Original Article

Vitamin D adjuvant effect on Angiotensin II level and other biochemical markers in hypertensive patients: A prospective study

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Abstract

There is credible evidence that many people have insufficient levels of vitamin D, which can lead to damage to the heart and arteries. involving elevating levels of parathyroid hormone, stimulating the renin-angiotensin axis, and elevating insulin resistance, hence cause hypertension, left ventricular hypertrophy, elevated risk of atherosclerosis and cardiovascular disease events. Adaptive immunity, vascular inflammation, cardiomyocyte maturation, differentiation, and responsiveness of vascular endothelial cells are a few examples of the various mechanisms that could be altered and decreases renin-angiotensin-aldosterone system activity via suppressing renin gene expression.

The objective of the study is to prospectively assess the potential effectiveness of vitamin D3 adjuvant therapy for patients with stage one and stage two essential hypertension. From September 2016 to May 2017, a prospective, randomized, controlled trial was done on forty patients who were visiting the Imam Al-Hussein medical facility in Karbala.. The patients were divided into two groups: group one, which consisted of twenty hypertensive patients who were given vitamin D3 100,000 IU orally every 2 weeks for 8 weeks as part of the standard treatment for hypertension, and group 2, which consisted of twenty patients with hypertension who had vitamin D insufficiency. will only be given antihypertensive medication The results of the study revealed that the vitamin D3 the serum levels increased significantly ($P< 0.01$) in the treated group. endogenous vitamin D. Additionally, the intervention group's serum angiotensin II level decreased in a highly significant manner (P0.01) (conventional therapy with vitamin D3) compared with the control group (conventional therapy only). Moreover, there were There were no noticeable improvements in either research group's atherogenic index, Fasting blood sugar or lipid profiles. The vitamin D3-treated group had significantly lower systolic and diastolic blood pressure than the control group $P< 0.05$ after supplementation. Regardless of age group, gender, BMI, disease duration, smoking status, or angiotensin II level, vitamin D3 supplementation had a substantial impact on both levels of endogenous vitamin D and angiotensin II. meanwhile, Total cholesterol, low-density lipoprotein cholesterol, and systolic and diastolic blood pressure was changed according to specific patient characteristics particularly age group and the duration of disease.

Conclusion: Restoring sufficient endogenous vitamin D level reduced renin-angiotensin system activity and decreasing BP levels Vitamin D3 supplementation is a low-cost treatment option that can be used in conjunction with antihypertensive medications. It is of utmost importance to conduct future research on the possibility of using vitamin D in the treatment of many dangerous and common diseases, as it can be a lifesaver treatment for people suffering from chronic diseases, in addition to its abundance in the market, ease of use by patients, being safe and not causing dangerous side effects even in high doses.

Keywords: Hypertension; Vitamin D3 Deficiency; Angiotensin II; Patient demographics.

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Introduction

Insufficient sun exposure, a lower vitamin D intake from food, circumstances that decrease vitamin D absorption, and other factors can all lead to vitamin D deficiency. that affect the liver, kidney which impair vitamin D conversion into active metabolites, and hereditary disorders(1).

Vitamin D exerts its effect on cardiovascular cells Immature cells are developed by modifying response regions in the vascular endothelial growth factor promoter. Additionally, a vitamin D metabolite reduced vascular tone, and endothelium-dependentvascular smooth muscle contractions, via influencing the outflow of calcium towards endothelial cells (2).

But only a few studies have looked at how vitamin D therapy affects vascular function, and the results are conflicting so far (3). However, the research at hand suggests that a vitamin D deficit may worsen vascular dysfunction.(4).

