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Vitamin D and Hypertension

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Abstract

Nowadays, hypertension is one of the most important causes of death all over the world because of its adverse effects on cardiovascular system. For this reason its study is very valuable. Vitamin D is one of the important factors that may influence blood pressure. Many studies have shown the modulatory effect of this vitamin on rennin-angiotensin system as well as its inhibitory effect on vascular smooth muscle hypertrophy. According to the fact that vitamin receptors are distributed in almost all organs of human body, we can't consider its role just as factor in calcium homeostasis. Therefore many other important roles could be attributed to it. So vitamin D deficiency could arise many problems. There are many causes for vitamin D deficiency. The most important is insufficient exposure to UV-B. In epidemiological studies the vitamin D deficiency is considered to be associated with high blood pressure, as emphasized in many cross-sectional studies. Concerning the cohort prospective studies, the relationship between vitamin D deficiency and hypertension is reported in some cases. The interventional studies about the association between vitamin D and hypertension are not many and the results are different or contradictory. Controversial results might be due to differences in dose of supplements or duration of supplement therapy. The aim of this systematic review is to assess the researches about the association between vitamin D deficiency and hypertension and discuss the power of them. This can be helpful to lighten the path to prospective investigations.

Introduction

Nowadays, hypertension can be fatal. Hypertension has adverse effects on cardiovascular system. When systolic and diastolic blood pressures are equal or more than 140 and 90 mm Hg respectively, they are considered high. It has been specified that an increase of about 2 mm Hg systolic blood pressure can increase cardiovascular complications induced death rate [1, 2]. For this reason, studies about blood pressure and factors affecting it are one of the important topics in medical sciences. Vitamin D is one of the factors that can affect blood pressure. Nowadays, vitamin D has been considered, due to its various effects on health, and numerous studies have been conducted on its various effects on different parts of body and proper functioning of different organs and systems. It is also claimed that vitamin D deficiency leads to many chronic diseases. Thus, from 1980 onwards, vitamin D has become a particular interest of researchers, and it is no longer considered to be just a factor in regulating calcium homeostasis [3]. Due to the wide distribution of vitamin D receptors in most of body tissues, several roles have been attributed to them. In a number of the chronic diseases such as cancers, diseases related to the immune system, cardiovascular complications and diseases, especially Hypertension, vitamin D deficiency or dysfunction can be traced. Studies indicate that insufficient intake of vitamin D plays an important role in pathogenesis and progression of hypertension. Vitamin D and its deficiency was well known in early 20th century after discovering its clinical effects on bone and its role in the development of several diseases such as rickets in children and osteoporosis in adults. So that in the years 1999 and 2000, the Institute of Medicine recommended that people younger than 50, from 51 to 70, and above 70 years old need, 200 IU, 400 IU, and 600 IU of vitamin D daily respectively. Later it was found that these amounts are sufficient when a person gets adequate sun exposure daily. In other words if people were not suffering vitamin D deficiency, these amounts are sufficient, but if the person was suffering from vitamin D deficiency or could not get enough sunlight due to his/her residence or age conditions, he/she would probably need higher doses of vitamin D. Vitamin D is fat-soluble and accounted steroid hormone. There are two major forms of vitamin D: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Exposure of skin to sunlight is the major source of vitamin D for human, which provides approximately 95% of daily requirement [4]. The remaining 5% is supplied by diet. Foods like fish-liver oil, oily fish, liver, and egg yolk contain vitamin D [5]. In the United States certain foods such as milk, fruit juice, and cereals are fortified with vitamin D_2 [6]. This vitamin is the product of yeast and plants exposure to sunlight [7].

