Original Article

Association between vitamin D and hypertension in people coming for health check up to a tertiary care centre in South India

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Abstract

Introduction: Vitamin D has many effects apart from its role in calcium metabolism and bone health. Vitamin D is derived from endogenous ultraviolet-B induced vitamin D synthesis in the skin, and the current high prevalence of vitamin D deficiency in India, can be attributed to lifestyle related low sunlight exposure. Identification of the vitamin D receptor (VDR) in almost all human cells, suggests a role in extra skeletal diseases. Studies have shown that vitamin D deficiency is an independent risk factor for hypertension. **Aim:** To evaluate the association between vitamin D and hypertension in people coming for health check up to a tertiary care center in South India. **Materials and Methods:** Study was carried out as a cross sectional study in a tertiary care hospital in South India. Participants (520) were both males and females (337 males and 183 females), between the age group of 20-60 years attending the comprehensive health check up clinic of our hospital. **Statistical Analysis:** Statistical analysis was done using IBM SPSS statistics 20.0. **Results:** Severe vitamin D deficiency was highly prevalent in people with hypertension than in people without hypertension (*P* value <0.001). **Conclusion:** Since India is a tropical country, till recently it was believed that vitamin D deficiency and its ill effects are uncommon. But it was found that, vitamin D deficiency was highly prevalent in people with hypertension in South India, emphasizing the need of early vitamin D supplementation. Therefore, to reduce cardiovascular morbidity, early identification of vitamin D deficiency and appropriate vitamin D supplementation may be of primary importance in population, especially like ours, having high prevalence.

Keywords: Hypertension, vitamin D, vitamin D receptor

Introduction

Vitamin D deficiency is very common and of great public health interest in India. Many of the musculoskeletal diseases are associated with vitamin D deficiency.[1-3] To prevent rickets and osteoporosis, vitamin D supplementation is recommended.[4-6] Vitamin D regulates bone and mineral metabolism by calcium absorption in gut and providing calcium for mineralization.[7] Vitamin D receptors (VDRs) are present in all human cells.[8] Studies have shown association of vitamin D deficiency with a variety of chronic extraskeletal diseases.[9-15] In this context, aim of our study was to find association between vitamin D and hypertension in people attending tertiary care center in South India.

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Background

Physiology of vitamin D

Vitamin D was termed as "D" because it was the fourth vitamin known.[16] Chief source of vitamin D is endogenous vitamin D synthesis in the skin.[17] To induce the conversion of the precursor 7-dehydrocholesterol to vitamin D, ultraviolet-B

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spectrum of light is required.[1,8] Approximately 80-90% of vitamin D is derived from sunlight, whereas only minor amounts of vitamin D is from dietary sources.[18] Fish oil, egg yolk, and mushrooms are rich in vitamin D. To exert its biological effects, vitamin D has to be converted to its most active form, 1,25-dihydroxyvitamin D (calcitriol).[8] Serum concentrations of $1,25(OH)_2D$ are mainly determined by production of $1,25(OH)_2D$ by the kidneys. This is controlled by parameters of mineral metabolism, which help to maintain calcium and phosphorus levels within physiological ranges.[1,8] Parathormone (PTH) increases 1-alpha hydroxylation, whereas fibroblast growth factor-23 (FGF-23) or high phosphate levels decrease 1-alpha hydroxylation in the kidneys. It was believed that only the kidneys are able to synthesize significant amounts of $1,25(OH)_2D$.[8,19] Now, it was found that many extrarenal tissues are also able to synthesize $1,25(OH)_2D$ on a local and intracellular level.[19] Regulation of extrarenal 1-alpha-hydroxylase is different compared with the kidneys, and is significantly dependent on the availability of 25(OH) D.[19] Based on this, it can be assumed that local tissue levels of $1,25(OH)_2D$ are determined by concentrations of circulating 25(OH) D levels.[19] This is why serum levels of 25(OH) D and not of $1,25(OH)_2D$ are measured to assess and classify vitamin D status. Serum levels of 25(OH)D are up to 1,000-fold higher compared with $1,25(OH)_2D$. Affinity to the VDR is much higher for $1,25(OH)_2D$, which is thus often called the active vitamin D.

