REVIEW ARTICLE

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A REVIEW ON HYPERTENSION, VITAMIN D AND THE ROLE OF VITAMIN D IN HYPERTENSION

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ABSTRACT

Hypertension is a global public health concern and millions are affected by it. It is multifactorial and initial therapeutic means is to bring about life style changes with consumption of healthy diet and regular exercise. However, despite such changes there are many patients who require pharmacological management. Vitamin D is a micronutrient that has multiple functions like in the regulation of calcium ion and bone metabolism in our body and one such role may be its influence in blood pressure regulation. Lower vitamin D levels may cause rise in renin-angiotensin-aldosterone system (RAAS) and hence aggravate a rise in blood pressure. This narrative review aims to look in to the role of vitamin D in blood pressure control and the possible effect of supplementation in lowering blood pressure in hypertensive patients.Vitamin D may be used as adjuvant therapy and large scale future studies are required to assess the role of this nutrient in hypertension.

Keywords: Micronutrient, Blood pressure, RAAS, Multiple risk factors, Adjuvant therapy, Supplementation

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INTRODUCTION

Vitamin D has several functions within the human body.Homeostasis of calcium and bone metabolism requires vitamin D and the risk of fracture is reduced among the elderly when vitamin D supplementation is given to them[1]. Another role that has come into light through various clinical and epidemiological studies is its association with blood pressure homeostasis[2]. One of the serious factors of risk for cardiovascular disease like stroke, myocardial infarction and coronary artery disease is untreated hypertension[3].

It has been noted in different studies that deficiency of vitamin D may result in hypertension development and this deficiency has been marked as an independent risk factor of high blood pressure. Insufficient sunlight exposure, deficiency of vitamin D, raised plasma renin activity and hypertension have been linked in previous research work[3-5]. Blood pressure on average remains higher in winter when compared to that of summer suggestive of association between sunlight exposure, activated vitamin D and blood pressure maintenance[6-8].

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Th following section includes details about the method employed to conduct this review.

MATERIALS AND METHOD

This review gathers the current information related to vitamin D and hypertension. Online data base like PubMed, Scopus, Google search engine were used to retrieve the required research works. The keywords used to make the search included 'Vitamin D', 'Hypertension', 'Cholecalciferol', 'Vitamin D and blood pressure'.

The following sections deal with the detailed review on hypertension vitamin D and the role of vitamin D in hypertension.

HYPERTENSION (ARTERIAL)

When arterial blood pressure is raised above normal range, the condition is known as arterial hypertension (persistent blood pressure of ≥140/90 mmHg) and indicates that there is a constant elevation of the force of blood which exerts lateral pressure on the arterial wall. As a result the heart requires to pump with more force than normal[9,10]. A balance between vascular resistance and cardiac output (dependent on heart rate and stroke volume) is needed for maintaining blood pressure within normal range. Nervous regulation of blood pressure involves the sympathetic nervous system and the neurotransmitters norepinephrine. Renin-angiotensin-aldosterone system (RAAS) is a key player in the regulation of blood pressure. Heart rate, vasodilation and vasoconstriction of arterioles are the mechanical components of blood pressure maintenance[11].

Some of the risk factors of hypertension which are known include obesity, family history, age, lack of physical exercise, diet high in salt, consumption of high quantity of alcohol, smoking and pregnancy in some cases[9]. In addition to risk factors pertaining to lifestyle, there are certain medications that may induce hypertension and these include non-steroidal anti-inflammatory drugs, oral contraceptives, glucocorticoids and ciclosporin [12].