Vitamin D decreases RAAS activity via suppressingrenin gene expression(88, 89) by controlling renin offspring via a cis-DNA region in the renin gene entrepreneur, hence decreasing the activity of the RAAS. (5). Also,vitamin D was found to regulate renin expression independently through calcium metabolism(6)

The antiatherogenic impact of vitamin D has been attributed to a variety of possible mechanisms, including endothelial function protection, reduction of smooth muscle cell proliferation, enhancement of lipid profile, and others.(7)

Chronic vitamin D deficiency raises insulin resistance, results in secondary hyperparathyroidism, impairs the function of beta-pancreatic cells, and promotes the onset of metabolic syndrome and diabetes mellitus. In addition, vitamin D has an impact on the pancreas by controlling the genes that are responsible for producing insulin.(8)

kidney plasma flow is increased by vitamin D. decreasing mean atrial pressure as a result, moreover, there is a higher renal plasma flow decline and higher aldosterone secretion after angiotensin II infusion followed vitamin D therapy(9). Vascular tone and arterial stiffness are increased by renin-angiotensin-aldosterone activation(10). Consequently, a lack of vitamin D may promote vascular dysfunction and long-term activation, according to the currently available data. whereas adequate vitamin D levels may allow for proximal inhibition. Only a small number of research have, however, looked at how Despite mixed results, vitamin D supplementation impacts vascular function.

Materials and Methods

During their visits to a private interventional cardiologist clinic and a nearby hospital, forty potential hypertension patients were selected. They ranged in age from forty to seventy and included twenty men and twenty women. According to the diagnosis, all patients had stage one or stage two hypertension. according to the Joint National Committee 8 (JNC8) guideline and were selected to be lacking in vitamin D < twenty ng/ml. Twenty hypertensive with vitamin D insufficiency were placed in group 1 and given conventional treatment vitamin D3 (100,000 IU) orally every two weeks for eight weeks to treat hypertension. 20 hypertension patients in Group 2 who had vitamin D insufficiency were randomized to receive conventional therapy for hypertension only (control group). The conventional therapy includes angiotensin receptor blockers alone or combined with diuretic (Losartan potassium 50 mg alone or combined with hydrochlorothiazide 12.5 mg), diuretic (Furosemide 40 mg) or calcium channel blockers (Diltiazem 60, 90 mg). The study measurements included plasma25(OH) vitamin D level, serum angiotensin II, fasting blood sugar, creatinine, aspartate aminotransferase, calculation of lipid profile, along with the degree of obesity. Monitoring the subjective and objective measures both before (baseline) and after the 8-week course of treatment was used to evaluate the patient.

Results

Patients Demographic and Disease Characteristics

The age range for the groups was between (40-70) years, and the demographic and illness features Of the forty patients, twenty were men, and twenty were women, or fifty percent each. In terms of gender and mean age, there was no statistically significant difference across research groups (P>0.05). (Table 1). The majority of patients had average body mass indices and were obese for group 1 patients (32.15 ± 5.31) kg/m2, and for group2 patients was (23.67 ± 4.18) kg/m2, and There was no discernible statistical difference between them. (P>0.05). Eleven patients (55%) were smokers in group1 and 10 (50%) smokers in group 2 patients.

The duration of the disease were (11.4 ± 4.71) and (11.45 ± 5.61) years for group 1 and group 2 patients respectively. Liver enzyme SGPT and renal function test SCr showed Patients in groups one and two vary from each other at P>0.05, respectively.

Table (1): Disease and Demographic Properties of Study Groups

Groups of the study			
Variable	**Gr 1**	**Gr2**	**P_value**
Sex	**n(%)**	**n(%)**	**–**
Male	10(50%)	10(50%)	1.000NS
Female	10(50%)	10(50%)	
Age(year)	58.30 ± 10.33	57.30 ± 8.27	0.737 NS
BMI(kg/m^2)	32.15 ± 5.31	31.67 ± 4.18	0.758NS
Smoking state	n(%)	n(%)	0.751 NS
Smoking	11 (55)	10(50)	
Non smoking	9 (45)	10(50)	
Duration of disease(year)	11.40 ± 4.71	11.45 ± 5.61	0.976 NS
SGPT (IU/L)	20.60 ± 4.81	17.84 ± 3.62	0.295 NS
S.cr (mg / dl)	0.79 ± 0.06	0.81 ± 0.09	0.327NS

Data existing as mean ± SD.

There were no significant variations in the number of patients (n) or the percentage (NS; P > 0.05).

Two-sample t-test is used for statistical analysis of (age, BMI, and duration of the

disease, SGOT, SCr).

For statistical analysis of gender and smoking status, the Chi-square test is used.