Link between vitamin D and hypertension

Vitamin D plays an important role in the pathophysiology of arterial hypertension. Vitamin D receptor knockout mice showed an increased renin expression and arterial hypertension.[20-22] Vitamin D exerts its effect on the renin angiotensin aldosterone system (RAAS).[22] Increase in PTH levels, a hallmark of vitamin D deficiency, may also increase blood pressure.[23,24] Studies show a positive association between PTH levels and blood pressure.[23] In the cardiovascular system, PTH receptors are present and PTH infusions increase blood pressure.[23,24] PTH is therefore an independent risk factor for cardiovascular events.[25,26] Nephroprotective actions of vitamin D have also been proved.[27] These involve anti-inflammatory actions of vitamin D, by suppressing nuclear factor-κB (NF-κB).[27] Increase in sodium intake increases urinary calcium loss, affecting the metabolism of vitamin D.[28] High salt intake can cause adverse effects on vitamin D status and its metabolism, by increased urinary loss of vitamin D metabolites.[28] Calcium is involved in the regulation of peripheral vascular resistance by modulating contractility of vascular smooth muscle cells.[29] Vitamin D has got a direct effect on the vasculature.[30,31] Anti-atherosclerotic effects of VDR activation has been studied.[30,31] These include vitamin D induced decrease of endothelial adhesion molecules, increase in nitric oxide (NO) production, and inhibition of macrophage to foam cell formation.[32,33] Relationship between vitamin D deficiency and endothelial dysfunction has been studied.[34,35] So, several pathophysiological mechanisms exist between vitamin D deficiency and arterial hypertension.

Aim

To evaluate the association between vitamin D and hypertension in people coming for health check up to a tertiary care center in South India, since studies from Kerala were limited.

Materials and Methods

Study was done as a cross-sectional study in a tertiary care center in South India. Participants (520) were both males and females (337 males and 183 females), between the age group of 20-60 years attending the health check up clinic of our hospital for a period of 3 months. Each subject was interviewed and a standardized questionnaire was computed, containing information on demographics, anthropometric profile, individual characteristics associated with major risk factors for cardiovascular disease, past medical history, details of sun exposure (type of job and average time of sun exposure in a day), and biochemical parameters. Hypertension was identified from self-reports or doctor measurement on the baseline and follow-up measures or questionnaires meeting at least one of three JNC8 criteria: systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or use of antihypertensive medicines. Incident hypertension was defined as newly developed hypertension among those free of baseline hypertension. The definition of incident hypertension is patient self-report or doctor measurement. All participants gave their written informed consent to participate in the study that was approved by the institution ethics committee.

Inclusion criteria

- Age group—20-60 years
- Both sex
- People with hypertension diagnosed for the first time or on antihypertensive medications.

Exclusion criteria

- Age group below 20 years and above 60 years
- People with chronic renal, hepatic, cardiac, gastrointestinal, skeletal, endocrine diseases, diabetes, acute critical illness, and pregnancy
- People on calcium or vitamin D supplementation.

Biochemical analysis

Peripheral venous blood samples (4 ml) were collected from all the participants after an overnight fast of 12-14 h. Serum was separated by centrifuging at 3,000 rpm for 5 min. Blood glucose was estimated by hexokinase method on Olympus AU2700 analyzer. Blood urea was estimated by enzymatic urease method and serum creatinine by Jaffe's method. Serum calcium was estimated by Arsenazo III method. Liver function was estimated by colorimetry method on Olympus AU2700 analyzer. HDL, LDL, VLDL, and triglycerides were estimated by enzymatic method on Olympus AU2700 analyzer. For assessing vitamin D levels, peripheral venous blood samples (2 ml) were collected from all the participants. Serum was separated by centrifuging at

3,000 rpm for 5 min. Vitamin D remains stable up to 72 h in room temperature and up to 10 years if stored in -20°.[36] The minimal detectable limit of vitamin D assay is 3 ng/ml. Participants were classified as vitamin D deficient, insufficient, and sufficient on the basis of vitamin D concentration of <20 ng/ml, 20-30 ng/ml, and >30 ng/ml, respectively, according to recent consensus.[37,38] Vitamin D deficiency can be classified as severe (<10 ng/ml) and mild-moderate deficiency (10-20 ng/ml) depending on the vitamin D levels.[37] The quantitative estimation of 25-OHD_3 is done using ARCHITECT 25-OH assay, which is a Chemiluminescent Microparticle Immuno Assay (CMIA). The estimated vitamin D is a sum total of both vitamin D_2 and vitamin D_3.