One and 25-dihydroxyvitamin D are the active form of vitamin D, but 25-hydroxyvitamin D is used as a serum marker for the diagnosis of vitamin D deficiency due to its higher plasma concentration and longer half-life [8]. Basically, vitamin D deficiency is defined as: serum 25-hydroxyvitamin D level is less than 20 ng/ml (50 nmol/l). However, 21 to 29 ng/ml levels of 25-hydroxyvitamin D are considered to be insufficient [9]. Researches indicate that low levels of vitamin D are common and maybe

epidemic in children and adults around the world [10-12]. It is estimated that about 1 billion people worldwide are suffering from some degrees of vitamin D deficiency [13]. In Iran, according to researchers conducted by Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences, 40 to 80% of people are suffering from vitamin D deficiency [14]. The results from studies conducted in different regions within Iran are: in a study in Tehran on a population aged 20-69 years old, the prevalence of vitamin D deficiency was 79.6% [15]; also in another study the prevalence was 77% in healthy people and 70% in diabetics [16]; the prevalence was 50.8% in Isfahan [17]; and the prevalence of vitamin D deficiency was 85.2% in Zahedan [18]. Vitamin D deficiency can occur for a number of reasons, which are presented in table 1. Given that exposure of skin to sunlight is the most common way to get vitamin D, limited sunlight exposure and as a result the lack of receiving UVB are the major and the most common causes of vitamin D deficiency [7]. Other factors might be the latitude of residence, skin color and aging (Table 1). On the other hand, hypertension is more common in higher latitudes [19]. Also, people with darker skin are more prone to high blood pressure and incidence of hypertension increases with age [20]. These cases may support the hypothesis maintaining that there is a relationship between vitamin D and hypertension.

Materials and Methods

In this review study the results of epidemiological, cross-sectional, and cohort studies on the relationship between serum vitamin D level and blood pressure are investigated. Interventional studies were also performed in order to study the effect of vitamin D supplement on blood pressure. For this purpose, a literature search of PubMed, ISI, Web of Knowledge, and Google Scholar database was conducted using vitamin D and (high) blood pressure as keywords. The collected studies were examined, after being classified based on the type of the study. Finally, in accordance with review article framework, the obtained results were placed in the tables by study type.

Observational Studies: Observational studies details (epidemiologic, cross-sectional, and cohort) on the relationship between vitamin D and blood pressure are listed in table 2.

1. **Epidemiologic Studies:** In most of these studies it has been stated that the prevalence of vitamin D deficiency and also hypertension arise with increasing distance from the equator (i.e. higher latitudes) [21-23]. Studies conducted on people with dark skin indicated that the prevalence of vitamin D deficiency was higher among them than white people. They are also more prone to hypertension [24-25]. Also, black people who emigrated from North Africa to the countries in the higher latitudes had higher blood pressure than native people of Northern Africa and their serum 25-hydroxyvitamin D level was lower [26-27]. In addition some of these studies have pointed out the seasonal variation in blood pressure and its relationship with vitamin D synthesis level, meaning that vitamin D synthesis level is lower in cold season than in hot seasons and blood pressure is higher in cold seasons than in hot seasons [24-25].

2.**Cross-Sectional Studies:** A relationship between vitamin D and hypertension has been observed in cross-sectional studies, indicating that UVB ray is needed for vitamin D synthesis. As sunlight weakens due to greater distance from the equator or in cold seasons, the serum 25-hydroxyvitamin D level decreases and blood pressure elevates [28-29]. In some of these cross-sectional studies it was found that by increasing plasma 25-hydroxyvitamin D levels, blood pressure will decrease [30-32]. In these studies it was also determined that sunlight played an important role in vitamin D synthesis [33-34]. However, these findings do not prove the relationship between vitamin D deficiency and hypertension individually, but considering that they address this relationship between diet and disease, and not at the nutrient levels, these findings are quite important and can be helpful in proposing hypothesis on the relationship between vitamin D and hypertension [35].

3.**Cohort Studies:** Despite a limited number of cohort studies on this topic, following results have been obtained: The largest study was performed by Forman et al., on the participants in Health Professionals Follow-Up Study and Nurse's Health Study, indicated that people with serum 25-hydroxyvitamin D levels were less than 15 ng/ml were more prone to develop hypertension compared with those with serum 25-hydroxyvitamin D levels more than 30 ng/ml. In this study, serum 25-hydroxyvitamin D levels of 613 men from the Health Professionals Follow-Up Study and 1198 women from the Nurse's Health Study were measured. The participants, then, were followed for 4 to 8 years. After 4 years, the relative risk of hypertension among two groups of men with vitamin D levels less than 15 ng/ml and serum vitamin D levels were greater than or equal to 15 ng/ml were determined.