HYPERTENSION TYPES

The blood pressure levels may vary when depending on where it is being measured since in clinical setting blood pressure may be elevated in patients but out of clinic their readings are normal (often found in untreated subjects) and is known as white coat hypertension[13,14] . On the other hand, there are patients whose blood pressure is found to be high in out of clinic setting while at the clinic the values are normal. This is known as masked hypertension and is observed in treated patients[13]. There are certain patients in whom hypertension remains uncontrolled despite being treated with 3 or more antihypertensive drugs at highest appropriate dosage. This condition is known as resistant hypertension[15]. Blood pressure of 130-139 mmHg (Systolic) and /or 85-89 mmHg (Diastolic) is regarded as high normal blood pressure. Hypertension Grade 1 is 140-159 mmHg (Systolic) and 90-99 mmHg (Diastolic) ; Grade 2 is 160-179 mmHg (Systolic) and/or 100-109 (Diastolic); Grade 3 is ≥180 mmHg (Systolic) and/or ≥110 mmHg (Diastolic); and isolated systolic hypertension is ≥140 mmHg (Systolic) and <90 mmHg (Diastolic)[16]. The European Society of Cardiology (ESC) has made the following recommendation for diagnosing hypertension in 2024[17] (Figure 1).

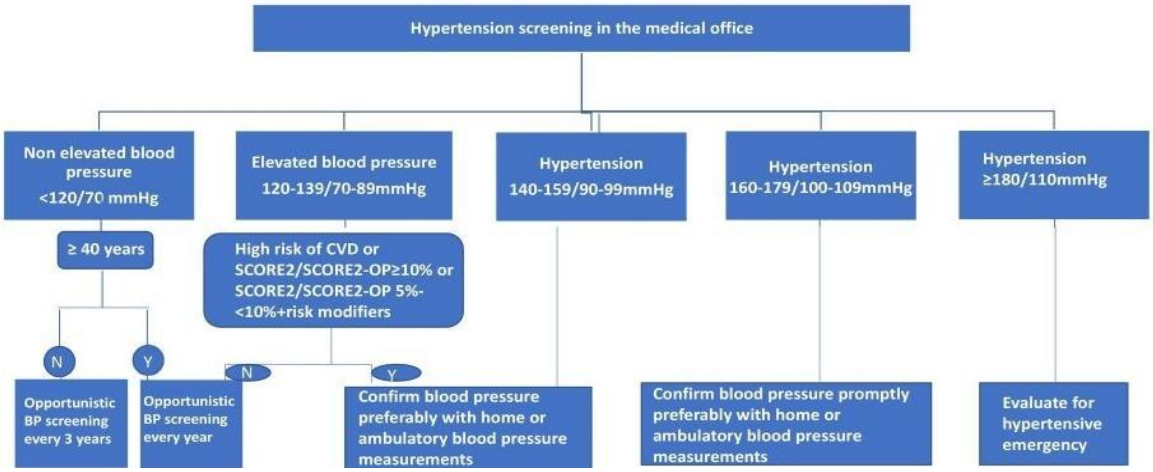

Figure 1 : Displays the recommendation for diagnosing hypertension. SCORE 2: risk prediction algorithms: new models to estimate 10 year risk of cardiovascular disease in Europe; SCORE2-OP: risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions.Y: Yes; N: No. Image credit: Rahnuma Ahmad.

EPIDEMIOLOGY OF HYPERTENSION

Globally hypertension is the 3rd leading reason of disease burden[18]. Hypertension prevalence in adults is about 1.28 billion (30% to 45%) worldwide with almost 2/3rd residing in low and middle-income countries[19,20]. This value is expected to rise by 15% to 20% by year 2025[21]. Disability-adjusted life due to hypertension since the year 1990 has risen by 40% even though sufficient knowledge regarding prevention strategies and treatment of hypertension exists[22,23]. Hypertension related deaths may take place when cardiovascular disease develop like ischemic heart disease lead to about 4.9 million demises, ischemic stroke lead to 1.5 million deaths and hemorrhagic stroke cause 2.0 million demises[2,24]. A study done with 2017-2018 Bangladesh Demographic and Health Survey observed the age-standardized prevalence of hypertension was 23.5% for men and 28.9% incase of women. Among those who were hypertensive only 31.1% received medication to manage hypertension[25].