Biological principles in the procedure

The ARCHITECT 25-OH is a delayed one-step immunoassay, including a sample pretreatment for the quantitative estimation of vitamin D in human serum using CMIA technology with flexible assay protocols, referred to as Chemiflex. The measuring interval of this method is from 8 ng/ml (20 nmol/L) to 160 ng/ml (400 nmol/L). This method has high sensitivity and specificity, and the potential interference from hemoglobin, bilirubin, triglycerides, protein, rheumatoid factor, and red blood cells is designed to be less than 10%.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 20. For all the categorical variables, the results were given as %. Pearson's Chi-square test was applied to test the relationship between two categorical variables. *P* value of <0.05 were considered as statistically significant.

Results

A total of 520 subjects [337 (64.8%) males and 183 (35.2%) females] participated in the study [Figure 1]. 31.54% were below 40 years and 68.46% were above 40 years [Graph 1]. Average age of the participants were 45.92 ± 9.77. Prevalence of hypertension in our study was 86.2% [Table 1]. Among hypertensive patients, 67.6% (303) were males and 32.4% (145) were females [Table 2]. Among hypertensive patients, 25.7% (115) were below 40 years and 74.3% (333) were above 40 years [Table 3]. Among total participants (520), 78.8% (410) had vitamin D deficiency, 8.1% (42) had vitamin D Insufficiency, and 13.1% (68) had

Table 1: Prevalence of hypertension

Hypertension	Frequency	Percent
Yes	448	86.2
No	72	13.8

Table 2: Distribution of males and females among hypertensives

Gender	Frequency	Percent
Male	303	67.6
Female	145	32.4

Table 3: Distribution of age category among hypertensives

Age	Frequency	Percent
<=40 years	115	25.7
>40 years	333	74.3

Table 4: Prevalence of vitamin D deficiency, insufficiency, and sufficiency

Vitamin D status	Frequency	Percent
Vitamin D deficiency	410	78.8
Vitamin D Insufficiency	42	8.1
Vitamin D sufficiency	68	13.1

Table 5: Prevalence of severe, mild-moderate vitamin D deficiency, vitamin D insufficency, and vitamin D sufficiency among hypertensives

Vitamin D status	Frequency	Percent
Severe deficiency	345	77
Mild Moderate deficiency	39	8.7
Insufficiency	27	6
Sufficiency	37	8.3

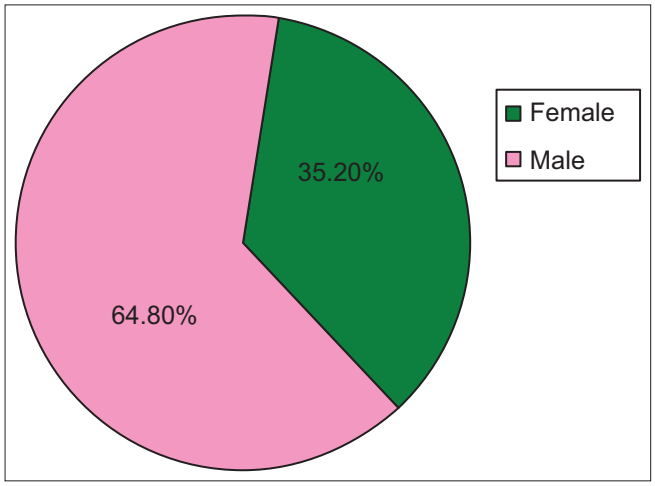
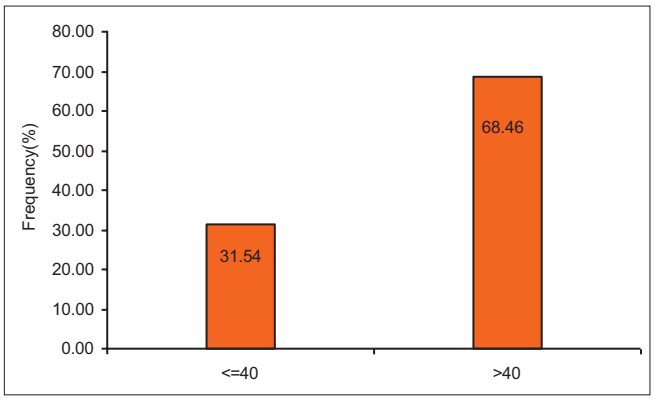


