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Research Article

Vitamin D and High Blood Pressure

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Abstract:

Introduction: Cardiovascular diseases are the main cause of death in the world, and some of these diseases can be controlled or avoided with a healthier lifestyle. These diseases are often associated with the emergence of other diseases such as diabetes mellitus, obesity, high cholesterol levels and high blood pressure. Research has shown that vitamin D deficiency can be a factor that also helps in the appearance of these diseases, since if the serum levels of vitamin D are adequate, it can help in the control and prevention of these diseases.

Objectives: To evaluate the relationship between vitamin D and cardiovascular diseases, specifically systemic arterial hypertension and its effects.

Methods: A systematic review was carried out by searching for original articles in scientific databases: Pubmed, Science Direct, Lilacs and Scielo in English and Portuguese.

Results: No conclusive data were found for the indication of vitamin D supplementation in the treatment of systemic arterial hypertension, due to its lack of efficiency so far, requiring further research to better clarify the subject.

Conclusion: The results obtained do not present conclusive data for the indication of vitamin D supplementation in the treatment of systemic arterial hypertension, due to its lack of efficiency up to the present moment, more research is necessary for a better clarification on the subject.

Keywords: Vitamin D, Cholecalciferol, Arterial hypertension.

1. Introduction

Cardiovascular diseases are the main causes of death in the Brazilian population[1,2], and are responsible for at least 20% of deaths in our population over 30 years of age[3].

Recent studies have shown an association between vitamin D deficiency and an increased risk of cardiovascular complications[4], especially hypertension[5,6]. Hypertension is an important risk factor for other cardiovascular diseases and is a popular health problem worldwide[7-10] where some research confirms how vitamin D supplementation is associated with the reduction of important markers of cardiovascular risk in inflammation and hypertrophy left ventricular[11], as well as associated with several other biological processes, including blood pressure modulation. Among the proposed mechanistic pathways for the development of high blood pressure, studies show the relationship between vitamin D and the inhibition of the renin-angiotensin-aldosterone system[12].

According to several studies that evaluated the effects of vitamin D supplementation on blood pressure results, what was observed is the inconsistency in relation to their results, since there are studies that aim to evaluate the potential causal relevance of vitamin deficiency D and high blood pressure, updating the evidence on the effect of vitamin D supplementation on circulating 25(OH)D levels, as well as its impact on systolic and diastolic blood pressure. In addition, some researchers also present evidence of a genetic association of 25(OH)D and blood pressure levels[13].

Currently, trials of vitamin D supplementation and heart rate have shown mixed results. A meta-analysis of 11 studies concluded that vitamin D was beneficial in people with a high heart rate (defined as >140/90 mm Hg), but not in people whose arterial compression was normal[14]. However, another meta-analysis of 10 trials found that vitamin D supplementation caused a non-significant reduction in systolic blood pressure (-1.9 mm; 95% confidence interval, -4.2 to 0.4), although had no effect on diastolic pressure[15].

Given this, strategies aimed at improving the management of people already affected by cardiovascular disease should be an integral component of a comprehensive approach to the prevention and control of cardiovascular disease. Hypertension is a health problem worldwide due to increased longevity and the prevalence of contributing factors such as obesity, physical inactivity and unhealthy diet[16,17]. Its current prevalence in many developing countries, particularly in urban societies, is already as high as that observed in developed countries[18], where data estimate that hypertension is responsible for 7.1 million premature deaths and 4.5% of the disease burden. (64 million disability-adjusted life years) worldwide[19].

With this, this study aimed to evaluate the relationship of vitamin D in relation to the treatment of cardiovascular diseases, supplementation, and the consequence of deficiency.

2. Methodology

To carry out this systematic review, a search was carried out in the databases: LILACS, MEDLINE and SCIENCE DIRECT using Boolean operators in the keywords in English: Vitamin D OR Cholecalciferol AND Arterial hypertension.

