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Association of vitamin D status with coronary artery disease in postmenopausal women

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Abstract

The relationship between coronary artery disease (CAD) and low serum 25-hydroxyvitamin D (25(OH)D) levels has emerged. Postmenopausal (PM) women are at increased risk of CAD and vitamin D (VitD) deficiency.

To investigate the relationship between CAD and VitD levels in PM women.

This case–control study included 93 consecutive female patients aged 50 to 79 years old undergoing coronary angiography for evaluation of CAD and 119 age-matched controls. Serum 25(OH)D concentrations were classed as adequate (serum 25(OH)D: ≥20 ng/mL); insufficient (serum 25(OH)D: 10 to <20 ng/mL); and deficient (serum 25(OH)D: <10 ng/mL). Major cardiovascular risk factors were also explored.

CAD occurred in 67/127 (52.8%) patients with VitD deficiency; 21/66 (31.8%) patients that were VitD insufficient; and in 5/19 (26.3%) patients with adequate VitD levels. Multivariate regression analysis suggested that a deficiency of VitD increased CAD (odds ratio = 2.891; 95% confidence interval = 1.459–7.139, $P < .001$).

VitD deficiency should be evaluated in PM women as a possible cause of CAD.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, CRP = C-reactive protein, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, MA = meta-analysis, OR = odds ratio, PM = postmenopausal, SD = standard deviation, TC = total cholesterol, TG = triglyceride, VitD = vitamin D.

Keywords: 25-hydroxyvitamin D, coronary artery disease, postmenopausal women, vitamin D deficiency

1. Introduction

Vitamin D (VitD) is a fat-soluble prohormone required for Ca^{2+} metabolism, bone growth, and nonskeletal processes.[1] Emerging evidence supports a link between VitD deficiency and cardiovascular disease including heart failure, peripheral vascular disease, dyslipidemia, diabetes, hypertension, and coronary artery disease (CAD).[2–4]

CAD is a major cause of morbidity and mortality. VitD receptors are present in the cardiovascular system and epidemiological studies highlight the association of VitD status to CAD risk.[5] In a meta-analysis (MA) of 19 prospective studies that included 65,994 participants, an inverse association between circulating VitD and cardiovascular disease was reported.[6] In direct contrast to these studies, the assessment of 813 men showed no VitD association with cardiovascular disease.[7] A MA assessing the effects of VitD supplements to cardiovascular outcomes also showed minimal association.[8]

VitD deficiency is common during menopause, higher latitudes, reduced sunlight exposure, skin pigmentation, and a low-VitD diet.[9,10] The risk of VitD deficiency in older women is higher than aged men, thought to be due to reduced estrogen production.[11] Here, we investigated the association of VitD with CAD in postmenopausal (PM) women.

2. Materials and methods

This study was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region. It was conducted according to the standards of the Declaration of Helsinki. Written informed consent was obtained from all of the participants.

2.1. Study population

The patient population included 93 CAD patients and 119 age-matched female controls admitted to the Department of Geriatrics, People's Hospital of Xinjiang Uygur Autonomous Region, China, from January 1, 2018 to August 31, 2018. This unit primarily admits elderly patients with respiratory and cardiovascular disease. The inclusion criteria were: PM women; aged ≥50 years; over 50% angiographic stenosis of at least 1 coronary artery; not receiving Ca^{2+} or VitD. Exclusion criteria: metabolic VitD disorders, thyrotoxicosis, hyperparathyroidism, renal failure, or malignancies liver associated disease.

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Table 1

Demographics of the study population, mean ± SD, n (%).

Parameters	Serum 25(OH)D			P
	Deficiency (<10 ng/mL)	Insufficient (10 to <20 ng/mL)	Adequate (≥20 ng/mL)	
Number	127	66	19	
Age (yrs)	69.13 ± 5.37	65.58 ± 6.47	64.12 ± 7.91	<.001
BMI (kg/m^2)	23.53 ± 2.81	22.83 ± 3.13	23.67 ± 4.04	.2774
Diabetes mellitus	39 (30.71%)	17 (25.76%)	5 (26.32%)	.7479
Hypertension	78 (61.42%)	45 (68.18%)	13 (68.42%)	.5976
Smoking	2 (1.57%)	0	0	
Family history of CAD	26 (20.47%)	12 (18.18%)	7 (36.84%)	.2039

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages.
The *P* value of the continuous variables was calculated by the unpaired *t* test. The *P* value of the categorical variables was calculated Chi-squared test.
25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, CAD = coronary artery disease, SD = standard deviation.

