Published in final edited form as:

Atherosclerosis. 2015 June ; 240(2): 526–528. doi:10.1016/j.atherosclerosis.2015.04.795.

A Randomized Controlled Trial of the Effects of Vitamin D Supplementation on Arterial Stiffness and Aortic Blood Pressure in Native American Women

Adam D. Gepner, MD¹, Irina V. Haller, PhD², Diane C. Krueger, BS¹, Claudia E. Korcarz, DVM¹, Neil Binkley, MD¹, and James H. Stein, MD¹

¹University of Wisconsin School of Medicine and Public Health; Madison, WI

²Essentia Institute of Rural Health; Duluth, MN

Abstract

Objective—It is unclear if vitamin D supplementation improves central blood pressure or arterial stiffness in Native American (NA) women.

Methods—Healthy postmenopausal NA women were randomized to receive 400 IU or 2,500 IU of vitamin D for 6 months. Central systolic blood pressure (cSBP), central pulse pressure (cPP) and aortic augmentation index (AIx) were estimated by tonometry at baseline and after 6 months.

Results—Study volunteers (n=98) were 61 (7.3) years old. 25(OH)D was 26.4 (11.0) ng/mL. 25(OH)D was similar between the two treatment groups (p=0.291), as were baseline cSBP, cPP, and CVD risk factors (all p>0.1). Treatment with 2,500 IU of daily vitamin D3 did not affect cSBP, cPP, or AIx (all p>0.1) compared to 400 IU daily.

Conclusions—Despite low serum 25(OH)D at baseline, 6 months of vitamin D supplementation did not improve central blood pressure parameters or arterial stiffness in NA women.

Keywords

Arterial stiffness; vitamin D; central blood pressure; cardiovascular disease risk

© 2015 Published by Elsevier Ltd.

Address for Correspondence: James H. Stein, MD, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, H4/520 CSC (MC 3248), Madison, WI 53792, Phone: (608) 265-4188, Fax: (608) 263-0405, jhs@medicine.wisc.edu.

Clinical trials.gov identifier: NCT01490333

Disclosures

AD Gepner: None; IV Haller: None; DC Krueger: None; CE Korcarz: None; N Binkley: None; JH Stein: Wisconsin Alumni Research Foundation.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Cardiovascular disease (CVD), hypertension and low vitamin D levels are common in the United States, especially among Native American (NA) women.¹ Low vitamin D status is associated with hypertension, and CVD.^{2,3} Vitamin D supplements often are used in attempt to prevent CVD and to treat CVD risk factors, despite the absence of robust data from clinical trials.^{2,4–6}

Materials & Methods

This was a prospective, double-blind, randomized trial of postmenopausal NA women without known CVD and with screening serum 25-hydroxyvitamin D [25(OH)D] between 10–60 ng/mL. This study was approved by the University of Wisconsin Health Sciences Institutional Review Board. It was conducted according to the principles expressed in the Declaration of Helsinki. All subjects provided written consent.

These women were randomized to receive low-dose (400 IU) or high-dose (2,500 IU) vitamin D₃ daily for 6 months. Using arterial tonometry (AtCor Medical, Sydney, Australia), we assessed 3 prespecified primary outcome measures at baseline and following 6 months of supplementation: 1) aortic systolic blood pressure (aSBP), 2) aortic pulse pressure (aPP), and 3) aortic augmentation index (AIx). Comparisons between variables at baseline and 6 months initially were performed using paired 2-tailed student's t-tests. Pearson correlations were used to determine associations with baseline 25(OH)D levels. Then, general linear models adjusted for age and baseline 25(OH)D were used to evaluate the effect of supplementation on changes in cardiovascular outcomes over time. Models included the interaction effects of duration of therapy with treatment group and with baseline 25(OH)D level. Randomization was carried out in a 1:1 ratio without blocking using computer-generated random numbers. One individual in the Osteoporosis Research Center was assigned to randomize subjects; this individual did not participate in recruitment, data collection, or analysis. All others, including volunteers, study staff, investigators, and data analysts, were blinded to the group assignment. There was no cross-over and all subjects were analyzed in an intention-to-treat manner. Enrollment was complete following recruitment of the pre-specified number of subjects. The sample size of 98 participants had adequate power to detect a 5.8% difference in AIx.⁷