As inclusion criteria, only original articles were used, which used vitamin D supplementation for the treatment of hypertension, while the exclusion criteria were articles with animal studies, as well as articles prior to the year 2013, setting the maximum period to be studied for 10 years and articles that did not present data on supplementation dosage and/or sample number.

For the inclusion of the articles, all the articles in the databases that contained the keywords were chosen. After initial analysis, the most suitable works were separated, which were used for this review.

Applied the inclusion and exclusion criteria, articles in the English language were selected for review. The analysis of the results was tabulated in an Excel spreadsheet and the following variables were compared: Country/population studied, N value, Author-year, blood pressure, BMI and age range of the sample, study objectives.

3. Results

After defining the inclusion and exclusion criteria, 10 articles were eligible, involving 6 countries, with 1 Asian, 4 American, 3 European and 2 Oceania studies.

In total, 2,461 individuals were involved as samples in the studies and received vitamin D supplementation, with tests to measure blood pressure. The largest sample group was the study by Arora et al.[20] with 534 people, carried out in the United States, and the smallest group was the article by Chai et al.[21] with 92 people, also carried out in the United States.

All studies used a randomized double-blind, placebo-controlled trial, with two studies using 4 sample groups, while the[22,23] other 8 using a test group and a placebo group. The studies did not use the same treatment group: (a) four studies used patients with some type of hypertension[20,24-26]; (b) three studies were performed with healthy people[23,27,28] and (c) the other three studies used patients with diabetes[22] or with colorectal adenoma[21] and postmenopausal women[29]. In all studies, it was observed that the people who participated were mostly elderly, although there were also adults, with an average age ranging from 38 years to 77 years.

Study time ranged from 8 weeks to 1.5 years and could have occurred continuously or with time intervals. The dosage used in the studies varied from 400IU to 200,000IU of vitamin D to verify which dosage could have an effect. Some studies presented the body mass index to help with the study parameters, although four did not do so [20,23,24,26].

For the study to be carried out on the efficiency of vitamin D, measurements of the blood pressure of the participants were carried out before the start of supplementation and after supplementation. In addition, some studies carried out measurements between the testing period, but the results shown in **Table 1** only show the results acquired after the treatment was completed, with blood pressure measurements ranging from 122.1 mmHg to 137.7 mmHg for systolic and, 78.4 mmHg to 81.8 mmHg for the diastolic after supplementation.

Table 1 – Data from articles evaluating blood pressure and dosage of vitamin D supplementation.

Author	Year	Treatment Group	Age	Nº Sample	Country/ Region	Time of Study	Amount of Vitamin D3	BMI	Blood pressure	Systolic pressure after treatment	Diastolic pressure after treatment
Tabesh et al.[22]	2015	Patients with type 2 diabetes.	Over 30 years old	118	Iran	8 weaks	1250 m g(50,000Ul) per week	Average 30Kg/m²	122,11 e 81,8 mmHG	8,2mm Hg (0,5mm Hg)	82,6mmHg (1,6mmHg)
Sluyter et al.[27]	2017	Healthy patients	Between 50 and 84 years old.	517	New Zealand	1 year and 1 month	2,5 m g (100,000 Ul) per week	Averange 28,7Kg/ m²	137,7 e 78,4 mmHg	125,5mmHg (12,2 mmHg)	72,8mmHg (5,6mm Hg)
Scragg et al.[28]	2014	Healthy patients	Averange 47,6 year	322	New Zealand	1 year and 6 months	4 capsules after randomization and again one month later (200,000 IU for those in the treatment arm), 2 capsules each month (100,000 IU in the treatment arm) for another 16 months	Averange 27,3Kg/ m²	123,4 / 76,3mm Hg	123,4mmHg (0,6 mmHg)	76,8 mmHg (0,5 mm Hg)