Table 1. The most important causes for vitamin D deficiency

Variable	Mechanism
Aging	Reduction in 7-dehydroxy cholesterol in skin particularly in people more than 70 years old
Hepatic failure	Decreased synthesis of 25-hydroxyvitamin D
Chronic renal failure	Decreased synthesis of 1-25-dihydroxyvitamin D
Malabsorption	Reduced bioavailability of vitamin D
Obesity	Retention of vitamin D in fat cells
Season/latitude/time of day	Reduced skin synthesis
Skin pigment	Decrease UVB absorption
Sun protection	Reduced skin synthesis
Increased catabolism	Anticonvulsant, glucocorticoid, highly active antiretroviral treatment, and some immunosuppressants

Table 2. Observational studies of the association of vitamin D and hypertension

Result	Design	Study/Year
Far from the equatorial, vitamin D decreased and blood pressure increased	Comparison between blood pressure and vitamin D level in equatorial residents and people in high latitude	Epidemiologicv Haddock et al.[29]
Seasonal variation in blood pressure. High prevalence of HTN in people with dark skin	Trend of hypertension in people 18-74 y in US during 1976 to 1980	Drizd and Engel [24] (epidemiologic)
Vitamin D status is lower in blacks compare with whites. Blood pressure is higher in blacks migrate from north Africa to higher latitude compare with people stay in north Africa.	Study of vitamin D status and HTN in people of north Africa compare with blacks migrate to higher latitude s and compare them with whites	M, Buyamba [26] (epidemiologic)
From north to south and near the equatorial, prevalence of HTN decreased.	Participants in national STROKE study in 1985 in 29 provinces in China	He et al. [22] (epidemiologic)
HTN is significantly associated with latitude.	More than 10 thousand	INTERSALT study[21] (epidemiologic)
Intake of calcium and vitamin D was associated with decrease in HTN.	Association of HTN with calcium and vitamin D intake in 308 women in different ages	Sower et al.[30] (cross-sectional)
Vitamin D stasus was inversely associated with HTN	measurement of vitamin D status in 34 middle age men and the association of it with HTN and cardiac risk factors	Lind et al. [31] (cross-sectional)
Systolic and diastolic blood pressure was higher in men with lower level of vitamin D.	Vitamin D measurement and blood pressure in 100 men aging between 25-64 y	kristal et al. [32] (cross-sectional)
Vitamin D status was lower in cold season. It was also lower in blacks compare to whites.	51 black women and 39 white women between 20-40 y in Boston	Harris and Huges [25] (cross-sectional)
There was no association between vitamin D and decrease in HTN.	participants from several cohort studies;77436 from Nurse' s health Study(NHS1), 93803 from NHS2 and 38074 from Health professional Follow up Study(HPFS),vitamin D status was detected through quintiles according to questionnaires	Forman et al. [39] (cohort)
Prevalence of HTN was lower in participants with higher levels of vitamin D.	Estimation of vitamin D status in participants from 2 cohort studies NHS and HPFS via questionnaires	Forman et al. [36] (cohort)
Prevalence of HTN was lower in participants with higher levels of vitamin D.	Detection of vitamin D status in 613 men from HPFS and 1198 women from NHS	Forman et al. [36] (cohort)
Vitamin D status was associated with HTN.	7186 men and 7902 women in the range of 20 years old and more, from Third National Health and Nutrition Examination Survey were chosen and vitamin D status was measured.	Martin et al. [38] (cohort)
Vitamin D deficiency could be associated with HTN and other cardiovascular disease.	1739 participants from Framingham Offspring Study (white race), mean age 59 y, without cardiovascular disease at beginning; vitamin D status was measured. About 5.4 y later, the first cardiovascular symptoms were emerged.	Wang et al. [37] (cohort)