Figure 1: Percentage of males and females



Graph 1: Age distribution of participants

Table 6: Comparison of vitamin D status among hypertensives and non hypertensives

Variable		Vitamin D levels				*P*
		Severe no. (%)	Mild-mod no. (%)	Insufficiency no. (%)	Sufficiency no. (%)	
HTN	Yes (448)	345 (77)	39 (8.7)	27 (6)	37 (8.3)	<0.001
	No (72)	16 (22.2)	10 (13.9)	15 (20.8)	31 (43.1)	

Table 7: Comparison of severe vitamin D deficiency among hypertensives and non hypertensives

Hypertension	Severe vitamin D Deficiency (NO)	Mean±Standard deviation	*P*
HTN(+)	345	4.44±1.50	<0.005
HTN(−)	16	5.50±1.12	

vitamin D sufficiency [Table 4]. Prevalence of severe and mild-moderate vitamin D deficiency in hypertensive patients were 77% (345) and 8.7% (39), respectively. Prevalence of severe and mild-moderate vitamin D deficiency in nonhypertensives were 22.2% (16) and 13.9% (10), respectively. Prevalence of vitamin D insufficiency and sufficiency in hypertensive patients were 6% (27) and 8.3% (37), respectively. Prevalence of vitamin D insufficiency and sufficiency in nonhypertensives were 20.8% (15) and 43.1% (31), respectively (*P* value < 0.001) [Tables 5 and 6]. Among hypertensives, mean vitamin D level in people with severe deficiency was 4.44 ± 1.50 and among nonhypertensives, mean vitamin D level in people with severe deficiency was 5.50 ± 1.12 (*P* value <0.005) [Table 7].

Conclusion

Our study showed a strong inverse association of 25(OH) D levels and hypertension. Vitamin D deficiency was associated with an increased risk of having hypertension in this demographic group.

Discussion

Arterial hypertension is a significant risk factor for cardiovascular disease. The incidence of hypertension is increasing and there is large hypertensive population at risk for cardiovascular morbidity and mortality in India. Recent studies shows that vitamin D plays a key role in parameters that regulate high blood pressure via proliferation of vascular smooth muscle cells, endothelial cell function, regulation of renin-angiotensin pathway, and in regulation of blood pressure via increased intracellular calcium leading to decreased renin activity. In our study, prevalence of hypertension was 86.2%. Prevalence of severe vitamin D deficiency in hypertensives was 77%. Prevalence of vitamin D sufficiency in hypertensives was 8.3%. Prevalence of severe vitamin D deficiency in nonhypertensives was 22.2%. Prevalence of vitamin D sufficiency in nonhypertensives was 43.1%. Hypertensives had very low levels of vitamin D compared with nonhypertensives (*P* value <0.001). A study on 25 hypertensive patients by Duprez *et al.*[39] showed that vitamin D levels inversely associated with SBP. Studies have shown that incidence of hypertension increases with higher latitude. Blood pressure recordings in winter months showed higher values and blood pressure increases by 2.5 mm of Hg, for each 10° North or South shift of the equator, and prevalence of hypertension increases by 2.5%. A study by Tomaschitz A. *et al.*,[40] showed that both 25(OH)D and 1,25(OH)D were inversely associated with plasma renin and angiotensin II concentrations. Retrospective studies have shown a significant inverse association between vitamin D and SBP[39,41,42] Prospective study in 1,448 women[43] demonstrated a 2.21-fold increase in hypertension in people with vitamin D deficiency versus control group. A study comprising of 613 men from health professionals follow-up study[44] and 1,198 women from nurses health study[45] showed that lower serum 25(OH) vitamin D levels of 15 ng/mL (<37 nmol/L) increased the relative risk for hypertension by 6.13 in males and 2.67 in females when compared with vitamin D sufficient population (>75 nmol/L). NHANES 3-Third national health and nutrition examination survey study,[46] a large cross-sectional study involving noninstitutionalized 12,644 patients aged more than 20 years, was used to evaluate the relationship between serum 25(OH) vitamin D and hypertension. The mean blood pressure varied inversely with serum 25(OH) vitamin D levels, with the association remaining significant after adjustment for age, gender, race, ethnicity, and physical activity. Women`s health initiative (WHI),[47] the largest trial till date, done on nonhypertensive subjects, failed to show any significant impact of a small dose of vitamin D (400 IU) with calcium 1,000 mg/day on SBP or diastolic blood pressure after a mean follow-up of 7 years in post-menopausal women. In a randomized controlled trial on 148 elderly women,[48] demonstrated that a modest amounts of vitamin D (400 IU) with calcium given over 8 week period, significantly reduced SBP by 9%. A cross-sectional study[49] conducted on 4,125 subjects showed a significant association between vitamin D deficiency and hypertension. In the narrative review conducted by Kheiri *et al.* in 2018, vitamin D deficiency was associated with an increase risk of cardiovascular disease risk factor, especially hypertension[50] In a study conducted by Suzanne E. Judd *et al.* in 2016, there was an increased risk of incident stroke in people with vitamin D deficiency.[51] In a study conducted by Delen and Sahim, vitamin D levels were lower in people with resistant hypertension.[52] In a prospective study and meta-analysis conducted by Dan *et al.* in 2017, lower levels of vitamin D in people with hypertension were found.[53] As far as India is concerned, India is a vast tropical country extending from 8.4° N latitude to 37.6° N latitude and majority of the population lives in areas with abundant sunlight. In our city, Kochi (also known as Cochin) is in southwest India's coastal