CONVENTIONAL MANAGEMENT OF HYPERTENSION

Lifestyle modification and treatment using antihypertensive drugs remain the well accepted means of managing hypertension[26]. DASH (Dietary Approaches to Stop Hypertension) is advised in national guidelines and suggests diet rich in vegetables, fruits and diet products low in fat[27]. Hypertension risk is reduced irrelevant of BMI, age and other risk factors when the individuals perform regular exercise[28].

Antihypertensive medication prescription is recommended when despite lifestyle modification, systolic blood pressure is ≥ 140 mmHg and diastolic blood pressure is ≥ 90 mmHg[29]. The 5 major classes of drugs prescribed as per recent guidelines include angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), diuretics, and angiotensin receptor blockers (ARBs), beta-adrenergic receptor blockers (BARBs)[30-39].

METABOLISM OF VITAMIN D

Photoconversion of 7-dehydrocholesterol occurs in the human skin to pre-vitamin D3. Isomerization of pre-vitamin D3 to vitamin D3 then takes place[40]. After formation of vitamin D3, its translocation into the circulation occurs by means of vitamin D-binding protein [41]. Transportation of vitamin D takes place either bound to vitamin D-binding protein or within chylomicrons to liver or into

body fat for storage[42]. Modulation of vitamin D into liver by means of plasma carriers, and in the liver vitamin D is converted to 25-hydroxycholecalciferol[42, 43]. Vitamin D status of an individual is monitored using this 25-hydroxycholecalciferol[43]. From the liver 25-hydroxycholecalciferol passes to kidney where 25-hydroxyvitamin D3-1α-hydroxylase (mitochondrial enzyme P450) converts it to 1, 25-dihydroxyvitamin D3 (biologically active form of vitamin D)[42, 44]. Homeostasis of calcium and phosphate, cellular differentiation and bone growth requires the action of 1, 25-dihydroxyvitamin D3[44].

Vitamin D is found in nature in 2 forms including ergocalciferol (plant source) and cholecalciferol (animal source[45]. It has been reported in research that cholecalciferol in humans is more active than ergocalciferol since cholecalciferol increases and maintains the levels of 25-hydroxycholecalciferol better than ergocalciferol[46].

RESPONSE OF VITAMIN D RECEPTOR

Vitamin D receptor has been found to be present and active in the intestine, bone, parathyroid gland, and kidney[47]. The responses to active form of vitamin D can be both nongenomic and genomic[48]. In case of genomic response, when vitamin D receptor is activated by vitamin D hormone, the receptor translocates into the nucleus and forms heterodimer complex with nuclear hormone receptors, particularly retinoid X receptor[48-50]. Recognition of vitamin D response element in the vitamin D regulated gene's DNA sequence[48]. There is recruitment of chromatin-active complexes that take part in transcription [51-53]. In case of non-genomic response to the active form of vitamin D3, the hormone binds to vitamin D receptor in the membrane and to the 1,25 D-membrane-associated rapid response steroid-binding protein. This step initiates multiple pathways of cell signaling pathways like Janus Kinase MAP kinase and MAP kinases ERK 5/ ERK1/ERK2[54-56]. Activation of protein kinase C promotes the active vitamin D3 functioning in the intestinal epithelial cells[55]. The non-genomic response also activates other molecules of signaling pathway like phosphatidylinositol-3-kinase, p21ras and phospholipase A_2. There is generation of second messengers that include 3-phosphoinositides, fatty acids,cyclic AMP, calcium.The targets downstream are transcription factors SP3, SP1 and retinoid X receptors which promote recognition of response element on vitamin D responsive gene promoters[58].