Table 3. Interventional studies of the effects of vitamin D on hypertention

Result	Design	Administration	Age	Study
No effect	39 patients with HTN received vitamin D_3 for 8 weeks Control group received placebo	1-α hydroxy vitamin D_3 tablet	middle age	Lind et al. [43]
Supplements did not have significant effect on HTN. Vitamin D status was high after supplementation	58 middle aged were divided randomly in to 4 groups; a-800 mg calcium + D_3 as placebo b-5µg vitamin D_3 + calcium as placebo c-800 mg calcium + 5 µg D_3 d-both as placebo	cholecalciferol tablet	50-70y	Pan et al.[44]
Blood pressure changes were equal in both groups. Vitamin d status was high after supplementation.	95 men and women received 2.5 mg cholecalciferol 94 person in control group received placebo	cholecalciferol tablet	63-76 y	Scragg et al. [45]
Decrease in BP about 6.6 mm Hg Increase in vitamin D status about 162%	3 times a week for 3 months in 18 patients with HTN	UVB irradiation with Helarium lamp	26-66 y	Krause et al. [41]
BP decreased in group with vitamin D supplementation	calcium supplementation compare with calcium plus cholecalciferol tablet tablet for 8 weeks	cholecalciferol tablet	more than 70 y	Pfeifer et al. [42]
Significant decrease in systolic BP in group supplemented with vitamin D	100 patients with HTN received only anti-hypertensive drugs; 100 patients received 33000IU vitamin D each 2 weeks additionally	cholecalciferol tablet	more than 35y	Goal and Harbans [40]

It was observed that the relative risk (6.13) was higher among those with lower vitamin D levels. With respect to women, the same result was yielded, and the relative risk in the group with serum vitamin D levels less than 15 ng/ml was 2.67. Then, the pooled relative risk, for male and female groups, was measured (3.18) using random-effects model. Forman et al. investigated the relationship between the estimated 25-hydroxyvitamin D level and blood pressure to strengthen the research capacity and achieve more accurate results. By doing this, they were able to study this relationship among all participants in these two large cohort studies consisting of 38388 men and 77531 women. They estimated the 25-hydroxyvitamin D levels of the participants based on the information obtained from them using Food Frequency Questionnaire (FFQ). Decile rating was undertaken based on serum 25-hydroxyvitamin D level for the participants. It was observed that by moving from the first decile (lower level of serum vitamin D) to the next deciles (higher levels of serum vitamin D) the risk of

hypertension decreased. That is, the relative risk in the women of the first decile was 2.31 compared with the last decile. This figure was 1.57 in men. It is worth mentioning that the correlation coefficients between the estimated 25-hydroxyvitamin D and measured 25-hydroxyvitamin D in HPFS and NHS were 0.54 and 0.15, respectively [36]. Therefore, a significant inverse correlation was detected in this study between serum vitamin D level and hypertension in a wide range of participants. In another study by Wang et al. 1739 participants with the average age of 59 years were selected from Framingham Offspring. Of them, 55% were women and the rest were men. By race, all subjects were white with no history of cardiovascular diseases. Their levels of 25-hydroxyvitamin D were measured. To adjust other hazard and risk factors, the Cox regression was employed. In general, in this group, vitamin D levels in 28% of the subjects were less than 25 ng/ml. During 4.5 years of follow-up, 120 subjects developed, at least, one cardiovascular symptom. Hazard ratio in those with serum vitamin D levels less than 15 ng/ml was 1.63 compared with those with serum vitamin D levels greater than or equal to 15ng/ml. This ratio (2.13) was bigger in the subjects with hypertension [37]. Therefore, it was determined that vitamin D deficiency could be associated with cardiovascular diseases, especially in those with hypertension. In another study by Martins et al. on adult Americans, they maintained a relationship between the serum vitamin D level and the incidence of hypertension. The subjects, all from Third National Health and Nutrition Examination Survey, included 7186 men and 7902 women, aged 20 or above. The level of 25-hydroxyvitamin D was measured and average of about 30 ng/ml (or 75 nmol/l) was obtained. Quartile rating was undertaken for the subjects in an ascending order, based on serum 25-hydroxyvitamin D. The subjects in the first quartile (1.30) were more prone to hypertension the fourth quartile [38]. In another study, in order to investigate the relationship between serum vitamin D level and blood pressure, a number of separate cohort studies were used. These studies included the Nurse's Health Study (NHS1) with 77436 participants, Nurse's Health Study (NHS2) with 93803 participants, and also Health Professional Follow-Up Study (HPFS) with 38074 participants. All cohorts were followed up for more than 8 years, during which the subjects received vitamin D supplement. Quintile ranking was undertaken for the subjects based on serum vitamin D level. Then, the relative risk of hypertension was determined. In contrast to other studies, the result indicated that the use of vitamin D had no correlation with reduction of blood pressure. Multifactorial relative risk for hypertension was, in turn, as following for each study: 0.98, 1.13, and 1.03. It is worth mentioning that the daily degrees of receiving vitamin D supplement in the first and last quintiles were less than 400 IU and higher than 1600 IU [39].