Blood pressure readings and the impact of vitamin D3 supplementation effects

Following adjustment of the baseline means for the intervention group and control group in accordance with covariance analysis, the overall effect of vitamin D3 supplementation on biochemical markers and blood pressure of patients with stage I and stage II hypertension was provided in table (2). After two months of treatment, serum Ag II levels in patients in the treatment group (G1) were significantly lower than those in patients in group (G2) (p<0.01), according to the results. Additionally, there was a significantly significant rise (P< 0.01) in endogenous vitamin D levels in groups1 patients compared to groups2 patients. The results showed that neither group's patients' fasting blood sugar levels changed significantly (P > 0.05)., and also after adjustment After two months of therapy, there were no appreciable changes in the baseline averages for the treatment and control groups for Triglycerides, high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein all showed significant differences (P 0.05). But the mean SBP dramatically decrease. After two months of treatment, there was a highly significant increase in mean DBP (P>0.05) and a substantial decrease in mean DBP (P>0.01) in the treatment group patients compared to the control group patients.

interaction = 0.041and 0.004 respectively)(figure 1).The changes in the atherogenic index showed that After two months of therapy, there was no discernible alteration amongst the 2 groups. (P > 0.05)

Table (2): Blood Pressure Readings and Biochemical Markers results after 2 months of treatment with vitamin D3

Variable	Group	Mean (before-treatment)	Mean (after-treatment)		P_value
			Mean	SER	
Ag II (pg/ml)	G1	170.50	58.84	7.34	<0.001**
	G2		172.47	7.34	
D3 ng/ml	G1	11.85	38.47	1.24	<0.001**
	G2		11.44	1.24	
FBS mg/dl	G1	105.03	103.60	1.80	0.672 NS
	G2		104.70	1.80	
TC mg/ dl	G1	200.87	179.22	6.60	0.157 NS
	G2		192.72	6.60	
TG mg/dl	G1	167.95	161.96	3.94	0.580 NS
	G2		165.08	3.94	
HDL mg/dl	G1	40.73	38.59	0.90	0.102 NS
	G2		40.75	0.90	
LDL mg/dl	G1	123.48	106.25	6.77	0.201 NS
	G2		118.73	6.77	
VLDL mg/dl	G1	33.82	32.59	0.78	0.524 NS
	G2		33.31	0.78	
SBP mmHg	G1	144.40	131.74	3.64	0.041*
	G2		136.06	3.64	
DBP mmHg	G1	90.73	84.92	0.68	0.004**
	G2		87.88	0.68	
Atherognic Index.	G 1	0.58	0.60	0.01	0.320 NS
	G 2		0.58	0.01	

G1 =Group 1, G2=Group 2

Statistics presented as mean ± SER

NS: No significant alterations (P>0.05), (*) Significant variance (P<0.05), (**) Highly Significant difference (P<0.01)

Analysis of covariance (ANCOVA) test rummage-sale to associate post-treatment between (G1 ,G2) patients, after adjustment of baseline reading of the same variables.

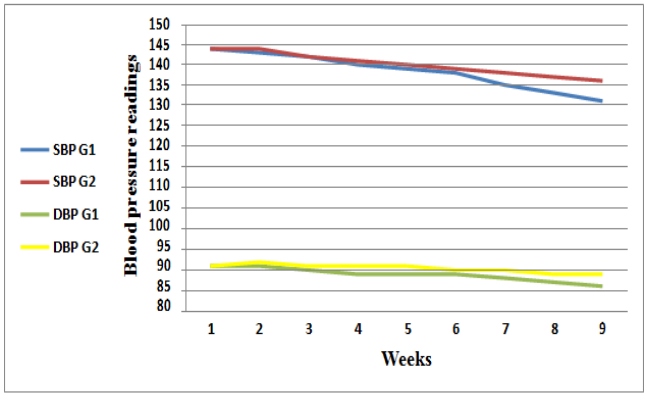

Figure (1) Changes on the SBP and DBP throughout the study

Discussion

According to normal SGOT and SCr levels, the patients in this study had no conditions that might disturb the activation or breakdown of vitamin D, namely renal or hepatic disease. Additionally, the analysis of covariance was utilized to adjust the baseline reading for any potential effects of the various medications used in the traditional antihypertensive regimen. Altogether of the hypertension Patients in the present study ranged in age from forty to seventy years., and both sexes were included in the study. According to several deaths from IHD and CVD that were recorded from Western countries, this was consistent through the age- calibration to the age categories (45-74) (11,12)