VITAMIN D3 FUNCTIONS

The functions of vitamin D3 are mediated mostly by the genomic response in multiple target tissues[59]. There are about 11 genes (encode effectors of mineral and bone homeostasis) whose expression is regulated by active form of vitamin D[60]. Regulation of expression of gene for calcium ATPase PMCA1b, calbindin, intestinal TRPV6, TRPV5 and renal TRPV5 calcium channel is carried out by vitamin D3 (active form) and thus promote intestinal absorption and renal reabsorption of calcium and increase mineralization of skeleton[60,61]. Phosphate release is inhibited by vitamin D[62]. Vitamin D stimulates the expression of Na^+/phosphate cotransporter NaPi-2b/Slc34a2 in the intestine and therefore promotes phosphate absorption[64]. In the kidney 1, 25 dihydroxycholecalciferol inhibits renal Na^+/phosphate cotransporter 2a and 2c that promote excretion of phosphate in urine and in the bone this hormone causes expression of phosphaturic peptide and thus influence phosphate homeostasis[64]. 1, 25 dihydroxy cholecalciferol also plays an essential role in bone remodeling and resorption. Expression of RANKL (receptor activator of nuclear factor kappa beta) on stromal cells/osteoblasts is upregulated by 1, 25 dihydroxycholecalciferol and therefore there is promotion of osteoclastogenesis.

This results in bone resorption[65]. 1, 25 dihydroxycholecalciferol controls osteoblast transcription and thus causes formation of proteins of bone matrix like collagen, osteocalcin, and osteopontin[60,66].

Other than its involvement in bone and mineral balance, 1, 25 dihydroxycholecalciferol also participates in immune response modulation. The evidence for its regulatory role in both adaptive and innate response is that vitamin D receptors and vitamin D metabolizing enzymes are found in monocytes, macrophage, activate T and B cells, and dendritic cells[67]. It has been reported that vitamin D receptor activation improves vascular and endothelial function by means of suppressing activity neurohormonal[68]. Plasma renin activity has also been linked to levels of 1, 25 dihydroxycholecalciferol[69]. Raised activity of renin and angiotensin II has been noted in mice without vitamin D receptor activity[70]. Such studies suggest existence of interrelationship between activation of vitamin D receptor and renin-angiotensin-aldosterone system (RAAS) indicating a connection between vitamin D and arterial hypertension[2].

HYPERTENSION AND VITAMIN D

Deficiency of vitamin D is one of the risk factors of hypertension and the level of vitamin D is related inversely to blood pressure and the incidence of hypertension[71]. The vitamin D deficiency may lead to raise in the RAAS activity in the kidney and systemically as has been observed in previous study[72]. Elevation of the activity of sympathetic nervous system and increase in intra-glomerular pressure due to raised plasma concentration of renin would provoke arterial hypertension, fall in glomerular filtration rate (GFR), with eventual damage to the cardiovascular system[73]. In mice with knocked out vitamin D receptor or the gene for 1α-hydroxylase have been noted to develop an upregulation in activity of RAAS and aggravate hypertension[74,75]. On the hand when these mice are given 1, 25 dihydroxycholecalciferol, the RAAS activity is suppressed[75]. Diastolic activity, relaxation of muscle and influx of calcium in the vascular tissue like smooth muscle of blood vessels, myocardium, and juxtaglomerular apparatus that forms renin are influenced directly by vitamin D[76, 77].

Plasma concentration of calcium ion is decreased when there is a deficiency in vitamin D levels, this in turn would promote parathyroid hormone secretion from parathyroid gland chief cell [2]. Increased levels of systolic and diastolic blood pressure and raised hypertension prevalence due to rise in plasma parathyroid hormone level have been reported in various studies[78-80]. Administration of parathyroid hormone in healthy individuals have led to rise in values of blood pressure in some studies[81,82]. It has been suggested that hypercalcemia resulting from increased parathyroid hormone may cause impairment of function of endothelium[83]. 1α-hydrolase enzyme (involved in converting 25-hydroxycholecalciferol to calcitriol) is expressed by smooth muscle of both vascular and endothelial[84]. Lipopolysaccharides and TNF-α are some of the molecules of inflammation that are able to activate this enzyme in Human Umbilical Vein Endothelial Cells (HUVECs)[85]. Vitamin D has also been reported to decrease influx of calcium and therefore directly influence the tone of blood vessel[86]. Hypertension development risk and complications related to hypertension have been associated with low levels of 25 hydroxy cholecalciferol by previous studies [87-99] which indicates towards vitamin D supplementation for such patients[2].