4**. Interventional Studies:** There are not a lot of studies on examining the association between vitamin D intake and changes in blood pressure. Goel and Harbans in a study compared a group of 100 hypertensive patients who were given antihypertensive drugs with another group of 100 hypertensive patients who, in addition to hypertensive drugs, were supplemented with vitamin D (33000 IU, after every 2 weeks, for 3 months). Vitamin D supplementation group showed a significant decrease in systolic blood pressure, this group also showed an increase in calcium level with a decrease in serum phosphorus. Results of this study confirmed that vitamin D supplementation has a role in reducing blood pressure in hypertensive patients. Researchers of the study noted that vitamin D supplementation could be effective along with hypertensive drugs [40].

In an interesting study, Krause et al. tested UVB irradiation for 3 times a week and observed a 162% increase in 25-hydroxyvitamin D level. They also concluded that the 24-hour mean blood pressure will decrease by an average of 6.6 mm Hg [41]. In a double-blind study on investigating the effect of vitamin D on blood pressure, Pfeifer et al. examined the effects of 8 weeks of supplementation with calcium versus calcium plus 800 IU vitamin D_3 on blood pressure. The group under study consisted of 145 women above 70. They found that in women with stage 1 hypertension, calcium plus vitamin D supplementation leads to a greater blood pressure reduction than calcium alone. In this case, the subjects in the calcium group showed a decrease in systolic blood pressure of 5.7 mm Hg and diastolic blood pressure of 6.9 mm Hg. While compared to vitamin D_3 and calcium group, a decrease in systolic blood pressure of 13.1 mm Hg and diastolic blood pressure of 7.2 mm Hg was observed. Also, in patients who received supplementation, serum 25-hydroxyvitamin D reached 64.8 nmol/l from 25.6 nmol/l [42]. In another study on 39 patients with stage 1 diastolic hypertension, one group received 1 alpha-hydroxy-vitamin D_3 in the form of a tablet, while the control group, received placebo. No changes were observed in their blood pressure. However, these patients did not necessarily suffered from vitamin D deficiency [43].Of course, all the interventional studies do not share the same view towards the effectiveness of vitamin D in reducing blood pressure. For instance, in a double-blind intervention study by Pan et al., 58 residents of an elderly nursing home were selected. They were, then, randomly divided into 4 groups. The first group received 800 mg calcium per day, along with vitamin D_3, as placebo. The second group was given 5µg vitamin D_3 per day. This group also received placebo instead of calcium. The third group was given calcium and vitamin D_3 and the fourth group only received placebo. In all groups, calcium level and 25-hydroxyvitamin D were directly correlated with supplementation. The mean systolic blood pressure showed a slight decrease in the group who received only calcium supplement. However, it was interesting that the mean systolic pressure in the group who received calcium plus vitamin D supplement increased. The results were reported as following: calcium supplements of 800 mg per day or 5 micrograms of vitamin D daily did not have a significant effect on blood pressure after 11 weeks [44]. In another study in England, Scragg et al. provided 95 men and women (mean age

above 70 years) 2.5 mg cholecalciferol, while another group of 94 aged-matched subjects received the same amount of placebo. A five weeks follow-up was pursued in this experiment. The results indicated that 25-hydroxyvitamin D level in the group with supplementation was higher than the other one, while changes in blood pressure were similar in both groups, without a significant difference. The researchers concluded that the increased blood pressure in cold seasons is not due to serum vitamin D level reduction [45].