Forman et al.[23]	2013	Exclusively healthy black patients	Average 51 years	283	United State of America	6 months	group divided into 4, a placebo, one receiving 1000IU, another 2000IU, or 4000IU units of cholecalciferol per day.	Average 31,0 Kg/m²	122/78 mmHg	120,6 mmHg (1,4mmHg)	77,5mmHg (0,5mmHg)
Gaksch et al.[24]	2015	Patients with hypertension	Average 60,1 years	200	Austria	8 weaks	2800 IU of Vitamin D3 per day in the form of oily drops.	Not available	131,4/78, 1mmHg	131,0 mmHg (0,4 mmHg)	78,3 mmHg (0,2mmHg)
Witham et al.[25]	2013	Patients with hypertension	Average 77 years	169	UK	1 year	100,000 IU of oral cholecalciferol or placebo every three months.	Not available	136/71 mmHg	136,0mmHg (1,0 mmHg)	71,0 mmHg (no change)
Larsen et al.[26]	2012	Patients with hypertension	Average 61 years	112	Denmark	20 weaks	75 ug (3000 IU) cholecalciferol per day.	Not available	131/77 mmHg	130,5mmHg (1,5 mmHg)	76,9mmHg (1,1mmHg)
Gepner et al.[29]	2012	Patients exclusively postmenopausal women	Average 63,9 years	114	United State of America	4 months	500 IU oral D3 or placebo daily.	Average 27,1kg/m²	116,7/73, 5 mmHg	118,6mmhg (1,9mmHg)	74,3 mmHg(0,8mmHg)
Chai et al.[21]	2013	Patients with colorectal adenoma	Average 60,2 years	92	United State of America	6 months	3.800 IU Vitamin D and Calcium 2.0 g (alone or in combination, in divided doses twice daily with meals.	Average 29,4 Kg/m²	125,9/76, 5 mmHg	125,2mmHg (-0,7 mmHg)	76,5mmHg (sem alteração)
Arora et al.[20]	2014	Patients with altered systolic blood pressure	Average 38 years	534	United State of America	6 months	high-dose (4000 IU/day) and low-dose (400 IU/day) oral vitamin D3.	Not available	131/82 mmHg	127,0 mmHg (0,8 mmHg)	77mmHg (1,2mmHg)

4. Discussion

Analyzing the data, we observed that the groups used for sampling are very heterogeneous, with no classification of the groups by specific diseases, having been used from patients with type 2 diabetes, patients with colorectal adenoma and postmenopausal women, with the possibility of a non-conformity of the final data.

Another factor analyzed was the age of the patients. In this regard, we observed that the vast majority were elderly, with a mean age of 77 years, although adults were also used in the studies. In view of this, these data may also contribute to an inconsistency in the results, since that that the elderly are more prone to nutritional deficiency due to difficulty in ingestion, chewing and digestion, altering the absorption of the vitamin.

When analyzing the duration of the studies, we observed that they ranged from 8 weeks to 1.5 years. According to studies by Forman et al.[25], this is necessary to prevent exposure to sunlight from influencing the results, since the main way of absorbing vitamin D is through skin production during exposure to the sun, which is why the study was carried out in two winters of consecutive years. On the other hand, other studies considered that since in winter in North American countries the sun appears with less intensity, this factor should not be considered, to the point of triggering interference in the results[23,24].

Of the analyzed studies, six of them presented the BMI of the participants to make it possible to analyze the influence of having arterial hypertension, and thus, to help in the analysis of the results. Therefore, when analyzing these data, we found that all participants had an average BMI greater than 27.1 kg/m², making it possible to classify them as obese and overweight, which according to Forman et al.[25] makes it possible to state that these patients have risk factors for cardiovascular disease, such as hypertension.

Another data analyzed was in relation to the dosage of Vitamin D used in the studies, where we observed a dosage ranging from 400UI to 200,000UI per day. According to Henry et al.[9], the daily recommendation for vitamin D is 600UI per day for adults and 800UI for the elderly. In the analyzed studies, we observed that most of them used a higher dosage than the recommended one, since the intention was to verify the efficiency of the higher dosage of the vitamin, and if in higher doses the effect would be different. This factor was not confirmed even with the large variation in the value of the doses.