Effect of Vitamin D3 Supplement on Serum Angiotensin II (Ag II) Levels

With reference to the mechanism mentioned earlier, The RAAS is regulated by vitamin D, and a lack of vitamin D increases the likelihood that the RAAS will be activated, leading to hypertrophy of the left ventricle and smooth muscle cells (13).and that vitamin D3 supplementation cause suppressing renin gene expression downregulating the system RAA (2). In the current investigation, vitamin D3 supplementation significantly reduced the serum level of angiotensin II in hypertensive patients with hypovitaminosis D compared to control patients receiving standard hypertension treatment.

Numerous researchers have skillfully examined how vitamin D affects the level of the hormone angiotensin II, and there is strong evidence linking vitamin D deficiency to cardio vascular disease risk factors. Experimental research by Li,et al. (2002) exposed vitamin D is a powerful inhibitor of the renin-angiotensin system(14), and decreasing the vitamin D receptor produce additional renin angiotensin II than normal, which results in hypertension, cardiac hypertrophy, and increased water consumption (15). Moreover experimentally, vitamin D receptor knockout mice were used to examine D3 affects heart activities, at least in part, via the RAS, according to research on the role of the cardiac RAS in the progression of ventricular hypertrophy, the production of renin and angiotensinogen, and the relationship between these two signaling pathways. (16, 17).

According to a 2007 study by Forman et al., there is a connection amid measured vitamin D insufficiency a higher danger of incident hypertension in humans. concludes that there may be a connection between high blood pressure and vitamin D. arbitrated through how it affects vascular function and the renin-angiotensin system (18). According to a recent Romanian study, patients with hypertension and vitamin D insufficiency had a greater RAA level than those with hypertension and sufficient vitamin D. (19). Another study In people with hypertension, endogenous vitamin D levels and RAA levels are inversely correlated. (20). In his interventional study, Vaidya et al.(2012) found that a dose of vitamin D3 (15,000IU/day) for one month modified tissue sensitivity to Ag II similar to converting enzyme inhibition(21), which come in agreement with the present results and exploring the pinpoint leading to further cardiovascular events. However, despite the fact that the vitamin D group's mean 25(OH)D concentration was higher than forty ng/L, Scragget et al. (2017) reported that monthly vitamin D supplementation of 100,000 IU in adults with cardiovascular disease and serum endogenous vitamin D levels of less than thirty ng/ml for two–four years did not prevent cardiovascular disease. Additionally, this study supported the need for vitamin D doses larger than twnty ng/mL in comparison to (22), He did acknowledge some limitations in his research, though, such as the fact that vitamin D is more easily absorbed by cells than 25(OH)D and that daily or weekly vitamin D doses are more effective at preventing disease than monthly doses because vitamin D would only have been in the blood circulation for a short period of time after each monthly dose. (23, 24). (22).

Effect of Vitamin D3 Supplement on Serum Endogenous Vitamin D Level

According to the obtainable data, a sizable section of the populace has inadequate vitamin D levels, which might negatively affect the cardiovascular system. According to ecological research, cardiovascular disease mortality is higher in the winter and in areas with less sun exposure to ultraviolet. (13).

In the current investigation, the vast majority of hypertension patients Insufficient baseline levels of endogenous vitamin D of twenty ng/ml rather than sufficient levels of thirty ng/ml were found in both study groups. In order to maintain a normal level of 25-hydroxyvitamin D, one study recommended that those who don't get enough sun everyday consume more vitamin D than 600 IU, most likely 1000 IU (25).

The treatment group in this study experienced a highly significant increase in mean total endogenous vitamin D when compared to pre-treatment levels, with a significant difference from the control group taking traditional antihypertensive medications. The treatment involved taking an oral vitamin D dosage of 100,000 IU every2weeks.

The following factors can be used to explain these results: first, only the serum 25-OH vitamin D level, which is thought to be It was determined that the best circulating biomarker of vitamin D metabolic state, which represents the endogenous vitamin D level from diet and solar exposure in addition to the liver's conversion of adipose tissue to vitamin D, was present. Compared to the active form of vitamin D which has a brief half-life26 , this biomarker (25-OH vitamin D) was more stable (27).

