The Study Advance on The Role of Vitamin D in Hypertension and Cardiovascular Disease (CVD)

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Abstract: This article summarizes the evidence for an association between vitamin D find and recent investigation on the Vitamin D with the notable function; The Vitamin D discovery and to used since the year of 1940, it has long been known to be an important factor for normal calcium metabolism and skeletal health. But in the past decade, resurfacing interest and new research has implicated vitamin D deficiency as a potential contributor to the pathophysiology of many extra-skeletal conditions, including vascular diseases such as high blood pressure and kidney disease. And the recent experimental animal and observational human studies have repeatedly suggested that supplementation with vitamin D metabolites may lower the risk for hypertension and kidney injury, but definitive human trials favoring the adoption of vitamin D therapy for the primary or secondary prevention of these conditions are still pending. So that, this article would be as the basic data to fulfill the Vitamin D to be a novel agents to make the bigger contribution on the Hypertension and all the cardiovascular disease (CVD).

Hypertension and all the cardiovascular disease (CVD) as are the high incidence in human with the increasing day by day. Its high growing prevalence, and its complications have become a major cause of mortality in the worldwide. Studies were identified that it is urgent to have a good way by searching a agents to help prevent and treat the hypertension and CDV.

One of the many challenges in evaluating the biologic role of vitamin D in influencing blood pressure. And the recent years, there are many research and clinical practical demonstrate that the serum vitamin D concentration is related the hypertension, CVD and diabetes etc. And these issued data have been provide a novel background for the pathogenesis and treatment on the hypertension, CVD and diabetes. This article aims to summarizes the value data for the advance study on the Vitamin D to treat the hypertension and CVD.

Keywords: Hypertension; Cardiovascular disease (CVD); Diabetes; Vitamin D; 25 hydroxyvitamin D; 1; 25(OH)D; Cardiovascular risk, vitamin D receptor (VDR).

1. Background
Hypertension and all the cardiovascular disease (CVD) are as the high incidence in human with the increasing day by day. Its high growing prevalence, and its complications have become a major cause of mortality in the worldwide. Studies were identified that it is urgent to have a good way by searching a agents to help prevent and treat the hypertension and CDV.

One of the many challenges in evaluating the biologic role of vitamin D in influencing blood pressure. And the recent years, there are many research and clinical practical demonstrate that the serum vitamin D concentration is related the hypertension, CVD and diabetes etc. And these issued data have been provide a novel background for the pathogenesis and treatment on the hypertension, CVD and diabetes. This article aims to summarizes the value data for the advance study on the Vitamin D to treat the hypertension and CVD.

2. The Discovery and Study of Vitamin D
2.1. The History of Discovery and Study on the Vitamin D;

Vitamin D was started to be the early studies by McCollum and Davis in the year of 1913, when the first vitamin was discovered, until 1940, these work's contribution is the lead to the identification of vitamin D and its role in bone formation and prevention of hypocalcemic tetany. Most noteworthy was the work by Sir Edward Mellanby, who demonstrated that he could produce rickets in dogs by feeding them the diet characteristic diet; unknown to Sir Edward Mellanby was the fact that he deprived those dogs of sunlight. Because of the work of McCollum and Davis in discovering fat-soluble vitamin A, Mellanby attributed the ability of cod liver oil to cure the rachitic condition in dogs as being another property of vitamin A. McCollum very cleverly destroyed the vitamin A activity of cod liver oil by bubbling oxygen through the solution and heating it, but the ability to cure rickets remained in the preparation. McCollum correctly concluded that this represented a new vitamin, called vitamin D.

One after another, there are different report about the Vitamin D; the rachitic children could be cured with exposure to sunlight or artificially produced ultraviolet light. The puzzle was ultimately solved when Steenbock and Black discovered that irradiation not only of the skin of animals but also of the food they consumed imparted antirachitic activity to either the animals but also of the food they consumed imparted antirachitic activity to either the animals or their food. Furthermore, Goldblatt and Soames showed that livers taken from irradiated rats could heal rickets in rats. Therefore, 2 important discoveries were occurred. First, Steenbock and Black conceived that foods could...
be irradiated to impart vitamin D and rickets as a major medical problem would disappear\(^{(10)}\). The second is that the irradiation of fat-soluble substances extracted from tissues could be used to generate large amounts of vitamin D for later characterization. The structure of vitamin D2 was deduced in 1931 by Askew et al.\(^{(12)}\), and the structure of vitamin D3 was determined through synthetic means by Windaus et al.\(^{(10)}\). Vitamin D was discovered with many other vitamins and is classed as a vitamin even now.

