Excess Vitamin D and its Relationship to Vascular Calcifications in the Lower Extremity

Cody Izydor PMS-III, Andre Moezzi PMS-III, Max Morton PMS-III, Mason Regan PMS-III Dr. Richey DPM, Dr. Haas DPM
Midwestern University, Arizona College of Podiatric Medicine

Abstract

Vascular calcification has been associated with a variety of different disorders, including but not limited to, hypertension, atherosclerosis, diabetes mellitus, and chronic kidney disease. As it currently stands, there is no standardized therapy and/or treatment that has been proven to reverse or cure vascular calcification. Studies have demonstrated that elevated levels of serum calcium correlate with increased levels of vessel deposition. Additionally, there is plenty of evidence to support the role of vitamin D in calcium absorption and maintenance.

This review aims to evaluate a relationship between excess vitamin D supplementation and calcified vessels of the lower extremity secondary to hypercalcemia.

Electronic databases were utilized to search for articles relating to vascular calcification, vitamin D, and the lower extremity. Articles were evaluated for relevance, quality and potential bias. Although there is clear evidence that Vitamin D toxicity can be a major cause of hypercalcemia and animal models support that increased Vitamin D supplementation causes increased aortic calcifications, more research is needed to fully understand the extent to which this impacts vascular calcification in the lower extremity.

Methods

A PubMed search was performed. Keywords included “vessel calcification” AND “hypervitaminosis D” AND ”lower extremity”. Three reviewers independently extracted data and evaluated for bias. 20 studies were initially discovered. Following further examination of relevancy, purpose, overall credibility, and industry funded biased, 2 studies remained. Utilizing relevant citation references from the beginning sample size, an additional 5 studies were discovered. A total of 7 studies were utilized in our final analysis.

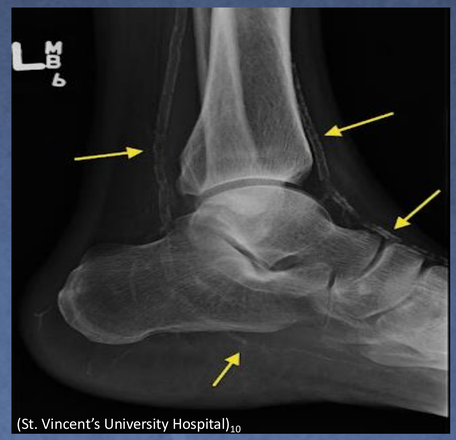
Introduction

Calcium plays a variety of roles in the body, from neural transmission to enzymatic activity. Given the integral role calcium plays, it is essential for the body to have easy access to the ion. It is estimated that 45% of the body’s calcium reserve is bound to proteins, 45% exists as the active/ionized form, and 10% is bound to anions. With the numerous important roles of calcium in the body, it is somewhat surprising that only 10-15% of dietary calcium is absorbed via the gut. Despite this, vitamin D supplements increase absorption of calcium to 30-40%. With the help of vitamin D, calcium absorption from the gut almost triples. This creates new questions, such as what are the consequences of excess vitamin D on blood calcium levels; for reference, the FDA currently recommends a daily supplementation of vitamin D at 600-800 IU/day with the upper limit being 4000 IU/day.

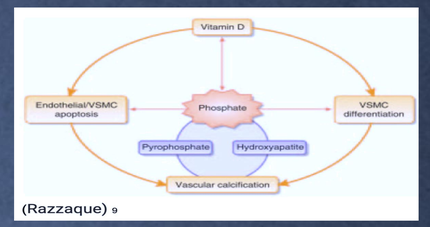
High blood calcium levels can be caused by a variety of pathologies and medications including, but not limited to, cancer, kidney failure, thiazide diuretics, and hyperthyroidism (Pan 2023)$_1$. However, a study done by Nazia found that Vitamin D toxicity is one of the major causes of hypercalcemia Nazia (2024)$_3$. Regarding high serum calcium levels, Rubin saw a positive correlation between elevated serum calcium levels and carotid plaque thickness in a study conducted in Northern Manhattan with 1194 subjects (Rubin 2006)$_2$.

Additionally, a positive correlation was found between dietary supplementation of vitamin D in goat/pig models and the development of aortic and coronary calcific lesions (Wang 2018)$_4$. Administration of sub-lethal Vitamin D doses and nicotine (7.5mg/kg) within rat models resulted in 10-40-fold increase of calcium deposition within the aorta. Another study found vitamin D administration of 500,000 IU/kg/day for 3 consecutive days resulted in severe aortic calcification within a 7-day period (Kang 2010)$_5$. When the dosage was reduced to 100,000 IU/kg/day over a course of a 7-day trial, moderate aortic calcification was produced (unpublished). These findings point towards the relationship between hypervitaminosis and vessel calcification.

