Original Article

Correlation of serum vitamin D with lipid profiles in middle-aged and elderly Chinese individuals

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Background and Objectives: Deficiency of vitamin D has been associated with various health conditions. The purpose of this study was to evaluate the associations between the serum 25OHD concentration and lipid profiles in Chinese individuals. **Methods and Study Design:** Serum 25OHD and lipid profiles were obtained for a cross sectional sample of 10100 individuals aged 40-75 years from Lanzhou city, which is located in western China. Linear-by-linear association, partial correlation analysis and multiple logistic regression analysis were used to evaluate associations between serum 25OHD concentration and lipid profiles. **Results:** 10038 subjects aged 40-75 years were included in the study. The 25OHD deficient and insufficient groups had higher TC, LDL-C and TG when compared to the optimal group. The dyslipidemia rates of vitamin D deficiency, insufficiency, and sufficiency groups were 45.4%, 41.6%, 38.8%, respectively. The prevalence rates of dyslipidemia, high cholesterol, high LDL-C, hypertriglyceridemia and mixed type hyperlipidemia exhibited decline trend in vitamin D deficiency, insufficiency and sufficiency groups. The correlation coefficients in between TC and 25OHD, LDL-C and 25OHD, TG and 25OHD were -0.033, -0.022, -0.044, respectively. Low 25OHD levels were associated with the risk of onset of dyslipidemia [OR 1.225 (95% CI 1.075-1.397), p=0.002] in the logistical regression analyses. **Conclusions:** Deficient serum 25OHD is associated with higher TC, LDL-C, and TG in middle-aged and elderly Chinese individuals. These findings suggest that low 25OHD levels observationally is simply a marker for elevated atherogenic lipoproteins and question a role for vitamin D supplementation in the prevention of cardiovascular disease.

Key Words: Vitamin D deficiency, lipid profiles, cross-sectional study, atherosclerotic cardiovascular disease, northwest China

INTRODUCTION

The prevalence of dyslipidemia especially in middle aged and elderly individuals has increased significantly in recent decades and is now reaching epidemic proportions,[1] therefore dyslipidemia represents a public health problem, which is associated with increased mortality, concomitant complications, and reduced quality of life. Vitamin D exerts autocrine and paracrine effects such as direct intracellular effects via its receptors and the local production of 1,25(OH)2D3.[2] Intra cellular vitamin D receptors and the 1-alpha hydroxylase enzyme are distributed ubiquitously in all tissues suggesting a multitude of functions of vitamin D.[2] Vitamin D possesses numerous biological functions and vitamin D inadequacy is now recognized as a worldwide concern.[2-4] Serum 25-hydroxyvitamin D (25OHD), a generally accepted indicator of vitamin D status, is associated with improved glucose tolerance, lipid profiles, blood pressure, and decreased prevalence of obesity and certain types of cancer following its classic role in bone homeostasis and calcium-phosphorus metabolism.[4-6]

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death and disability-adjusted life years lost worldwide. Low circulating 25-hydroxyvitamin D concentration has been linked to a high prevalence of cardiovascular disease.[7] Elevated serum concentration of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) and low concentration of high-density lipoprotein cholesterol (HDL-C) are known to be major risk factors for developing CVD.[8] Furthermore, considerable evidence suggests that a high level of cardiorespiratory fitness can reduce the risk of developing CVD, in part by improving the blood lipid profiles,[9] and recent studies suggested that increased cardiorespiratory fitness is significantly associated with high 25OHD con-