Besides, it is metabolized only in the liver by 25-hydroxylase(16), meanwhile, the active form is metabolized in both the kidneys and extrarenal site, and its formation is under the control of parathyroid hormone and calcitonin(28).

Second, Higher significant increases in mean endogenous vitamin D heights in hypertensive patients preserved with vitamin D3 the deficiency to the acceptable normal level (38.5 1.243ng/ml), allowing researchers to investigate the true benefit of treatment on blood pressure readings. supplement compared to traditional therapy gave a moral indication of the potency impact of study obtrusion in bringing the insufficiency to the acceptable normal level.

Effect of Vitamin D3 Supplement on Glycemic Status, Lipid Profile.

Restoration to normal levels of endogenous vitamin D in the current study fixed not touch the blood glucose levels. Since most of the study patients possess the upper acceptable limit of fasting blood glucose-related possibly to metabolic effect

of hypertension.

One randomized controlled trial done by Withamet al. (2010), detecting vitamin D supplementation had no impact on insulin sensitivity when it came to the markers of vascular health in type two diabetes patients, according to research on the effects of various vitamin D3 levels. (29). Robinson et al. (2011) conducted another investigation and founds no link between the risk of diabetes and low vitamin D levels. (30). On the contrary, Scragg et al. (2004) reported that Insulin resistance and endogenous vitamin D concentrations are inversely correlated. But, his study had some limitations such that he didn't measure parathyroid hormone that may have an indirect effect on insulin resistance, also, his results depend on a single measurement of serum endogenous vitamin D.

Furthermore, The direct connection between vitamin D and bone health., parathyroid hormone, calcium, and phosphate, that any of these factors may have direct or indirect effect on insulin resistance and glucose homeostasis(31).

The increased mortality in subjects with vitamin D deficiency is particularly related to cardiovascular diseases (CVD)(32).Which could be explained by the relations between elevated Blood pressure and BMI and low serum vitamin D levels (33, 34). However, many studies are still ambiguous about the relationship between blood vitamin D and serum lipids, which are among the main risk factors for the emergence of cardiovascular disease(35) (36, 37). The serum lipid levels may be impacted by vitamin D in a number of ways. One method involves enhancing the absorption of fat and calcium in the stomach while decreasing the development of calcium-fatty soaps. Calcium causes malabsorption of bile acids, which contributes to malabsorption of fat, besides the stimulatory effects on lipolysis(38). In a meta-analysis by Wang et al. (2012)reviewing the randomized controlled trials about He claimed that vitamin D3 administration could raise LDL cholesterol concentrations as a result of The plasma lipid profile is impacted by vitamin D, however, TC, HDL cholesterol, and TG are not considerably impacted (39). Ramiro-Lozano et al. (2015) are currently in court again of vitaminD

16,000 IU of calcifediol to be taken orally once a week for at least eight weeks as a supplement, it significantly decreases TC and a non- significant reduction in LDL, VLDL, and TG were reported, whereas, HDL did not change(40). Additionally, Muñoz-Aguirre et al. (2015) in his randomized controlled trial in postmenopausal women with diabetes, conclude shows vitamin D treatment 4000 IU/d may improve blood TG levels without impacting levels of other lipids (41). Finally, and most recently, Patwardhan et al. (2017) came to the conclusion that cholecalciferol supplementation increased TC and HDL concentrations while increasing vitamin D concentrations by solar exposure dramatically reduced TC, LDL, and HDL concentrations (42).

Effect of Vitamin D3 Supplement on Blood Pressure (BP) profile

Collecting all the previous evidence, the potential correlation between endogenous vitamin status and the development of cardiovascular events could be speculated. In fact, one sunlight According to one exposure (tanning) study, tanning three times per week for three months increased 25(OH)D levels by roughly 200% and decreased systolic and diastolic blood pressure by 6 mm Hg (13). From the current findings study, there was a significant decrease in SBP and also pronounced reduction in DBP after vitamin D3 supplementation for 2 months. This result put some argument with some previous studies.