Results

Participants (n=98) were mean (standard deviation) 61 (7.3) years old. Baseline 25(OH)D was <20 ng/mL in 29 (30%) and between 20–30 ng/mL in 39 (40%) participants. Baseline characteristics are shown in table 1. At baseline, higher 25(OH)D was weakly associated with lower aSBP (r=−0.20; p=0.05) but not aPP or AIx (p>0.05).

Following 6 months of vitamin D supplementation, serum 25(OH)D increased by 15.5 ng/mL in the high-dose versus 5.1 ng/mL in the low-dose (p<0.001) group; 43 (88%) of women in the high-dose group, but only 23 (47%) subjects in the low-dose group achieved 25(OH)D levels >30 ng/mL. Only 3 (3.1%) subjects in either group had 25(OH)D <20 ng/mL at the study conclusion. AIx decreased from baseline in the high-dose group (−1.9

[5.2]%; $p=0.015$) but not the low-dose group (-0.6 [6.2]%; $p=0.5$). No significant changes from baseline were seen in aSBP or aPP (both $p>0.1$). There also were no significant differences between changes in aSBP ($p=0.9$), aPP ($p=0.7$) or AIx ($p=0.7$) over the 6 month time period when comparing the high- and low-dose groups. High sensitivity C-reactive protein levels also did not change or differ between treatment groups (Table 1, $p>0.1$). General linear models showed no significant effect of treatment group on changes in aSBP, aPP or AIx over time (all $p>0.2$; Figure 1). Baseline medication use was similar in both groups (Table 1).

Discussion

We compared the effects of two vitamin D supplementation doses on central blood pressure and aortic stiffness in Native American, postmenopausal women who generally had low 25(OH)D levels. After 6 months of supplementation, AIx decreased from baseline in the high-dose, but not the low-dose group. However, aortic blood pressure, aortic pulse pressure and AIx were not affected by vitamin D supplementation.

Vitamin D receptors have been isolated in vascular endothelial cells and cardiac myocytes, making it plausible that low vitamin D status could have deleterious effects on the development of atherosclerosis and increased CVD risk through dysregulation of systemic calcium metabolism.⁵ Indeed, in this study serum 25(OH)D was inversely associated with systolic blood pressure. However, despite a clear increase in serum 25(OH)D levels to levels widely viewed as optimal in nearly 90% of participants, no significant differences in aortic blood pressures or arterial stiffness were observed in NA postmenopausal women. We cannot exclude the possibility that supplementation with even higher doses of vitamin D or for a longer time duration could improve central blood pressure and arterial stiffness measures; however, interventions that reduce blood pressure and CVD tend to improve arterial stiffness soon after initiating treatment.^{8,9} This reaffirms findings from our prior report in Caucasian women and challenges the hypothesis that vitamin D supplementation reduces CVD risk.^{2,4,10}

Conclusion

This study does not support the use of high-dose vitamin D supplementation to reduce CVD risk, however larger, long-term outcomes studies of this intervention are needed to determine if low vitamin D status is causally related to hypertension and CVD.

Acknowledgments

We acknowledge the Sunweavers volunteers and collaboration with the Stockbridge-Munsee Health & Wellness Center without whom this study would not have been completed.

Funding

Supported by NIMHD Comprehensive Centers of Excellence, P60/R01: MD 003428-01 and was supported in part by a T32 HL 07936 from the NHLBI.