HYPERTENSION AND VITAMIN D CLINICAL TRIALS

Some clinical trials performed with vitamin D and hypertension have been displayed in Table 1.

Table 1: Clinical trials with vitamin D supplementation in hypertension:

Research title	Study design	Intervention	Parameters measured/Timeline of measurement	Results	Conclusion
Short-term vascular effects and oxidative status of calcium and vitamin D supplementation of postmenopausal hypertensive black women (2020)[100]	Double-blind, randomized, and parallel clinical trial with 22 recruits	The study subjects included patients taking stable antihypertensive therapy for at least 3 months Subjects given Calcium: 1000 mg calcium tablet/day for 8 weeks Vitamin D / calcium given: 1000 mg/800UI of vitamin D / calcium tablet per day for 8 weeks	Alteration in 24 hour blood pressure and serum malondialdehyde from before beginning trial to week 8	No significant diurnal changes in systolic blood pressure $p = 0.630$ (Calcium vs. vitamin D/calcium) However, Uric acid levels reduced significantly in those receiving vitamin D/Calcium combination in comparison to those only taking calcium(16mg/L vs. 11 mg/L) $p = 0.020$.	Diurnal blood pressure and inflammatory markers decreased with supplementation with vitamin D/Calcium combination in postmenopausal hypertensive women
Effects of vitamin D on blood pressure and cardiovascular risk factors (2014)[68,101]	Double blind, placebo controlled study done at a single center	Subjects included patients with hypertension and 25 hydroxycholecalcifer ollevel below 30ng/mL. Treatment group: 2800 IU vitamin D_3 / day for 8 weeks Placebo group: placebo for 8 weeks	24-h systolic and diastolic ambulatory blood pressure , concentration of renin, aldosterone in plasma, triglyceride, HDL NT-pro-BNP, 24-h excretion of albumin in urine after 8 weeks	There was no significant decrease in 24 hour systolic blood pressure ($p = 0.712$). A significant rise in triglyceride level was observed in treatment group ($p = 0.013$). There was significant rise in vitamin D level in plasma ($p < 0.001$) and a significant fall in Parathyroid ($p = 0.003$)	There was no significant effect on blood pressure upon vitamin D supplementation
DAYLIGHT: Vitamin D therapy in individuals at high risk of hypertension (2017)[102]	Double-blind, randomized, controlled trial with 534 recruits	Subjects included patients with systolic blood pressure between 120mmHg and 159 mmHg and diastolic blood pressure ≤ 99 mmHg, not taking any antihypertensive drugs. Their 25 hydroxycholecalcifer ol level below 25 ng/mL. Participants divided in to 2 groups subjects given high dose of vitamin D3: 4000 IU/d for 6 months Subjects given low dose of vitamin D3: 400 IU/d for 6 months	Alterations in 24 hour systolic and diastolic blood pressure after 6 months of intervention. Alterations in mean systolic and diastolic blood pressure (daytime and night time ambulatory).Alterations in mean clinic diastolic, systolic, pulse after 6 months of trial	No significant change was observed in the parameters following intervention	Vitamin D supplementation did not bring about any change in blood pressure in pre-hypertensive or those with stage 1 hypertension