Consuming vitamin D decreased systolic blood pressure by a non-significant two mm Hg in a meta-analysis of 10 clinical trials. but, did not lower diastolic BP (42). Another small study found that patients with T2DM and low baseline 25 D levels responded favorably to a single dose of 100,000 IU vitamin D2, with a 14 mm Hg reduction in systolic blood pressure and an improvement in endothelial function as measured by forearm blood flow (43). Hsia et al. (2007) reported no correlation between vitamin D3 supplementation and cardiovascular events when using 365 IU of vitamin D3 per day for 2 years(44), and he explained this results as follows; The study drug was not taken as prescribed, the vitamin D dosage was insufficient, and concurrent postmenopausal hormone therapy may interfere with treatment. In a different trial, obese hypertensive patients receiving high-dose cholecalciferol therapy (15 000 IU/day for 1 month) experienced improved renal plasma flow (RPF) and reduced mean arterial pressure (21). In addition, a 2012 study by Larsen et al. investigated the effects of vitamin D3 supplementation during winter months in patients with HTN, showed that 3,000 IU per day cholecalciferol for 20 weeks significantly decrease SBP and DBP(45).

Judd et al. (2008) reported that in non-hypertensive white Americans, SBP is adversely correlated with serum vitamin D concentrations (46). A randomized, double-blind, placebo-controlled trial conducted on black patients by Forman et al. (2013) found that supplementing with vitamin D at levels of (1000, 2000, and 4000) IU per day for three months significantly reduced SBP but had no significant impact on DBP (47). This possibly could be explained by two points; the first, some of the patients involved in the study were taken antihypertensive medications which may mask the effect of vitamin D3 supplementation, and second, the range of the vitamin D3 dose was low to produce a advantageous effect on BP.

summary, the current findings come in agreement with the previously mentioned studies in respect to the effect on the SBP, and some controversy regarding the effect on the DBP. This is in one arm referring to the previously mentioned mechanisms by which vitamin D3 may lower BP, such that the effects on the renin-angiotensin system (RAS), The expression of one-

hydroxylase, the activity of vascular endothelium, and the presence of PTH receptors all have direct modulatory effects on vascular smooth muscle cells., suggesting that PTH may have direct regulatory impact on the artery wall. Inflammatory cytokines on the vasculature(48) and the presence of PTH receptor in these cells further support this theory (49, 50). In experimental studies, blood pressure increases during PTH infusion(51). Meanwhile, epidemiologic studies showed independent relations between PTH and BP(52, 53). Data from the US National Health and Nutrition Examination Surveys that are cross-sectional provide credence to the theory that PTH may serve as a mediator in the relationship between vitamin D and blood pressure. (54).

In another arm, the potential effect might be related to the endogenous vitamin D status and also to the vitamin D dose and the dosage regimen.

Conclusion:

Restoring sufficient endogenous vitamin D level reduced renin-angiotensin system activity and decreasing BP levels Vitamin D3 supplementation is a low-cost treatment option that can be used in conjunction with antihypertensive medications. It is of utmost importance to conduct future research on the possibility of using vitamin D in the treatment of many dangerous and common diseases, as it can be a lifesaver treatment for people suffering from chronic diseases, in addition to its abundance in the market, ease of use by patients, being safe and not causing dangerous side effects even in high doses.