References

1. Harwell TS, Oser CS, Okon NJ, Fogle CC, Helgeson SD, Gohdes D. Defining disparities in cardiovascular disease for American Indians: trends in heart disease and stroke mortality among American Indians and whites in Montana, 1991 to 2000. *Circulation*. 2005; 112(15):2263–2267. [PubMed: 16203905]
2. Anderson JL, May HT, Horne BD, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol*. 2010; 106(7):963–968. [PubMed: 20854958]
3. Vimalaewaran KS, Cavadino A, Berry DJ, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. *Lancet Diabetes Endocrinol*. 2014
4. Scragg R, Slow S, Stewart AW, et al. Long-Term High-Dose Vitamin D3 Supplementation and Blood Pressure in Healthy Adults: A Randomized Controlled Trial. *Hypertension*. 2014
5. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008; 117(4):503–511. [PubMed: 18180395]
6. Beveridge LA, Struthers AD, Khan F, et al. Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. *JAMA Intern Med*. 2015
7. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006; 113(9):1213–1225. [PubMed: 16476843]
8. Mackenzie IS, McEnery CM, Dhakam Z, Brown MJ, Cockcroft JR, Wilkinson IB. Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. *Hypertension*. 2009; 54(2):409–413. [PubMed: 19487582]
9. Lipsitz LA, Gagnon M, Vyas M, et al. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension*. 2005; 45(2):216–221. [PubMed: 15655124]
10. 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. [PubMed: 22586483]

Figure 1.
Change in Central Systolic Blood Pressure, Central Pulse Pressure and Aortic Augmentation Index from Baseline to 6 months*

Table 1

Participant Characteristics at Baseline and After 6 Months

	(Low-Dose Arm 400 IU) N=49			High-Dose Arm (2500 IU) N=49		
	Mean (SD)		p-value*	Mean (SD)		p-value*
	Baseline**	6 months		Baseline**	6 months	
Age (years)	61.8 (7.0)	--	--	60.7 (7.7)	--	--
25-hydroxyvitamin D (ng/mL)	25.1 (10.1)	30.1 (7.5)	<0.001	27.2 (9.3)	42.7 (11.6)	<0.001
Body-mass index (kg/m ²)	33.3 (7.3)	--	--	32.4 (6.4)	--	--
Peripheral systolic blood pressure (mmHg)	120.0 (18.4)	120.9 (17.7)	0.6	120.3 (13.8)	117.7 (14.9)	0.3
Peripheral diastolic blood pressure (mmHg)	74.9 (9.0)	74.3 (9.6)	0.8	74.6 (7.2)	73.2 (7.7)	0.3
Hypertensive medication (%)	27 (55)	-	-	27 (55)	-	-
Lipid-lowering medication (%)	21 (43)	-	-	23 (47)	-	-
Anti-glycemic medication (%)	13 (27)	-	-	10 (20)	-	-
Glucose (mg/dL)	111.4 (31.9)	111.6 (34.9)	1.0	116.2 (39.8)	114.1 (33.6)	0.6
Hemoglobin A1c (%)	6.4 (1.4)	6.4 (1.4)	0.7	6.6 (1.6)	6.5 (1.3)	0.5
High sensitivity C- reactive protein (mg/L)	4.7 (5.1)	6.1 (8.1)	0.3	4.6 (4.8)	5.9 (6.4)	0.1
Aortic augmentation Index (%) [†]	31.2 (7.9)	30.5 (7.6)	0.5	29.4 (7.4)	27.6 (6.7)	0.015
Aortic systolic pressure (mmHg) [†]	114.0 (17.8)	114.0 (17.1)	0.8	113.8 (13.0)	110.5 (13.6)	0.1
Aortic pulse pressure (mmHg) [†]	38.4 (13.6)	38.9 (12.6)	0.7	38.5 (9.6)	36.5 (10.2)	0.1

* P-values comparing changes from baseline after 6 months of supplementation by treatment group.

** Baseline mean values were similar in both treatment arms, all p 0.2.

[†] Comparing the high- and low-dose groups, there was no significant difference between change in aSBP, aPP, or AIx over the 6 month time period.