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centration in adults.[6] One highest possible explanation for this phenomenon is that there is an association between the serum 25OHD level and lipid profiles. Recent studies in humans suggested that 25OHD has beneficial effects on the cardiovascular system, partly via its actions against blood lipids.[7,10] We supposed that dyslipidemia plays a role in the process of vitamin D deficiency stimulating CVD events and mortality. Cross-sectional studies have found an association between deficiencies in serum vitamin D and an atherogenic lipid profile.[10-12] These studies have found that individuals with low serum 25-hydroxyvitamin D have higher LDL-C, higher TG, and lower HDL-C compared with those with higher levels of 25OHD. The impact of vitamin D supplementation on dyslipidemia risk reduction remains inconclusive and is a subject of much investigations. Epidemiologic studies regarding vitamin D and lipid profile have so far been generated mostly from western countries and evidence from China or Asian individuals is limited,[10-12] and data regarding the relationships between the 25OHD level and lipid profiles in natural population are limited too.[13,14] The inability of randomized controlled trials and cross-sectional studies to thus far agree on the associations between 25OHD and CVD risk may be due to confounders, such as glycemic status and lifestyle behaviours. Therefore, we performed a large, population-based cross-sectional study including Chinese individuals aged 40-75 years and analyzed the status of lipid profile, prevalence of dyslipidemia. We intend to find out the difference in dyslipidemia status based on the spectrum of vitamin D in middle-aged and elderly Chinese individuals taking into consideration confounding factors, including the gender, age, body mass index (BMI), sociodemographic factor, lifestyle behaviours, and dietary habits. By using this database with directly measured lipid values and adjusting for clinical variables, we can further elucidate the relationship between 25OHD and lipids with greater power.

METHODS

Study subjects

The present work was one part of the baseline survey from REACTION study investigating the association of diabetes and cancer, which was conducted among 259,657 adults, aged 40 years and older in 25 communities across mainland China, from 2011 to 2012.[15] Three communities were randomly selected from Lanzhou urban district as a part of REACTION study. Subjects aged 40-75 years were selected completely from the three communities, with a sample size of 10100 individuals. After excluding those who did not have adequate blood samples (n=62) for 25OHD measurement, 10038 individuals (2902 men and 7136 women) were eligible for the present analyses (These gender differences may be due to a higher proportion of women getting laboratory studies for 25OHD for osteoporosis or bone health screening). All participants provided written informed consent. The REACTION study has been approved by the ethics committee of Shanghai Jiao Tong University.

Data collection

The participants were interviewed by trained health workers to collect information such as gender, age, examination month (May, June, July, August, and September), education level (college or higher level of education versus not), lifestyle (tea, coffee, alcohol, and smoking), dietary habits (aquatic products, organ meats, and nutrients supplement) and dyslipidemia history. Lifestyle behaviours and dietary habits were classified into two categories according to current status on the basis of self-reported yes or not. Aquatic products include fish, shrimps and crabs. Nutrients supplements include minerals and vitamins.

After a questionnaire survey, all participants attended anthropometric measurements. Height and weight were measured using standard procedure with light clothing to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight in kg divided by height in meters squared. Overweight was defined as a BMI of 25.0 to 29.9 and obesity was defined as a BMI of 30.0 or higher.[16]

Biochemical analyses were performed on fresh samples of blood, which were obtained from all participants after overnight fasting (at least 8~10 h). Serum 25OHD concentration was tested by enzyme-immunoassay (EIA; IDS Ltd, UK). HbA1c was measured by high performance liquid chromatography using the VARIANT II Hemoglobin Testing System at a laboratory in the institute of endocrinology, the first hospital of Lanzhou University. The laboratory was certificated by the National Glycohemoglobin Standardization Program. Fasting serum samples were aliquoted and frozen at −80°C within 2 hours of collection and shipped by air in dry ice to the central laboratory in the Shanghai Institute of Endocrine and Metabolic Diseases to test lipids. Serum TC, LDL-C, HDL-C, and TG were measured using an autoanalyser (Abbott Laboratories).