The studies did not report significant antihypertensive activity of vitamin D alone. However, the daily recommended vitamin D dosage is from 200 to 600 UI/day [103]. It is advised that 600 IU/day of vitamin D consumption is needed for 25 hydroxycholecalciferol to reach around 50 nmol/L in blood as per latest guideline[104] .The European Food Safety Authority (EFSA) and the Institute of Medicine of the National Academies (IOM) have advised against consuming vitamin D3 dosage above 4000 UI/day as this may lead to hypercalcemia[105,106]. The mechanism which underlies the link between hypertension and low levels of plasma vitamin D may be complex which may not be corrected by means of simply supplementing with vitamin D. Patients have been found to have vitamin D receptor gene polymorphism and polymorphism of this gene and the genes involved in the signaling pathway downstream had associated with hypertension risk. Heart failure and hypertension incidence were found to be related to *FokI* single nucleotide polymorphism while *Bsm I*single nucleotide polymorphism was associated with higher risk of development of hypertension during gestation[107,108]. In postmenopausal women deficiency of vitamin D and genotype AA+AG of *Taq-I* Single nucleotide polymorphism was associated with hypertension (stage 2)[109]. Such findings of observational studies warrant more in depth research to reveal possible mechanisms in action here.

DISCUSSION

Blood pressure decreasing effect of vitamin D supplementation has only been noted in a few studies even though many research have found association between vitamin D, activity of RAAS, plasma renin concentration and hypertension [71]. Vitamin D supplementation (2800 IU/day) was carried out in a study by Pilz et al on 188 vitamin D deficient patients with hypertension. Their study found no significant effect on blood pressure [110]. Even in trial conducted for long time periods like the one performed by Arora et al., in which they gave high dose of vitamin D of 4000 IU/day to one group while 400 IU/day to another group for 6 months, could not observe any significant alteration in blood pressure among those with pre-hypertension and stage 1 hypertension[102] .Another meta-analysis by Beveridge et al. on clinical trials of vitamin D supplementation observed that there was no effect of this supplementation on its own up on blood pressure [111]. On the other hand , Panahi et al. performed a study in which essential hypertensive patients with plasma vitamin D levels of <20ng/mL and 20 to 30 ng/mL were given 50.000 IU/week and 1000 IU/day vitamin D3 respectively for 8 weeks and found decrease in blood pressure on vitamin D supplementation[112] .

Another double-blind interventional study was done by Chen et al. in which subjects receiving antihypertensive drugs were divided randomly in to 2 groups in which 1 group received vitamin D (2000 IU/day) while the other group received placebo for 6 months. Ambulatory blood pressure (24 hour daytime and night time blood pressure) was found to be significantly lower in the group who received vitamin D supplement[113]. Sheikh et al. also performed a similar double blind clinical trial and observed similar outcome in which blood pressure was lower in the vitamin D supplemented group[114]. Although standard pharmacological management may not be replaced by vitamin D at present as per the findings of several clinical trials and meta-analysis [72,110,102,111], it has the potential of being an adjuvant therapy since when given along with antihypertensive agents exhibits better control effect on hypertension [112-116]. Vitamin D has been found to be reasonably safe as a supplement in presence of cardiovascular risk[2]. Previous studies didnot observe adverse effect of vitamin D administration except of Pilz et al who found a rise in triglyceride level but he suggested that it

may not represent the real effect[110,102]. Hypertension in a disease influenced by multiple factors which may reduce the threshold for hypertension induction by deficiency of vitamin D (in case of comorbidities like obesity, smoking, metabolic syndrome and sedentary lifestyle[117]. Large scale studies need to be performed for evaluation of the vitamin D's role in hypertension[72].

CONCLUSION

The studies performed (both in human and animal) have shown inverse relationship between blood pressure and vitamin D levels in plasma which indicates a possible role of vitamin D supplementation to control blood pressure in hypertensive patients. However, research on vitamin D supplementation in hypertensive subjects produced inconclusive outcome with many studies showing no significant control of blood pressure. However, vitamin D therapy given along with antihypertensive drugs have displayed a more positive results showing better control of blood pressure in hypertension. Therefore, more extensive and long term studies are needed to understand clearly the mechanism and role of vitamin D in hypertension.

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