### 2.2. Production, Metabolism and Function of Vitamin D:

#### 2.2.1. Vitamin D is not a Vitamin

Vitamin D is normally produced in skin through a robust photolytic process acting on a derivative of cholesterol (ie, 7-dehydrocholesterol) to produce previtamin D, which is then slowly isomerized to vitamin D3\(^{(13)}\). Vitamin D3 is the natural form of vitamin D produced in skin, and vitamin D2 is derived from irradiation of ergosterol, which occurs to some degree in plankton under natural conditions and is used to produce vitamin D2 from the mold ergot (which contains as much as 2% ergosterol). We must move away from the concept that vitamin D is a vitamin. However, findings from the second half of the 20th century showed that vitamin D is truly a prohormone and not a vitamin. Vitamin D is virtually absent from the food supply. It is not found in plant materials (eg, vegetables, fruits, or grains) and is present in low abundance in meats and other animal food sources, except in rare cases such as fish liver oils and plants such as waxy-leaf nightshade (Solanum glaucophyllum).

In addition to causing mineralization of the skeleton and increasing serum calcium and phosphorus concentrations, vitamin D is known to regulate parathyroid growth and parathyroid hormone production; it plays a role in the islet cells of the pancreas, has a significant effect on the immune system, and can help in suppression of certain autoimmune diseases and certain cancers. To obtain maximal benefits of dietary vitamin D and to reduce the risks of these diseases, intakes of vitamin D higher than currently recommended are in order. Furthermore, a standardized 25(OH)D3 assay that provides true values must be developed; findings could provide a basis for understanding what levels of supplementation must be used to yield adequate amounts of 25(OH)D3.

#### 2.2.2. Vitamin D is a Hormone's that is with the Special Physiology Function

Follow the study on the vitamin D structure and function; the Vitamin was thought that is not only a conception to be not a Vitamin, but also is final conception from a prohormone to a Vitamin D hormone. The vitamin D hormone functions to increase serum calcium concentrations through 3 separate activities. **First**, it is the only hormone known to induce the proteins involved in active intestinal calcium absorption. Furthermore, it stimulates active intestinal absorption of phosphate. **Second**, blood calcium concentrations remain in the normal range even when an animal is placed on a no-calcium diet. Therefore, an animal must possess the ability to mobilize calcium in the absence of calcium coming from the environment, ie, through enterocytes. Two mechanisms play a role in increasing blood calcium concentrations, especially in the absence of intestinal calcium absorption. Vitamin D hormone stimulates osteoblasts to produce receptor activator nuclear factor-κB ligand (RANKL)\(^{(14)}\). RANKL then stimulates osteoclastogenesis and activates resting osteoclasts for bone resorption\(^{(14)}\). Therefore, the vitamin D hormone plays an important role in allowing individuals to mobilize calcium from bone when it is absent from the diet. It is very important to note, however, that in vivo both vitamin D and parathyroid hormone are required for this mobilization event\(^{(15,16)}\). Therefore, 2 keys are required, similar to a safety deposit box. **Third**, the distal renal tubule is responsible for reabsorption of the last 1% of the filtered load of calcium, and the 2 hormones interact to stimulate the reabsorption of this last 1% of the filtered load\(^{(17)}\). Because 7 g of calcium are filtered every day among humans, this represents a major contribution to the calcium pool.

A diagrammatic explanation of the role of the vitamin D hormone in mineralizing the skeleton and preventing hypocalcemic tetany is presented in Figure 1.