When analyzing the results, we observed that when comparing the values obtained by measuring blood pressure at the beginning of the treatment with the values obtained at the end of the treatment, it was verified that the study that presented the best result was Sluyter et al.[23], who were able to prove that the administration of doses of Vitamin D act in such a way as to favor blood pressure, and thus, reduce the probability of cardiovascular diseases.

According to Sluyter et al.[23], their results showed a reduction in systolic blood pressure from 137.7mmHg to 125.5mmHg (-12.2mmHg) after treatment, with diastolic blood pressure falling from 78.4 to 72.8 (-5.6mmHg).

However, other studies did not present such significant data, showing reductions in systolic blood pressure of 0.8 mmHg and diastolic blood pressure of 1.1 mmHg. In addition, some studies have even shown the opposite, with results showing an increase in systolic blood pressure of up to 1.9 mmHg and diastolic blood pressure of up to 1.6mmHg. And there were also studies by Witham et al[25] and Chai et al.[21] that showed no change in diastolic pressure.

All studies used the same randomized, double-blind, placebo-controlled study method, with two studies using four study groups to administer vitamin D with calcium[22] or to administer more than one dose of vitamin D[23].

The studies did not consider the patients' diet and the practice of physical activities, factors that can positively or negatively influence the results, since patients who use a lot of sodium in their diet can increase blood pressure values even with medication use. In addition, we also observed that not all studies showed whether the patients were using medication to control blood pressure directly with antihypertensive drugs or with the use of medication that helped in the treatment, such as diuretics.

From the general balance analyzed in all the studies observed, we verified that the alterations are more visible in the systolic arterial pressure, presenting a small decrease, while in the diastolic arterial pressure, what was observed was a very low or null alteration. These results may have been obtained by differences in the studies or by the inefficiency in the treatment of vitamin D supplementation in relation to arterial hypertension.

If there is a relationship between vitamin D and arterial hypertension, it is still necessary to establish the mechanism that makes the relationship through more randomized clinical studies with larger sample groups and with longer carefully planned follow-up periods.

Therefore, we can say that the results did not reach the specific objectives of this review, as we did not find a dose capable of providing some relationship between vitamin D and arterial hypertension.

6. Conclusion

The results obtained from this systematic review do not present conclusive data for the indication of vitamin D supplementation in the treatment of systemic arterial hypertension, due to its lack of efficiency up to the present moment, more research is necessary for a better clarification on the subject.

Referências

1. Mansur AP, Favarato D, Souza MF, Avakian SD, Aldrighi JM, César LA, Ramires JA. Trends in death from circulatory diseases in Brazil between 1979 and 1996. Arq Bras Cardiol. 2001 Jun;76(6):497-510. English, Portuguese. doi: 10.1590/s0066-782x2001000600007. Erratum in: Arq Bras Cardiol 2001 Aug;77(2):204. PMID: 11449295.
2. Mansur Ade P, Favarato D. Mortality due to cardiovascular diseases in Brazil and in the metropolitan region of São Paulo: a 2011 update. Arq Bras Cardiol. 2012 Aug;99(2):755-61. English, Portuguese. doi: 10.1590/s0066-782x2012005000061. Epub 2012 Jun 28. PMID: 22735870.
3. de Souza Mde F, Alencar AP, Malta DC, Moura L, Mansur Ade P. Serial temporal analysis of ischemic heart disease and stroke death risk in five regions of Brazil from 1981 to 2001. Arq Bras Cardiol. 2006 Dec;87(6):735-40. English, Portuguese. doi: 10.1590/s0066-782x2006001900009. PMID: 17262111.
4. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med. 2008 Jun 9;168(11):1174-80. doi: 10.1001/archinte.168.11.1174. PMID: 18541825; PMCID: PMC3719391.
5. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007 May;49(5):1063-9. doi: 10.1161/HYPERTENSIONAHA.107.087288. Epub 2007 Mar 19. PMID: 17372031.
6. Sypniewska G, Pollak J, Strozecki P, Camil F, Kretowicz M, Janikowski G, Mankowska-Cyl A, Pater A, Manitius J. 25-hydroxyvitamin D, biomarkers of endothelial dysfunction and subclinical organ damage in adults with hypertension. Am J Hypertens. 2014 Jan;27(1):114-21. doi: 10.1093/ajh/hpt174. Epub 2013 Sep 16. PMID: 24042165.
7. Holick MF. Vitamin D deficiency. N Engl J Med. 2007 Jul 19;357(3):266-81. doi: 10.1056/NEJMra070553. PMID: 17634462.
8. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008 Apr;87(4):1080S-6S. doi: 10.1093/ajcn/87.4.1080S. PMID: 18400738.
9. Henry HL, Bouillon R, Norman AW, Gallagher JC, Lips P, Heaney RP, Vieth R, Pettifor JM, Dawson-Hughes B, Lamberg-Allardt CJ, Ebeling PR. 14th Vitamin D Workshop consensus on vitamin D nutritional guidelines. J Steroid Biochem Mol Biol. 2010 Jul;121(1-2):4-6. doi: 10.1016/j.jsbmb.2010.05.008. Epub 2010 May 24. PMID: 20561983.
10. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, Shoenfeld Y, Lerchbaum E, Llewellyn DJ, Kienreich K, Soni M. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmun Rev. 2013 Aug;12(10):976-89. doi: 10.1016/j.autrev.2013.02.004. Epub 2013 Mar 28. PMID: 23542507.