Kerala state. It has been a port since 1341, when a flood carved out its harbor and opened it to Arab, Chinese, and European merchants. Kochi is at 9.9312°N, 76.2673°E. The winter season in Kochi begins from December and lasts till the month of February. The temperature usually hovers between 20°C and 32°C. Summers begin in Kochi from March and lasts till May. Kochi experiences a hot and humid weather during this season. Kerala is subject to vagaries of the monsoon. The monsoons arrive in June and it rains almost until the end of August. People cover themselves almost throughout the year. Staple diet is rice. Diet is also not rich in vitamin D. This finding of high prevalence correlates very well with other studies done in various parts of the world. There are studies which showed widespread prevalence of vitamin D deficiency in India.[37,38] Poor sun exposure due to modern lifestyle, vegetarian diet, skin pigmentation, and cultural practices like parda and burka may be the reasons for this high prevalence in our population. Vitamin D is synthesized when the UV rays from the sun fall on the skin. Till recently, it was believed that Indians had sufficient amount of vitamin D. Since Indians are now confined to more indoor jobs, and thus less sun exposure, most of us are now vitamin D deficient. Absence of sunlight hits production of vitamin D in the body, adversely affecting blood pressure. Salt intake, smoking, obesity, and heredity are now considered as the contributors for HTN. In the coming years, vitamin D deficiency may be included as a fifth contributor for HTN.

As a family physician, hypertension is one of the most common conditions encountered in primary care. Nonpharmacologic strategies like lifestyle modifications, diet rich in vegetables and fruits, whole grains, restricting sodium intake to less than 2,400 g/day and exercising three or four times a week for an average of 40 min per session have been recommended by American Heart association and have been shown to help lower blood pressure. Other strategies include weight loss, tobacco cessation, decreased alcohol consumption, biofeedback, and self-measured blood pressure monitoring. A recent trend developed by family physicians in United States and Canada is complementary and alternative medicine (CAM) antihypertensive therapies. Complementary and alternative medicine describes the field of inquiry into therapies that are not widely taught in medical schools or generally available in hospitals. Canadian use of CAM therapies is similar to that in the United States, where 36% of people regularly use CAM.[54] In CAM, there are evidences for lowering of blood pressure by vitamin D supplementation.[54] Vitamin D supplementation is inexpensive and can be provided through primary health centers all throughout our country, so that the needy people who are not exposed to tertiary centers nearby will get the full benefit out of it. Vitamin D supplementation not only reduces the risk of hypertension but also almost all the cardiovascular disease risk factors, skin diseases, respiratory diseases, and musculoskeletal diseases.[1-3] So in this way, vitamin D supplementation is multibeneficial. Fortification of widely consumed staple foods with vitamin D is another viable solution toward attaining vitamin D sufficiency in India. Early identification of vitamin D deficiency and appropriate intervention may be of primary importance in a population, especially like ours, having high prevalence, to prevent one of the cardiovascular disease risk factors like hypertension.