2.2. Cardiovascular risk factors

Height, weight, and body mass index (BMI) were calculated (kg/m^2). Hypertension was defined as systolic blood pressure ≥140 mm Hg or an average diastolic blood pressure ≥90 mm Hg recorded in a minimum of 2 independent medical examinations. Diabetes was defined as fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL) or normal glucose values ≥11.1 mmol/L (200 mg/dL). Those who smoked at least once per day were classified as "smokers," and those who consumed at least 1 drink per week were classified as "drinkers."

2.3. Blood assessments

Biochemical parameters were measured from the peripheral blood of fasted patients. Total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, and triglycerides were measured using commercial kits. Serum 25-hydroxyvitamin D (25(OH)D) was measured via chemiluminescence microparticle immunoassays using an Architect system. The intra/interassay coefficients of variation were 4.1% and 5.7%, respectively. VitD deficiency was classed as 25(OH)D < 10 ng/mL; VitD insufficiency was classed as 10 to <20 ng/mL. Normal VitD levels are 25(OH)D ≥20 ng/mL.

2.4. Statistics

Data were compared using SPSS (SPSS, Inc., Chicago, IL). version 20.0. Gaussian distributions were used to measure continuous variables which are presented as the mean ± standard deviation. Non-Gaussian distributions are shown as median values in the 25th and 75th percentiles. Normal distributions were verified using the Kolmogorov–Smirnov test. Continuous variables was calculated by the unpaired t test. Categorical variables was calculated Chi-squared test. Intergroup differences were compared using unpaired *t* test. Chi-squared tests were used for categorical variables and logistic regression analysis was used to identify independent CAD risk factors. $P < .05$ indicated statistical significance.

3. Results

Table 1 shows the patient characteristics of the study population. The cohort included 212 PM females (mean age 67.32 ± 6.51 years). Based on VitD status, subjects were classed as adequate (n = 19), insufficient (n = 66), and deficient (n = 127). The mean age of the groups significantly differed but all other demographics and laboratory measurements were comparable (Table 2).

Prevalence of CAD in PM women based on VitD status is shown in Figure 1. CAD occurred in 5/19 (26.3%) patients in the VitD adequate group; 21/66 (31.8%) patients in the VitD insufficient group; and 67/127 (52.8%) patients in the VitD deficient group. CAD prevalence increased from adequate to deficient groups ($P = .006$) (Fig. 1).

Multivariate logistic regression analysis was used to investigate the association between VitD status and CAD after adjusting for age (base model), and risk factors (full model) (Table 3). Multivariate regression analysis of the full model revealed that VitD deficiency increased CAD prevalence as an independent correlate (odds ratio = 2.891; 95% confidence interval = 1.459–7.139, $P < .001$) in addition to age, BMI, diabetes, and

Table 2

Laboratory parameters of the patients, mean ± SD.

Parameters	Serum 25(OH)D			P
	Deficiency (<10 ng/mL)	Insufficient (10 to <20 ng/mL)	Adequate (≥20 ng/mL)	
Number	127	66	19	
TC (mmol/L)	4.03 ± 1.31	4.21 ± 1.26	4.43 ± 0.97	.3508
LDL-C (mmol/L)	2.16 ± 0.75	2.32 ± 0.53	1.98 ± 0.47	.101
HDL-C (mmol/L)	0.97 ± 0.21	1.01 ± 0.19	1.05 ± 0.25	.188
TG (mmol/L)	1.76 ± 0.75	1.67 ± 0.91	1.81 ± 0.65	.6933
Creatinine (mg/dL)	72.17 ± 24.7	71.16 ± 21.9	69.10 ± 25.6	.86

Continuous variables are expressed as mean ± SD.
The *P* value of the continuous variables was calculated by the unpaired *t* test.
25(OH)D = 25-hydroxyvitamin D, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

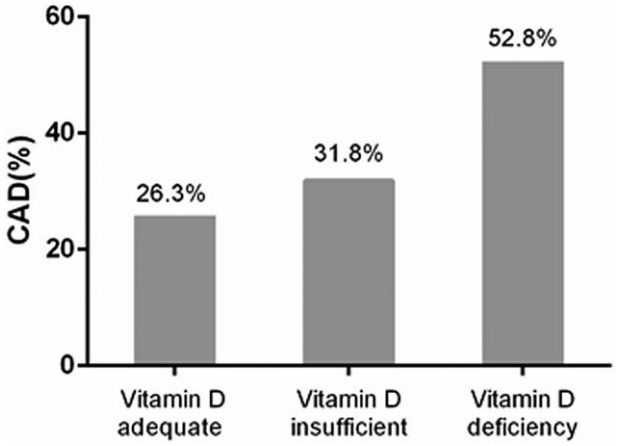

Figure 1. Prevalence of CAD increases gradually in patients with vitamin D adequate, vitamin D insufficient, and vitamin D deficiency with a significant level ($P = .0057$). CAD = coronary artery disease.

hypertension, smoking, family history of CAD, TC, LDL-C, HDL-C, TG, and creatinine.