Assessment of dyslipidemia, vitamin D status

The guideline for prevention and treatment of dyslipidemia in Chinese adults (Revised Edition 2016)[1] was used to diagnose dyslipidemia. Results of blood lipid concentration were categorized as follows: High cholesterol (TC ≥6.2 mmol/L), High LDL-C (LDL-C ≥4.1 mmol/L), hypertriglyceridemia (TG ≥2.3 mmol/L), mixed type hyperlipidemia (TC ≥6.2 mmol/L and TG ≥2.3 mmol/L), and Low HDL-C (HDL <1.0 mmol/L). Previously diagnosed dyslipidemia was defined by an affirmative response from the participants to the question, “Have you ever been diagnosed dyslipidemia by a doctor?” Total dyslipidemia included both previously diagnosed and undiagnosed dyslipidemia. Vitamin D status was defined as “deficiency” (25OHD <20 ng/mL), “insufficiency” (25OHD ≥20, and <30 ng/mL), and “sufficiency” (25OHD ≥30 ng/mL) level.[2] The optimal level (sufficiency) was chosen as 30 ng/mL based on previous studies and the Endocrine Society’s recommendations.

Statistical analysis

Descriptive characteristics for participants were expressed as mean and standard deviation for continuous variables or as proportions for categorical variables. Chi-square, One-way ANOVA and Wilcoxon rank sum tests were used for categorical variables, normally distributed and nonnormally distributed continuous variables to assess

the differences across serum 25-hydroxyvitamin D concentration categories and dyslipidemia. The linear-by-linear association test and Chi-square test value for trends were used to evaluate the difference in serum 25OHD concentration groups (deficiency, insufficiency, and sufficiency) based on the blood lipid subgroups. To find the most important factors predicting the outcome of dyslipidemia, partial correlation analyses and multivariate logistic regression were performed. Confounders contained gender, age, examination month, lifestyle behaviours, dietary habits, sociodemographic factor (education), and known dyslipidemia risk factors (BMI, HbA1c and dyslipidemia history). The results of partial correlation analysis were presented as partial correlation coefficient. In multivariate logistic regression, we divided the participants into four groups according to quartiles of serum 25OHD concentration, instead of the diagnostic criteria of vitamin D deficiency and insufficiency because vitamin D deficiency or insufficiency universally exists in the general population and only 2.3% had serum 25OHD ≥30 ng/mL. The results from the logistic regression were presented as odds ratio (OR) and 95% confidence interval (CI). $p<0.05$ was considered statistically significant. IBM SPSS Statistics 19 software (IBM Corporation, USA) was used for the analyses.

RESULTS

Characteristics of study participants were shown in Table 1 and Table 2. 10038 subjects aged 40-75 years were included in the study. 71.1% were females, the mean age of the study population was 58.0 years (58.0±8.5 years), and the mean 25OHD was 16.4 ng/mL (16.4±7.0 ng/mL). The prevalence of vitamin D deficiency (25OHD <20 ng/mL) is 75.2%, and detailed vitamin D nutritional status has been described in other papers of our research team.[17,18] 1007 subjects have dyslipidemia history and 286 participants (28.4%) among them took lipid lowering drugs (data not show). The prevalence rate of dyslipidemia was 44.4%, which contained high cholesterol (5.7%), high LDL-C (3.1%), hypertriglyceridemia (20.5%), mixed type hyperlipidemia (2.7%) or low HDL-C (23.3%) participents. The same study characteristics of Table 1 stratified by serum 25OHD concentration and dyslipidemia were shown in Table 2. The 25OHD deficient and insufficient groups were more likely to be female, and had higher TC, LDL-C and TG when compared to the optimal group. The dyslipidemia participants were more female, older, and had lower 25OHD compared to the patients with normal plasma lipid.

The dyslipidemia rates of the vitamin D deficiency, insufficiency, and sufficiency groups were 45.4%, 41.6%, 38.8%, respectively. The rate of high cholesterol, high LDL-C, hypertriglyceridemia, mixed type hyperlipidemia

Table 1. Characteristics of study subjects

	Study subjects (n=10038)
Age (y)	58.0±8.5
Female sex-no. (%)	7136 (71.1%)
25OHD (ng/mL)	16.4±7.0
Vitamin D deficiency (<20ng/mL)	7545 (75.2%)
TC (mmol/L)	4.6±1.0
LDL-C (mmol/L)	2.6±0.8
TG (mmol/L)	1.8±1.2
HDL-C (mmol/L)	1.2±0.3
Dyslipidemia	4452 (44.4%)
High cholesterol	568 (5.7%)
High LDL-C	307 (3.1%)
Hypertriglyceridemia	2053 (20.5%)
Mixed type hyperlipidemia	271 (2.7%)
Low HDL-C	2339 (23.3%)

no.: number of participants for the characteristics; 25OHD: Serum 25-hydroxyvitamin D; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol.