References

1. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine 18E Vol 2 EB: McGraw Hill Professional; 2012.
2. Tamez H, Kalim S, Thadhani RI. Does vitamin D modulate blood pressure? Current opinion in nephrology and hypertension.2013;22(2):204.
3. Ferder M, Inserra F, Manucha W, Ferder L. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. AmericanJournal of Physiology-Cell Physiology.2013;304(11):C1027-C39.
4. Wang C. Role of vitamin d in cardiometabolic diseases. Experimental Diabetes Research. 2013;2013.
5. Ish-Shalom M, Sack J, Vechoropoulos M, Shaish A, Entin-Meer M, Kamari Y, et al. Low-dose calcitriol decreases aortic renin, blood pressure ,and atherosclerosis in apoe-null mice. Journal of atherosclerosis and thrombosis. 2012;19(5):422-34.
6. Cumhur Cure M, Cure E, Yuce S, Yazici T, Karakoyun I, Efe H. Mean platelet volume and vitamin D level. Annals of laboratory medicine. 2014;34(2):98-103.
7. Lee JH, O'Keefe JH, Bell D ,Hensrud DD, Holick MF. Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor? Journal of the American College of Cardiology. 2008;52(24):1949-56.
8. Vanlint S. Vitamin D and obesity. Nutrients. 2013;5(3):949-56.
9. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency:an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism.2011;96(7):1911-30.
10. Sun Q, Shi L, Rimm EB, Giovannucci EL, Hu FB, Manson JE, et al. Vitamin D intake and risk of cardiovascular disease in US men and women. The American journal of clinical nutrition. 2011;94(2):534-4.2
11. Manson JE, Bassuk SS, Lee I-M, Cook NR, Albert MA, Gordon D, et al. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemporary clinical trials.2012;33(1):159-71.
12. Müller-Nordhorn J, Binting S, Roll S, Willich SN. An update on regional variation in cardiovascular mortality within Europe. European heart journal. 2008;29(10):1316-26.
13. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease: will it live up to its hype? Journal of the American College of Cardiology. 2011;58(15):1547-5.6
14. Li YC, Kong J, Wei M, Chen Z-F, Liu SQ, Cao L-P. 1, 25-Dihydroxyvitamin D 3 is a negative endocrine regulator of the renin-angiotensin system. The Journal of clinical investigation.2002;110(2):229-38.
15. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin–angiotensin system and blood pressure. The Journal of steroid biochemistry and molecular biology. 2004;89:387-92.
16. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocrine reviews. 2008;29(6):726-76.
17. Xiang W, Kong J, Chen S, Cao L-P, Qiao G, Zheng W, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. American Journal of Physiology-Endocrinology and Metabolism. 2005;288(1):E125-E32.
18. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49(5):1063-9.
19. Mozos I, Marginean O. Links between vitamin D deficiency and cardiovascular diseases. BioMed research international. 2015;2015.
20. Kota SK, Kota SK, Jammula S, Meher LK, Panda S, Tripathy PR, et al. Renin–angiotensin system activity in vitamin D deficient, obeseindividuals with hypertension: An urban Indian study. Indian journal of endocrinology and metabolism. 2011;15(Suppl4):S395.
21. Vaidya A, Sun B, Larson C, Forman JP, Williams JS. Vitamin D3 therapy corrects the tissue sensitivity to angiotensin ii akin to the action of a converting enzyme inhibitor in obese hypertensives: an interventional study. The Journal of Clinical Endocrinology & Metabolism. 2012;97(7):2456-65.
22. Scragg R, Stewart AW, Waayer D, Lawes CM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessmentstudy: a randomized clinical trial. JAMA cardiology. 2017;2(6):608-16.
23. Hollis BW, Wagner CL. The role of the parent compound vitamin D with respect to metabolism and function: why clinical dose intervals can affect clinical outcomes. The Journal of Clinical Endocrinology & Metabolism. 20.28-4619:)12(98;13
24. Jones K, Assar S, Harnpanich D, Bouillon R, Lambrechts D, Prentice A, et al. 25 (OH) D2 half-life is shorter than 25 (OH) D3 half-life and is influenced by DBP concentration and genotype. The Journal of Clinical Endocrinology & Metabolism. 2014;99(9):3373-81.
25. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Thomsen J, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. Journal of internal medicine. 2000;247(2):260-8.
26. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. The Journal of nutrition. 2005;135(2):317-22.