11. Bucharles S, Barberato SH, Stinghen AEM, Gruber B, Piekala L, Dambiski AC, Custodio MR, Pecoits-Filho R. Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without hyperparathyroidism. J Ren Nutr. 2012 Mar;22(2):284-291. doi: 10.1053/j.jrn.2011.07.001. Epub 2011 Sep 10. PMID: 21908203.
12. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol. 2008 Dec 9;52(24):1949-56. doi: 10.1016/j.jacc.2008.08.050. PMID: 19055985.
13. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013 Nov;37(7):658-65. doi: 10.1002/gepi.21758. Epub 2013 Sep 20. PMID: 24114802; PMCID: PMC4377079.
14. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. J Hypertens. 2009 Oct;27(10):1948-54. doi: 10.1097/HJH.0b013e32832f075b. PMID: 19587609.
15. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med. 2010 Mar 2;152(5):307-14. doi: 10.7326/0003-4819-152-5-201003020-00009. PMID: 20194237; PMCID: PMC3211092.
16. Singh RB, Suh IL, Singh VP, Chaithiraphan S, Laothavorn P, Sy RG, Babilonia NA, Rahman AR, Sheikh S, Tomlinson B, Sarraf-Zadigan N. Hypertension and stroke in Asia: prevalence, control and strategies in developing countries for prevention. J Hum Hypertens. 2000 Oct-Nov;14(10-11):749-63. doi: 10.1038/sj.jhh.1001057. PMID: 11095165.
17. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001 Nov 27;104(22):2746-53. doi: 10.1161/hc4601.099487. PMID: 11723030.
18. Khor GL. Cardiovascular epidemiology in the Asia-Pacific region. Asia Pac J Clin Nutr. 2001;10(2):76-80. doi: 10.1111/j.1440-6047.2001.00230.x. PMID: 11710361.
19. Vorster HH. The emergence of cardiovascular disease during urbanisation of Africans. Public Health Nutr. 2002 Feb;5(1A):239-43. doi: 10.1079/phn2001299. PMID: 12027290.
20. Arora P, Song Y, Dusek J, Plotnikoff G, Sabatine MS, Cheng S, Valcour A, Swales H, Taylor B, Carney E, Guanaga D, Young JR, Karol C, Torre M, Azzahir A, Strachan SM, O'Neill DC, Wolf M, Harrell F, Newton-Cheh C, Wang TJ. Vitamin D therapy in individuals with prehypertension or hypertension: the DAYLIGHT trial. Circulation. 2015 Jan 20;131(3):254-62. doi: 10.1161/CIRCULATIONAHA.114.011732. Epub 2014 Oct 30. PMID: 25359163.
21. Chai W, Cooney RV, Franke AA, Bostick RM. Effects of calcium and vitamin D supplementation on blood pressure and serum lipids and carotenoids: a randomized, double-blind, placebo-controlled, clinical trial. Ann Epidemiol. 2013 Sep;23(9):564-70. doi: 10.1016/j.annepidem.2013.07.003. PMID: 23958407; PMCID: PMC4339268.