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Conflicts of interest

There are no conflicts of interest.

References

1. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
2. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab 2011;96:53-8.
3. 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. J Clin Endocrinol Metab 2011;96:1911-30.
4. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, *et al.* A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40-9.
5. Jain V, Gupta N, Kalaivani M, Jain A, Sinha A, Agarwal R. Vitamin D deficiency in healthy breastfed term infants at 3 months & their mothers in India: Seasonal variation & determinants. Indian J Med Res 2011;133:267-73.
6. Balasubramanian S. Vitamin D deficiency in breastfed infants and the need for routine vitamin D supplementation. Indian J Med Res 2011;133:250-2.
7. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001;22:477-501.

8. 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. Endocr Rev 2008;29:726-76.
9. Muscogiuri G, Sorice GP, Ajjan R, Mezza T, Pilz S, Prioletta A, *et al*. Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. Nutr Metab Cardiovasc Dis 2012;22:81-7.
10. Pilz S, Tomaschitz A, Drechsler C, Dekker JM, März W. Vitamin D deficiency and myocardial diseases. Mol Nutr Food Res 2010;54:1103-13.
11. Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, *et al*. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev 2010;9:709-15.
12. Mirković K, van den Born J, Navis G, de Borst MH. Vitamin D in chronic kidney disease: New potential for intervention. Curr Drug Targets 2011;12:42-53.
13. Soni M, Kos K, Lang IA, Jones K, Melzer D, Llewellyn DJ. Vitamin D and cognitive function. Scand J Clin Lab Invest 2012;243(Suppl):79-82.
14. Hewison M. Vitamin D and immune function: Autocrine, paracrine or endocrine? Scand J Clin Lab Invest 2012;243(Suppl):92-102.
15. Pilz S, Tomaschitz A, Obermayer-Pietsch B, Dobnig H, Pieber TR. Epidemiology of vitamin D insufficiency and cancer mortality. Anticancer Res 2009;29:3699-704.
16. Holick MF. McCollum award lecture, 1994: Vitamin D-new horizons for the 21st century. Am J Clin Nutr 1994;60:619-30.
17. Kochupillai N. The physiology of vitamin D: Current concepts. Indian J Med Res 2008;127:256-62.
18. Macdonald HM. Contributions of sunlight and diet to vitamin D status. Calcif Tissue Int 2013;92:163-76.
19. Peterlik M, Cross HS. Vitamin D and calcium insufficiency-related chronic diseases: Molecular and cellular pathophysiology. Eur J Clin Nutr 2009;63:1377-86.
20. Pilz S, Tomaschitz A, Drechsler C, Zittermann A, Dekker JM, März W. Vitamin D supplementation: A promising approach for the prevention and treatment of strokes. Curr Drug Targets 2011;12:88-96.
21. Pilz S, Tomaschitz A, Ritz E, Pieber TR. Vitamin D status and arterial hypertension: A systematic review. Nat Rev Cardiol 2009;6:621-30.
22. Li YC. Molecular mechanism of vitamin D in the cardiovascular system. J Investig Med 2011;59:868-71.
23. Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. Curr Osteoporos Rep 2008;6:77-83.
24. Fliser D, Franek E, Fode P, Stefanski A, Schmitt CP, Lyons M, *et al*. Subacute infusion of physiological doses of parathyroid hormone raises blood pressure in humans. Nephrol Dial Transplant 1997;12:933-8.
25. Pilz S, Tomaschitz A, März W, Drechsler C, Ritz E, Zittermann A, *et al*. Vitamin D, cardiovascular disease and mortality. Clin Endocrinol (Oxf) 2011;75:575-84.
26. Pilz S, Tomaschitz A, Drechsler C, Ritz E, Boehm BO, Grammer TB, *et al*. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography. Eur Heart J 2010;31:1591-8.
27. Dusso AS, Tokumoto M. Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: A downward spiral in kidney disease. Kidney Int 2011;79:715-29.
28. Thierry-Palmer M, Tewolde TK, Emmett NL, Bayorh MA. High dietary salt does not significantly affect plasma 25-hydroxyvitamin D concentrations of Sprague Dawley rats. BMC Res Notes 2010;3:332.
29. Guessous I, Bochud M, Bonny O, Burnier M. Calcium, vitamin D and cardiovascular disease. Kidney Blood Press Res 2011;34:404-17.
30. Brewer LC, Michos ED, Reis JP. Vitamin D in atherosclerosis, vascular disease, and endothelial function. Curr Drug Targets 2011;12:54-60.
31. Tare M, Emmett SJ, Coleman HA, Skordilis C, Eyles DW, Morley R, *et al*. Vitamin D insufficiency is associated with impaired vascular endothelial and smooth muscle function and hypertension in young rats. J Physiol 2011;589:4777-86.
32. Molinari C, Uberti F, Grossini E, Vacca G, Carda S, Invernizzi M, *et al*. 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. Cell Physiol Biochem 2011;27:661-8.
33. Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, *et al*. 1,25(OH)2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation 2009;120:687-98.
34. Harris RA, Pedersen-White J, Guo DH, Stallmann-Jorgensen IS, Keeton D, Huang Y, *et al*. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. Am J Hypertens 2011;24:557-62.
35. Witham MD, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients-a randomised controlled trial. Nutr Metab Cardiovasc Dis 2012;22:864-70.
36. Hollis BW. Assessment and interpretation of circulating 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in the clinical environment. Endocrinol Metab Clin North Am 2010 39:271-86.
37. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D. Vitamin D status in Andhra Pradesh: A population based study. Indian J Med Res 2008;127:211-8.
38. Lakshman LR, Pillai BP, Lakshman R, Kumar H, Sudha S, Jayakumar RV. Comparison of vitamin D levels in obese and non obese patients with PCOS in a South Indian population. Int J Reprod Contracept Obstet Gynecol 2013;2:336-43.
39. Duprez D, de Buyzere M, de Backer T, Clement D. Relationship between vitamin D an peripheral circulation in moderate arterial primary hypertension. Blood Press 1994;3:389-93.
40. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, *et al*. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen risk and cardiovascular health (LURIC) study. Clin Chim Acta 2010;411:1354-60.
41. Kristal-Boneh E, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. Hypertension 1997;30:1289-94.
42. Scragg R, Holdaway I, Singh V, Metcalf B, Baker J, Dryson E. Serum 25-hydroxycholecaliferol concentration is newly detected hypertension. Am J Hypertens 1995;8:429-32.
43. Scragg R, Sowens M, Bell C. Serum 25-hydroxyvitamin D,