Studies of Genetic Analysis of Vitamin D Receptor: Delmic et al. showed that the polymorphism in Taq1 region of vitamin D receptor-related gene and the differences in this region among the people can be a suitable marker to determine how susceptible a person is to diseases such as diabetes type II and hypertension [46]. In a study in Turkey, Vural and Matlas used RT-qPCR technique to investigate polymorphism in vitamin D receptor gene in 100 patients with either hypertension or diabetes type II versus 100 healthy people.

The aim of the study was to find out whether regional changes in this gene could imply to the disease. The results showed that distribution of TT, Tt, and tt genotypes among the patients was, in turn, 51%, 46%, and 3%. These figures were, in turn, 35%, 49%, and 16% among the healthy subjects. The frequency of T allele was significantly higher in the control group. According the obtained results, the use of RT-qPCR is helpful in determination of genotypes and detecting the persons susceptible to hypertension or diabetes type II [47]. In addition, another study on polymorphism in Fok1 region of vitamin D receptor gene was performed using PCR-RFLP technique. A number of 280 patients with hypertension were selected and compared with 200 subjects having normal blood pressure. The genotypic distribution of allele F was significantly higher in the patient group. To conclude, the presence of polymorphism in the FOK1 region of the vitamin D receptor gene is a good marker for detecting hypertension susceptible people [48].

Discussion

Epidemiological studies, in general, point out that vitamin D deficiency may correlate with hypertension, especially when 25-hydroxyvitamin D level is less than 15 ng/ml. Apparently, systolic blood pressure is highly associated with vitamin D level.

It seems that the greater prevalence of vitamin D deficiency in northern latitudes and regions far from the equator correlates with the prevalence of hypertension in these regions. We also know that blood pressure has a seasonal variation and is higher in cold seasons, just like vitamin D deficiency which occurs more in cold seasons of the year when there is pale sunlight. These evidences put emphasis on this hypothesis that vitamin D deficiency is correlated with hypertension. In a series of cohort and interventional studies a relationship was seen between serum vitamin D and blood pressure levels, while in some other no correlation was observed. The existence of polymorphism in vitamin D receptor gene can be a reason for these contradictory results, maintaining all people do not reflect the same response to vitamin D. Therefore, it is recommended that genetic variation, including differences in vitamin D receptor related genetic regions, to be included in future studies. Among interventional studies, there are a studies supporting the idea that vitamin D supplementation reduces blood pressure.

In contrast, there are studies claiming that vitamin D is not correlated with blood pressure. It seems that difference in dose and duration of vitamin D supplementation are the reason for this contradiction; it is worth mentioning that in order for vitamin D to affect blood pressure, 25-hydroxyvitamin D level should be greater than 30 ng/ml (75 nmol/L) which would not be obtained by previous recommendations on the use of 200 IU and 600 IU of vitamin D daily usage for young and elderly people respectively. [9].

For this reason, doses of 1000 to 2000 IU per day are recommended. It has been stated that even short-term use of 4000 IU per day as the loading dose not only is useful, but also can elevate the 25-hydroxyvitamin D level to more than 30 µg/m; in a shorter time [20]. Inadequate duration and dose of vitamin D supplementation can be the reason for non-effectiveness of this vitamin on blood pressure. Therefore, it is necessary for future studies to be conducted on a larger population using appropriate dose and enough duration of vitamin D usage to achieve more reliable result with respect to the effectiveness of vitamin D. In studies that a correlation between vitamin D_3 and hypertension has been observed, it should be clearly determined whether this relationship is directly due to the effect of vitamin D on blood pressure or due to its effects on anthropometric factors (e.g. weight and fat mass) or on the inflammatory markers, indirectly leading blood pressure reduction. Therefore, for the purpose of future studies, it is better to moderate the interfering factors first, and then investigate and report the results.

Finally, when it is difficult to express a relationship between a specific nutritious factor as a cause and a chronic disease as the consequence, due to the varieties of interfering factors in diet, it is better to study this relationship in a more general area. In other words, the relationship between regular dietary habits of individuals and the chronic disease should become apparent first. Obviously, demonstration of such relationship in this way would be more precise, scientific, and of course costly.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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