#### 2.3. Molecular Mechanism of Vitamin D Actions:

Follow the biologic molecular skill developing and face the vitamin D hormone using in different disease, the studied data demonstrated that the vitamin D hormone functions through a single vitamin D receptor (VDR), and which has been cloned for several species including humans, rats, and chickens. It is a member of the class II steroid hormones, being closely related to the retinoic acid receptor and the thyroid hormone receptor\(^{(18,19,20)}\). It, like other receptors, has a DNA-binding domain called the C-domain, a ligand-binding domain called the E-domain, and an F-domain, which is one of the activating domains. Despite many statements to the contrary in the literature, a single receptor appears to mediate all of the functions of vitamin D, which complicates the preparation of analogs for one specific function rather than another. The human receptor is a 427-amino acid peptide, whereas the rat receptor contains 423 amino acids and the chicken receptor contains 451 amino acids. This receptor acts through vitamin D-responsive elements (VDREs), which are
usually found within 1 kilobase of the start site of the target gene. The VDREs, which are shown in Figure 2.

![Diagram](image)

**Fig.2** Partial list of VDREs found in the promoter regions of target genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sequence</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaBP 9K</td>
<td>GGTTGT</td>
<td>CGG AAGCCC</td>
</tr>
<tr>
<td>Rat osteocalcin</td>
<td>GGTTGA</td>
<td>ATG AGGACA</td>
</tr>
<tr>
<td>Human osteocalcin</td>
<td>GGTTGA</td>
<td>ACG GGGGCA</td>
</tr>
<tr>
<td>Mouse osteopontin</td>
<td>GGTTCA</td>
<td>CGA GGTTC</td>
</tr>
<tr>
<td>Rat 24-OHase distal</td>
<td>GGTTCA</td>
<td>GCG GGTGC</td>
</tr>
<tr>
<td>Human 24-OHase distal</td>
<td>ACTTCA</td>
<td>CCG GGTGC</td>
</tr>
<tr>
<td>Rat 24-OHase prox.</td>
<td>GAGTCA</td>
<td>GCG AGGCG</td>
</tr>
<tr>
<td>Human 24-OHase prox.</td>
<td>GAGTCA</td>
<td>GCG AGGCG</td>
</tr>
<tr>
<td>Mouse CaBP 28K</td>
<td>GGGGAT</td>
<td>GTG AGGAG</td>
</tr>
<tr>
<td>Human PTH</td>
<td>TCAACT</td>
<td>ATA GGTTCAGA</td>
</tr>
<tr>
<td>Rat PTHrp</td>
<td>GGTTGA</td>
<td>GAG GGGTGA</td>
</tr>
</tbody>
</table>

For referral information, see reference 20.

3. Vitamin D3 study on The Hypertension:

3.1. The Mechanisms of Association on The Role of Vitamin D in Hypertension:

Lower plasma renin activity with Vitamin D increasing; The relation of vitamin D with hypertension from the corollary human physiology studies, that have generally supported this evidence from animals; Nearly twenty-five years ago, Resnick et al. observed lower plasma renin activity with increasing 1,25(OH)2D (21). More recently, human mechanistic studies have shown that lower levels of 1,25(OH)2D and 25(OH)D are associated with higher plasma renin and angiotensin II concentrations (21,22), and that lower 25(OH)D levels are associated with higher systemic vascular-tissue RAS activity (23). Alternatively, other investigators have proposed a non-genomic effect of vitamin D on the RAS and blood pressure. Resnick and colleagues hypothesized that vitamin D was involved in regulating the flux of calcium into vascular smooth-muscle cells, therefore influencing intra-cellular calcium concentrations, vascular tone, blood pressure (21, 24), and decreasing renin secretion from juxtaglomerular cells (25,26). The development of vitamin D receptor (VDR) null mice has facilitated numerous experiments that have shed light on the relationship between vitamin D, the RAS, and hypertension (27). Li et al. reported that VDR null mice had significant elevations in renin activity.
and circulating plasma angiotensin II concentrations (28), and exhibited increased activity of the local cardiac-tissue RAS (28, 29). These mice displayed a phenotype of hypertension and cardiac hypertrophy that was attenuated when RAS antagonists were administered. A distinct mouse model of 1-alpha-hydroxylase deficiency also exhibited a phenotype of enhanced RAS activity, hypertension, and cardiac hypertrophy, that was attenuated by treatment with 1,25(OH)2D or RAS antagonists (30). The findings of these experiments were further consolidated with the demonstration that 1,25(OH)2D acts to suppress the expression of renin (28, 24), suggesting that the vitamin D-VDR complex may function as a negative regulator of the RAS, and could thereby exert protective downstream effects on blood pressure and cardiac tissue.