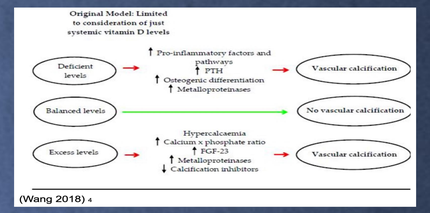
In a retrospective study, the severity and overall progression of vascular calcification was linked between vitamin D and individuals with chronic kidney disease, as well as undergoing extensive dialysis treatment (Goldsmith 1997)$_6$. Furthermore, similar findings were discovered within young adults with chronic kidney disease (Brise 2006)$_7$.



(St. Vincent’s University Hospital)$_{10}$



(Razzaque) 9



(Wang 2018) 4

Discussion

With various studies supporting the relationship of Vitamin D and vessel calcification, it comes as a surprise that Billington found no direct correlation between doses of vitamin D supplementation ranging from 400, 4000, and 10,000 IU daily and correlated tibial vessel calcification. The trial utilized high resolution peripheral quantitative computed tomography (HR-pQCT) to evaluate vessel calcification over a 3-year, double-blind, randomized control study (Billington 2020)8. The study included a sample size of 287 and a mean age of 62.2 years. The parameters were designed to target a Vitamin D deficient population (mid sixties) with various dosing groups of 400, 4000, 10,000 IU daily.

The lack of supporting evidence found between Vitamin D levels and tibial vessel calcification was surprising. There is plenty of data to link excess vitamin D supplementation to hypercalcemia, and there is data that links hypercalcemia to vessel calcification. This begins to raise new questions and requires further analysis of other variables. One of these variables is the length of the study. Another is the use of the tibial artery. Would the results differ if the study were longer, or if the study evaluated a vessel from the upper extremity? Are the results due to the role of vessel diameter or is there another physiological process that makes lower extremity vessels less prone to calcification compared to other vessels such as the coronary arteries?

References

1) Pan W, Jie W, Huang H. Vascular calcification: Molecular mechanisms and therapeutic interventions. MedComm (2020). 2023 Jan 3;4(1):e200. doi: 10.1002/mco2.200. PMID: 36620697; PMCID: PMC9811665.
2Rubin MR, Rundek T, McMahon DJ, Lee HS, Sacco RL, Silverberg SJ. Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. Atherosclerosis. 2007 Oct;194(2):426-32. doi:
3)Sadiq NM, Anastasopoulou C, Patel G, et al. Hypercalcemia. [Updated 2024 May 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
4) Wang J, Zhou JJ, Robertson GR, Lee VW. Vitamin D in Vascular Calcification: A Double-Edged Sword? Nutrients. 2018 May 22;10(5):652. doi: 10.3390/nu10050652. PMID: 29786640; PMCID: PMC5986531.
5) Kang YH, Jin JS, Yi DW, Son SM. Bone morphogenetic protein-7 inhibits vascular calcification induced by high vitamin D in mice. Tohoku J Exp Med. 2010 Aug;221(4):299-307. doi: 10.1620/tjem.221.299. PMID: 20647695.
6) Goldsmith DJ, Covic A, Sambrook PA, Ackrill P. Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. Nephron. 1997;77(1):37-43. doi: 10.1159/000190244. PMID: 9380236.
7) Briese S, Wiesner S, Will JC, Lembcke A, Opgen-Rhein B, Nissel R, Wernecke KD, Andreae J, Haffner D, Querfeld U. Arterial and cardiac disease in young adults with childhood-onset end-stage renal disease-impact of calcium and vitamin D therapy. Nephrol Dial Transplant. 2006 Jul;21(7):1906-14. doi: 10.1093/ndt/gfl098. Epub 2006 Mar 22. PMID: 16554325.
8) Billington EO, Burt LA, Plett R, Rose MS, Boyd SK, Hanley DA. Effect of high-dose vitamin D supplementation on peripheral arterial calcification: secondary analysis of a randomized controlled trial. Osteoporos Int. 2020 Nov;31(11):2141-2150. doi: 10.1007/s00198-020-05500-2. Epub 2020 Jun 15. PMID: 32556518.
9) Razzaque MS. The dualistic role of vitamin D in vascular calcifications. Kidney Int. 2011 Apr;79(7):708-14. doi: 10.1038/ki.2010.432. Epub 2010 Oct 20. PMID: 20962746; PMCID: PMC3120050.
10) St. Vincent’s University Hospital http://www.svuhradiology.ie/case-study/arterial-calcification-in-a-diabetic/

Conclusion

Although there is clear evidence that Vitamin D toxicity can be a major cause of hypercalcemia and animal models support that increased Vitamin D supplementation causes increased aortic calcifications, there is not enough data to support a direct association between increased vitamin D supplementation and vascular calcifications of the lower extremities in human subjects. More research is needed to fully understand the extent to which elevated Vitamin D levels impacts vascular calcification in the lower extremity.