ethnicity and blood pressure in the third national health and nutrition examination survey. Am J Hypretens 2007;20:713-9.

44. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, *et al.* Plasma 25-hydroxy vitamin D levels and risk of incident hypertension. Hypertension 2007;49:1063-9.
45. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, *et al.* Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 2006;29:650-6.
46. Forman JP, Curhan C, Taylor N. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension in young women. Hypertension 2008;52:828-32.
47. Margolis KL, Ray RM, Van Horn L, Manson JE, Allison MA, Black HR, *et al*. Effect of calcium and vitamin D supplementation on blood pressure: The Women's health initiative randomized trial. Hypertension 2008;52:847-55.
48. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of short term vitamin D and calcium supplementation on blood pressure and parathyroid harmone levels in elderly women. J Clin Endocrino Metab 2001;86:1633-7.
49. Jorde R, Figenschau Y, Emaus N. Serum 25-hydroxyvitamin D levels are strongly associated with systolic blood pressure. Hypertension 2010;55:792-8.
50. Kheiri B, Abdulla A, Osman M, Ahmed S, Hassan M, Bachuwa G. Vitamin D deficiency and risk of cardiovascular disease: A narrative review. J Clin Hypertens 2018;24:9. doi: 10.1186/s40885-018-0094-4.
51. Judd SE, Morgan CJ, Panwar B, Howard VJ, Wadley VG, Jenny NS, *et al.* Vitamin D deficiency and incident stroke risk in community living black and white adults. Int J Stroke 2016;93-102.
52. Delen E, Sahim I. Assessment of 25 hydroxy vitamin D levels in patients with resistant hypertension. Med Prin Pract 2016;25:25-30.
53. Qi D, Nie XL, Wu S, Cai J. Vitamin D and hypertension: Prospective study and meta analysis. PLoS One 2017;12:e0174298. doi: 10.1371/journal.pone.0174298. eCollection 2017.
54. Nahas R. Complementary and alternative medicine approach to blood pressure reduction. Can Fam Physician 2008;54:1529-33.