To date, the association of the Vitamin D and Hypertension summarized above; The association of vitamin D with blood pressure and hypertension has been described for over a quarter of a century (24). The most notable mechanism implicating vitamin D with hypertension is its role as a negative regulator of the RAS (28); inappropriately elevated RAS activity is known to contribute to human hypertension and cardiovascular risk (51, 33).

3.2. In Human Clinical and Future on the Role of Vitamin D in Blood Pressure:

Observational studies have suggested higher blood pressures in winter months and latitudes further from the equator; thus implicating insufficient ultraviolet radiation exposure and decreased cutaneous synthesis of vitamin D3 as potential culprits for vascular disease (33). Interventional studies to evaluate the effect of cutaneous vitamin D3 synthesis with ultraviolet radiation exposure have shed interesting but mixed results. Krause et al. randomized hypertensive subjects to receive total body ultraviolet radiation with either UVA or UVB, and observed that those receiving UVB had significant increases in 25(OH)D concentrations with concomitant decrements in 24-hour ambulatory systolic and diastolic blood pressures (~6 mmHg) (34). In a similar randomized study design, Scragg et al. evaluated normotensive individuals, but observed no changes in blood pressure despite significant rises in 25(OH)D concentrations (35). These findings of these studies may be limited by their relatively small sample sizes (n=18 and n=119, respectively), short durations of follow up (6 and 12 weeks, respectively), and focus on distinct study populations (hypertensive and normotensive, respectively).

Prospective studies have produced similarly mixed results. In a longitudinal analysis of men from the Health Professionals’ Follow Up Study and women from the Nurses’ Health Study followed for 4–8 years, Forman et al. observed a pooled adjusted relative risk for incident hypertension of 3.18 (95% C.I. 1.39 to 7.29) when comparing individuals with lower (<15 ng/mL) versus higher (30 ng/mL) concentrations of 25(OH)D (36). In a subsequent nested case-control analysis of normotensive women from the Nurses’ Health Study II, they observed an adjusted odds ratio for incident hypertension of 1.66 (P-trend 0.01) when comparing those with 25(OH)D levels in the lowest versus highest quartiles (37). The longitudinal Michigan Bone Health and Metabolism Study evaluated the risk for systolic hypertension in over 500 Caucasian women who had 25(OH)D and blood pressure assessments in 1993, and again 14 years later in 2007 (38). Although they observed no cross-sectional association between 25(OH)D concentrations and concurrent blood pressure at baseline in 1993, 25(OH)D concentrations of < 32 ng/mL at baseline were associated with a significantly increased risk for systolic hypertension in 2007 (adjusted odds ratio 3.0 [95% C.I.: 1.01 to 8.7]). In contrast, Jorde et al. reported conflicting observations from the Tromso study, which followed individuals naïve to anti-hypertensive therapy from 1994 to 2008 (39). They did note an inverse association between systolic blood pressure and quartiles of 25(OH)D at baseline in 1994, but these baseline 25(OH)D concentrations did not predict incident hypertension or future blood pressure. Regardless of whether the disparity in these findings was due to the narrow range of 25(OH)D concentrations within the study populations, or other unrecognized confounders, they underscored the need for definitive interventional studies.

According to Almarhoumi and Kadi’s study, correction of vitamin D deficiency may improve blood pressure control in hypertensive postmenopausal women. Interventional studies to evaluate if attainment of optimal vitamin D status may prevent hypertension are necessary (47). The expression of many bio-factors, such as ENaC and SGK1, etc, are abnormally regulated by dietary sodium in salt-sensitively hypertensive animals, and that this abnormal expression would be one of the factors causing salt-sensitive hypertension (48).

4. Conclusion:

If there is another factor hypothesized that is a unknown and potential decreasing the risk reason's factor to affect the development of hypertension and CVD, that might be Vitamin D. That of because there are many demonstrated data were evidence to showed that has been some value trail data to present in the clinical Curative effect with some strong support theory on the curing the hypertension and CVD.

Vitamin D has yielded a class of compounds that can be used for the treatment of a variety of
diseases. It would be necessary to be joined with all research staff to work hard and the government to provide the enough finance to move the incidence and morbidity of the hypertension and CVD.

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Reference


