was not contingent upon calcium or phosphorus concentrations. Mechanistic studies demonstrated that 1,25(OH)2D3 binds to the VDR, inhibiting the formation of cAMP-response element-binding protein complexes in the renin gene promoter, reducing renin gene expression. Individuals with chronic kidney disease (CKD) often have Vitamin D deficiency resulting from the urine excretion of vitamin D binding proteins, compromised cutaneous synthesis, diminished increased activity of 1α-hydroxylase, elevated levels of FGF23, and malnutrition [24]. Observational studies indicate a favorable correlation between 25(OH)D levels and flow-mediated dilation (FMD) in people with CKD [25]. Moreover, animal research has demonstrated that insufficient vitamin D activity reduces endothelial nitric oxide synthase synthesis, contributing to heightened arterial stiffness [26].

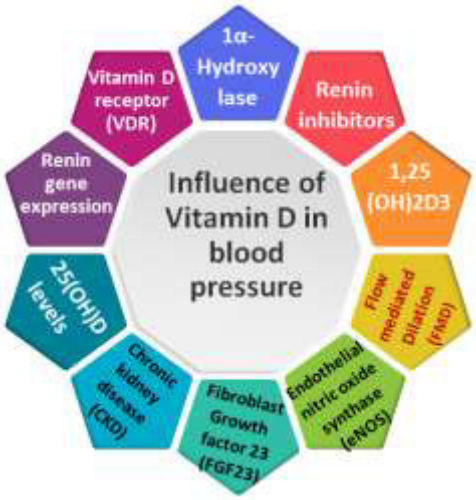

Fig 1: Influence of Vitamin D on Blood Pressure

1.6 The Effects of Vitamin D Supplementation on Hypertension

Despite several interventional research, the impact of vitamin D administration on the decrease of blood pressure in people remains contentious. Lind et al. exhibited a decrease in diastolic blood pressure after the injection using alphacalcidol, a synthetic counterpart of active vitamin D, in a double-blind, placebo-controlled trial involving participants with hypercalcemia or primary hyperparathyroidism [27]. However, they noted no impact of alphacalcidol on hypertension in individuals with impaired glucose tolerance throughout the same trial period [28]. Krause et al. revealed that short exposure to ultraviolet B lowered blood pressure in individuals with moderate untreated hypertension, concurrently elevating plasma vitamin D levels [29]. Numerous studies indicated that a substantial single dose of active vitamin D can lower SBP in individuals with type 2 diabetes. Nevertheless, maximum single doses of vitamin D3 failed to lower blood pressure in these patients, and daily consumption of vitamin D3 showed no benefit. Sharb-Bidar et al. noted that the conjunction of vitamin D3 and calcium supplementation affected SBP and DBP in patients with type 2 diabetes [30]. An eight-week regimen of this mixture also enhanced blood pressure in elderly women. The Women's Health Initiative for the Calcium/Vitamin D trial, involving postmenopausal women, showed no effect of daily vitamin D3 and calcium supplementation on blood pressure or hypertension risk throughout a seven-year follow-up period. Vitamin D may affect the lowering of blood pressure among some racial and ethnic groups. Skin pigmentation affects circulating vitamin D levels, and African Americans, who generally exhibit elevated hypertension rates, may benefit from supplementation. A decrease in systolic blood pressure following three months of vitamin D3 treatment in normotensive African Americans, with a more pronounced fall in individuals with lower vitamin D levels, was reported in early studies [31]. Conversely, Scragg et al. observed no impact of high-dose vitamin D3 on blood pressure regulation among predominantly white participants [32]. Nonetheless, alternative short-term studies with nonwhite populations did not demonstrate the impact of vitamin D on blood pressure, potentially attributable to limited sample sizes. Numerous recent meta-analyses have investigated the impact of vitamin D supplementation on hypertension. A randomized controlled trial study investigating oral vitamin D supplementation in normotensive and hypertensive people revealed that vitamin D considerably lowered SBP, with no effect on DBP [33]. Vitamin D has been shown to play a crucial role in vascular health by enhancing endothelial nitric oxide (NO) production. This potent vasodilator improves arterial compliance and lowers

blood pressure. Endothelial dysfunction, a hallmark of hypertension and obesity, is often accompanied by reduced NO bioavailability. Vitamin D mitigates oxidative stress and inflammation, impairing NO synthesis. This improvement in endothelial function is particularly significant in obese older individuals, who frequently exhibit heightened vascular stiffness due to chronic low-grade inflammation and metabolic disturbances. Combined vitamin D and weight-loss interventions amplify benefits by addressing multiple hypertension pathways. Weight loss reduces adipose tissue-mediated inflammation and improves insulin sensitivity, while vitamin D supplementation augments these effects by modulating the renin-angiotensin-aldosterone system (RAAS). Studies have reported synergistic reductions in systolic blood pressure (SBP) in obese individuals undergoing combined approaches [34]. Impaired renal function in obesity-related hypertension also underscores vitamin D's importance. Vitamin D regulates renin levels, preventing excessive RAAS activation—a critical driver of hypertension. Animal studies demonstrate that vitamin D deficiency increases renin expression, angiotensin II levels, and subsequent hypertension [35]. Thus, restoring adequate vitamin D levels may counteract RAAS over activation, improve renal function, and reduce systemic blood pressure in obese older adults.

2. CONCLUSION

Comprehensive cross-sectional studies demonstrated a robust link between vitamin D and blood pressure, supported by numerous biological mechanisms. Nevertheless, longitudinal and randomized experiments, many of which consider blood pressure as a secondary variable outcome, have produced conflicting results. Most research has utilized minimal doses of vitamin D or concentrated on persons with well-managed hypertension. Limited research has adequately considered the dosage of antihypertensive medications or the potential influence of inhibitors of the renin-angiotensin-aldosterone pathway, which may obfuscate interpretation and amplify bias towards the null hypothesis. Randomized studies, especially concerning hypertensive persons with substantial vitamin D deficiency, are necessary before endorsing routine screening or therapy for vitamin D insufficiency in individuals with elevated blood pressure. Randomized controlled studies and meta-analyses do not endorse vitamin D as a therapeutic intervention for hypertension in individual patients or as a population-wide approach to reducing blood pressure. These inconsistencies may stem from variations in patient characteristics, sample sizes, follow-up durations, and vitamin D dosages. Numerous studies suggest that vitamin D may influence blood pressure regulation through various mechanisms. Still, more randomized controlled trials are needed to confirm its true effect on blood pressure reduction and to determine the optimal dosage, frequency, and formulation of vitamin D for treatment.

3. AUTHORS CONTRIBUTION STATEMENT

John Abraham contributed to the literature review, data interpretation, and manuscript editing. Bino Benjamin played a significant role in study methodology and data validation. Debananda Sahoo assisted in data acquisition and ensured adherence to ethical guidelines. Vaishali Ashish Shirsat contributed to data analysis and graphical representation of results. Laitonjam Jonita Devi provided technical support, critically reviewed the manuscript, and assisted in finalizing the submission. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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