22. Tabesh M, Azadbakht L, Faghihimani E, Tabesh M, Esmaillzadeh A. Effects of Calcium Plus Vitamin D Supplementation on Anthropometric Measurements and Blood Pressure in Vitamin D Insufficient People with Type 2 Diabetes: A Randomized Controlled Clinical Trial. J Am Coll Nutr. 2015;34(4):281-9. doi: 10.1080/07315724.2014.905761. Epub 2015 Mar 4. PMID: 25738212.
23. Forman JP, Scott JB, Ng K, Drake BF, Suarez EG, Hayden DL, Bennett GG, Chandler PD, Hollis BW, Emmons KM, Giovannucci EL, Fuchs CS, Chan AT. Effect of vitamin D supplementation on blood pressure in blacks. Hypertension. 2013 Apr;61(4):779-85. doi: 10.1161/HYPERTENSIONAHA.111.00659. PMID: 23487599; PMCID: PMC3775458.
24. Pilz S, Gaksch M, Kienreich K, Grübler M, Verheyen N, Fahrleitner-Pammer A, Treiber G, Drechsler C, Ó Hartaigh B, Obermayer-Pietsch B, Schwetz V, Aberer F, Mader J, Scharnagl H, Meinitzer A, Lerchbaum E, Dekker JM, Zittermann A, März W, Tomaschitz A. Effects of vitamin D on blood pressure and cardiovascular risk factors: a randomized controlled trial. Hypertension. 2015 Jun;65(6):1195-201. doi: 10.1161/HYPERTENSIONAHA.115.05319. Epub 2015 Mar 23. PMID: 25801871.
25. Witham MD, Ireland S, Houston JG, Gandy SJ, Waugh S, Macdonald TM, Mackenzie IS, Struthers AD. Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. Hypertension. 2014 Apr;63(4):706-12. doi: 10.1161/HYPERTENSIONAHA.113.02177. Epub 2014 Jan 13. PMID: 24420547.
26. 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. Am J Hypertens. 2012 Nov;25(11):1215-22. doi: 10.1038/ajh.2012.111. Epub 2012 Aug 2. PMID: 22854639.
27. Sluyter JD, Camargo CA Jr, Stewart AW, Waayer D, Lawes CMM, Toop L, Khaw KT, Thom SAM, Hametner B, Wassertheurer S, Parker KH, Hughes AD, Scragg R. Effect of Monthly, High-Dose, Long-Term Vitamin D Supplementation on Central Blood Pressure Parameters: A Randomized Controlled Trial Substudy. J Am Heart Assoc. 2017 Oct 24;6(10):e006802. doi: 10.1161/JAHA.117.006802. PMID: 29066444; PMCID: PMC5721873.
28. Scragg R, Slow S, Stewart AW, Jennings LC, Chambers ST, Priest PC, Florkowski CM, Camargo CA Jr, Murdoch DR. Long-term high-dose vitamin D3 supplementation and blood pressure in healthy adults: a randomized controlled trial. Hypertension. 2014 Oct;64(4):725-30. doi:

10.1161/HYPERTENSIONAHA.114.03466. Epub 2014 Jun 30. PMID: 24980662.

29. Gepner AD, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. PLoS One. 2012;7(5):e36617. doi: 10.1371/journal.pone.0036617. Epub 2012 May 7. PMID: 22586483; PMCID: PMC3346736.