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.

Vitamin D deficiency leads to many chronic diseases. It is also claimed that 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 D₂ (ergocalciferol) and vitamin D₃ (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 D₂ [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
The relationship between vitamin D and hypertension is supported by the hypothesis that there is a correlation between high blood pressure and incidence of vitamin D deficiency [20]. These cases may be more prone to developing hypertension. On the other hand, hypertension is more common in areas with lower latitude of residence, skin color, and aging (Table 1). Vitamin D deficiency can occur for a number of reasons, which are presented in Table 1. Given that exposure of the skin to sunlight is the most common way to get vitamin D, limited sunlight exposure and as a result the lack of 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 vitamin D synthesis decreases and blood pressure 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.

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

Table 1. The most important causes for vitamin D deficiency
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 antihypertensive 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 D3 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 D3 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 D3 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 suffer 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 D3, as placebo. The second group was given 5µg vitamin D3 per day. This group also received placebo instead of calcium. The third group was given calcium and vitamin D3 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 to 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 D2 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.

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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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References