4. Discussion

We report that PM women with VitD deficiency/insufficiency have a higher prevalence of CAD compared to patients with normal VitD levels. From logistic regression analysis, 25(OH)D was an independent risk factor for CAD. The risk of CAD was 3-fold higher in those with 25(OH)D < 10 ng/mL compared to those with 25(OH)D ≥ 20 ng/mL. Serum 25 (OH)D levels are thus clinically relevant to CAD prevalence.

VitD deficient patients had a CAD prevalence of 52.8%, and those with VitD insufficiency had a prevalence of 31.8%. These results are similar to prior study from India that reported values of 51.2% and 44.6%, respectively.[12] Study from Mexico reported a CAD prevalence of 57.6% and 21.2%, respectively.[13] Moreover, the prevalence of hypovitaminosis D is more frequent in PM women compared to age-matched men.[14] These findings indicate that hypovitaminosis D is a common occurrence in PM women with CAD. Awareness and treatment for VitD deficiency are thus crucial interventions to improve CAD prognosis.

In a study performed in Saudi Arabia, the relationship between CAD and VitD Status was examined in 130 CAD cases and 195 age–sex matched controls. A direct association between VitD Status and CAD was shown.[15] Studies performed in individuals with no history of circulatory diseases demonstrated that the risk of cardiovascular incidents were 1.5-fold higher in patients with 25(OH)D ≤ 15 ng/mL.[16] In contrast, Messenger et al[7] found no association of VitD status with CAD in 813 men with VitD deficiency (>15 ng/mL) compared to those with normal VitD levels (<30 ng/mL). However, VitD deficiency has various classifications making interstudy comparisons challenging. We present data from a Chinese cohort but further studies in other ethnic groups are required to further our findings.

While VitD deficiency and CAD have been described extensively in the literature, their precise relationship remains unclear. Atherosclerosis in coronary arteries is critical to the pathogenesis of CAD.[17] Inflammation plays a key role in atherosclerosis and VitD deficiency is a known cause of inflammation.[18,19] Low VitD levels directly increase C-reactive protein (CRP) synthesis and the protective effects of VitD to CRP are evidenced by the distribution of VitD receptors in the vascular walls.[20] In vivo studies have shown that a loss of VitD receptor expression influences cardiac function. VitD knockout mice tend to develop left ventricular hypertrophy and heart failure.[21] VitD deficiency negatively affects the cardiovascular system through activation of the renin–angiotensin–aldosterone system.[22] Further studies should now investigate the common pathophysiological links between VitD deficiency and CAD.

This study had some limitations. First, our analysis was observational and no follow-up studies were performed. Secondly, the sample size was small and required verification in larger study cohorts. Information on VitD receptor expression, inflammatory cytokines, and sunlight exposure should also be included to identify the mechanisms associated with VitD deficiency and subsequent CAD.

In this study, we investigated the association between VitD deficiency and CAD in PM women and revealed an association. Our data also suggest that VitD deficiency is an appropriate diagnostic tool for CAD assessments. This would promote the earlier identification and treatment of CAD, which is an important part of CAD management in PM women.

Table 3

Multivariate regression analysis between vitamin D status and coronary artery disease.

Vitamin D status	OR	95% CI	P
Base model*			
Controls	1		
Adequate (≥20 ng/mL)	0.871	0.025–1.378	.164
Insufficient (10 to <20 ng/mL)	1.343	1.108–2.976	.038
Deficiency (<10 ng/mL)	2.575	1.984–6.532	<.001
Full model†			
Controls	1		
Adequate (≥20 ng/mL)	0.743	0.441–1.543	.432
Insufficient (10 to <20 ng/mL)	1.477	1.178–3.286	.057
Deficiency (<10 ng/mL)	2.891	1.459–7.139	<.001

BMI = body mass index, CAD = coronary artery disease, CI = confidence interval, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, OR = odds ratio, TC = total cholesterol, TG = triglyceride.