27. Jones G. Pharmacokinetics of vitamin D toxicity–. The American journal of clinical nutrition. 2008;88(2):582S-6S.
28. Tamašauskienė L, Gasiūnienė E, Lavinskienė S, Sakalauskas R, Šitkauskienė B. Evaluation of vitamin D levels in allergic and non-allergic asthma. Medicina. 2015.7-321:)6(51;
29. Witham M, Dove F, Dryburgh M, Sugden J, Morris A, Struthers A. The effect of different doses of vitamin D3 on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. Diabetologia. 2010;53(10):2112-9.
30. Robinson JG, Manson JE, Larson J, Liu S, Song Y, Howard BV, et al. Lack of association between 25 (OH) D levels and incident type 2 diabetes in older women. Diabetes Care. 2011;34(3):628-34.
31. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D ,diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes care. 2004;27(12):2813-8.
32. Pilz S, Dobnig H, Nijpels G, Heine RJ, Stehouwer CD, Snijder MB, et al. Vitamin D and mortality in older men and women. Clinical endocrinology. 2009;71(5):666-72.
33. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. The Journal of Clinical Endocrinology & Metabolism. 2005;90(7):4119-23.
34. Abbas R, Abdulridha M, Abdalfatah Shafek M. Correlation between Endogenous Vitamin D Status and Body Mass Index in Asthmatic Patients Receiving Adjuvant Vitamin D3 Supplement2017.
35. Kannel WB, Castelli WP, Gordon T, McNamaraPM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. Annals of internal medicine. 1971;74(1):1-12.
36. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among US adults. Diabetes care. 2005;28(5):1228-30.
37. John WG, Noonan K, Mannan N, Boucher BJ. Hypovitaminosis D is associated with reductions in serum apolipoprotein AI but not with fasting lipids in British Bangladeshis–. The American journal of clinical nutrition. 2005;82(3):517-22.
38. Reid IR. Effects of calcium supplementation on circulating lipids. Drugs & aging. 2004;21(1):7-17.
39. Ramiro-Lozano JM, Calvo-Romero JM. Effects on lipid profile of supplementation with vitamin D in type 2 diabetic patients with vitamin D deficiency. Therapeutic advances in endocrinology and metabolism. 2015;6(6):245-8.
40. Muñoz-Aguirre P, Flores M, Macias N, Quezada AD, Denova-Gutiérrez E, Salmerón J. The effect of vitamin D supplementation on serum lipids in postmenopausal women with diabetes: A randomized controlled trial. Clinical nutrition. 2015;34(5):799-804.
41. Patwardhan VG, Mughal ZM, Padidela R, Chiplonkar SA, Khadilkar VV, Khadilkar AV. Randomized control trial assessing impact of increased sunlight exposure versus Vitamin D supplementation on lipid profile in Indian Vitamin D deficient men. Indian journal of endocrinology and metabolism. 2017;21(3):393.
42. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, et al.
Systematic review: vitamin D and cardiometabolic outcomes. Annals of internal medicine. 2010;152(5):307-14.
43. Sugden J, Davies J, Witham M, Morris A, Struthers A. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabetic medicine. 2008;25(3):320-5.
44. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation.54-846:)7(115;2007 .
45. Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. American journal of hypertension. 2012;25(11) ;1215-1222.
46. Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey .–The American journal of clinical nutrition. 2008;87(1):136-41.
47. Forman JP, Scott JB, Ng K, Drake BF, Suarez EG, Hayden DL, et al. Effect of Vitamin D Supplementation on Blood Pressure in BlacksNovelty and Significance. Hypertension. 2013;61(4):779. --85
48. Zehnder D, Bland R, Chana RS, Wheeler DC, Howie AJ, Williams MC, et al. Synthesis of 1, 25-dihydroxyvitamin D3 by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. Journal of the American Society of Nephrology. 2002;13(3):621-9.
49. Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. Current osteoporosis reports. 2008;6(2):77.
50. Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates endothelialexpression of atherosclerotic parameters through protein kinase pathways. American Journal of Physiology- Renal Physiology. 2007;292(4): F1215-F8.
51. Hulter H, Melby J, Peterson J, Cooke C. Chronic continuous PTH infusion results in hypertension in normal subjects. Journal of clinical hypertension. 1986;2(4):360-70.
52. Jorde R, Sundsfjord J, Haug E, Bønaa KH. Relation between low calcium intake, parathyroid hormone, and blood pressure. Hypertension. 2000;35(5):1154.9-
53. Snijder M, Lips P, Seidell J, Visser M, Deeg D, Dekker J, et al. Vitamin D status and parathyroid hormone levels in relation to blood pressure: a popul ation- based study in older men and women. Journal of internal medicine. 2007;261(6):558-65.
54. He JL, Scragg RK. Vitamin D, parathyroid hormone, and blood pressure in the National Health and Nutrition Examination Surveys. American journal of hypertension. 2011;24(8):911-7.