* Adjusted for age.

† Adjust for age, BMI, diabetes mellitus, hypertension, smoking, family history of CAD, TC, LDL-C, HDL-C, TG, and creatinine.

Author contributions

Conception and design of the research: Rui Xu, Hong-Ni Yang; Acquisition of data and Analysis and interpretation of the data: Yan-Yan Li, Ling-Ling Ma; Statistical analysis: Rui Xu; Writing, review and editing of the manuscript: Rui Xu.

References

[1] Cashman KD. Calcium and vitamin D. Novartis Found Symp 2007;282:123–38.
[2] Darraj H, Badedi M, Poore KR, et al. Vitamin D deficiency and glycemic control among patients with type 2 diabetes mellitus in Jazan City, Saudi Arabia. Diabetes Metab Syndr Obes 2019;12:853–62.
[3] Hafez M, Musa N, Abdel Atty S, et al. Effect of vitamin D supplementation on lipid profile in vitamin D-deficient children with type 1 diabetes and dyslipidemia. Horm Res Paediatr 2019; 91:311–8.
[4] Rai V, Agrawal DK. Role of vitamin D in cardiovascular diseases. Endocrinol Metab Clin North Am 2017;46:1039–59.

[5] Ai S, He Z, Ding R, et al. Reduced vitamin D receptor on circulating endothelial progenitor cells: a new risk factor of coronary artery diseases. J Atheroscler Thromb 2018;25:410–21.
[6] Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819–29.
[7] Messenger W, Nielson CM, Li H, et al. Serum and dietary vitamin D and cardiovascular disease risk in elderly men: a prospective cohort study. Nutr Metab Cardiovasc Dis 2012;22:856–63.
[8] Chung M, Tang AM, Fu Z, et al. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med 2016;165:856–66.
[9] Hacker-Thompson A, Schloetter M, Sellmeyer DE. Validation of a dietary vitamin D questionnaire using multiple diet records and the block 98 health habits and history questionnaire in healthy postmenopausal women in northern California. J Acad Nutr Diet 2012;112:419–23.
[10] Webb AR, Engelsen O. Ultraviolet exposure scenarios: risks of erythema from recommendations on cutaneous vitamin D synthesis. Adv Exp Med Biol 2014;810:406–22.
[11] Harkness L, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. Osteoporos Int 2005;16:109–13.
[12] Akhtar T, Aggarwal R, Jain SK. Serum vitamin D level in patients with coronary artery disease and association with sun exposure: experience from a tertiary care, Teaching Hospital in India. Adv Med 2019;2019:6823417.
[13] Lopez-Bautista F, Posadas-Romero C, Cardoso-Saldana G, et al. Association of vitamin D deficiency with coronary artery disease in Mexican population: Genetics of atherosclerotic disease (GEA) study. Gac Med Mex 2017;153:566–74.
[14] Liao EY, Zhang ZL, Xia WB, et al. Calcifediol (25-hydroxyvitamin D) improvement and calcium-phosphate metabolism of alendronate sodium/vitamin D3 combination in Chinese women with postmenopausal osteoporosis: a post hoc efficacy analysis and safety reappraisal. BMC Musculoskelet Disord 2018;19:210.
[15] Aljefree NM, Lee P, Alsaqqaf JM, et al. Association between vitamin D status and coronary heart disease among adults in Saudi Arabia: a case-control study. Healthcare 2016;4:
[16] Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–11.
[17] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
[18] Mangge H, Weghuber D, Prassl R, et al. The role of vitamin D in atherosclerosis inflammation revisited: more a bystander than a player? Curr Vasc Pharmacol 2015;13:392–8.
[19] Goncalves de Carvalho CM, Ribeiro SM. Aging, low-grade systemic inflammation and vitamin D: a mini-review. Eur J Clin Nutr 2017;71:434–40.
[20] Boxer RS, Dauser DA, Walsh SJ, et al. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. J Am Geriatr Soc 2008;56:454–61.
[21] Nemerovski CW, Dorsch MP, Simpson RU, et al. Vitamin D and cardiovascular disease. Pharmacotherapy 2009;29:691–708.
[22] Cremer A, Tambosco C, Corcuff JB, et al. Investigating the association of vitamin D with blood pressure and the renin-angiotensin-aldosterone system in hypertensive subjects: a cross-sectional prospective study. J Hum Hypertens 2018;32:114–21.