Table 2. Characteristics of study participants according to serum 25OHD concentration categories and dyslipidemia

Characteristics	Serum 25OHD concentration categories			Dyslipidemia	
	Deficiency	Insufficiency	Sufficiency	Yes	No
Participants-no. (%)	7545 (75.2)	2266 (22.6)	227 (2.3)	4452 (44.4)	5586 (55.6)
Female sex-no. (%)	5687 (75.4)*	1336 (59.0)**	113 (49.8)	2932 (65.9)***	4204 (75.3)
Age (y)	58.2±8.6	57.3±8.2**	58.6±8.7	58.8±8.3***	57.4±8.7
25OHD (ng/mL)	13.7±3.7*	22.9±2.2**	41.0±19.3	16.1±7.2***	16.6±6.8
TC (mmol/L)	4.6±1.1*	4.5±1.0**	4.3±1.0	4.6±1.3	4.6±0.7
LDL-C (mmol/L)	2.6±0.8*	2.6±0.7**	2.4±0.7	2.5±0.9***	2.6±0.6
TG (mmol/L)	1.8±1.3*	1.7±1.0**	1.6±0.8	2.4±1.6***	1.3±0.4
HDL-C (mmol/L)	1.2±0.3	1.2±0.3	1.2±0.3	1.1±0.3***	1.3±0.2

no.: number of participants for the characteristics; 25OHD: Serum 25-hydroxyvitamin D; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol.
*, ** and *** indicated $p<0.05$ for comparisons vitamin D-deficiency versus -sufficiency, -insufficiency versus -sufficiency by post hoc tests and dyslipidemia yes vs no, respectively.

and low HDL-C according to vitamin D deficiency, insufficiency, and sufficiency groups were shown in Table 3. The highest prevalence rate appeared in the deficiency group except for the low HDL-C patients. Additionally, significant differences (linear-by-linear association test) were found among the vitamin D groups in the dyslipidemia, high cholesterol, high LDL-C, hypertriglyceridemia and mixed type hyperlipidemia rates, and the prevalence rates exhibited decline trend in the vitamin D deficiency, insufficiency and sufficiency groups (all $p<0.05$).

Meanwhile, the partial correlation analysis (Table 4) indicated that the correlation coefficients in between TC and 25OHD, LDL-C and 25OHD, TG and 25OHD were -0.035, -0.024, -0.055, respectively (all $p<0.05$) when controlling gender, age, and examination month. After further controlling the confounding factors of lifestyle behaviours, dietary habits, sociodemographic factor, and known dyslipidemia risk factors, the partial correlation matrix were still significant. The logistical regression study (Table 5) showed that low 25OHD levels were associated with the risk of onset of dyslipidemia [OR 1.225(95% CI 1.075-1.397), $p=0.002$] in the analyses when adjusted for these confounders.

DISCUSSION

Vitamin D is a steroid hormone that is present in some foods but is synthesized mainly in response to ultraviolet light exposure. After ingestion or endogenous synthesis, vitamin D is hydroxylated by the liver to form 25OHD, the predominant form of vitamin D in circulation. The impact of vitamin D deficiency on blood lipids, strong cardiovascular disease prognostic factors, is unknown. Limited studies have examined the influence of vitamin D on the levels of blood lipids in middle-aged and elderly natural population, and the findings were inconsistent. This cross-sectional study was performed to examine whether the serum 25OHD concentration or status is associated with the circulating lipid profiles in Chinese 40-75 years of age. Our results showed that the 25OHD deficient and insufficiency groups had higher TC, LDL-C and TG when compared to the optimal group. The dyslipidemia participants had lower 25OHD when compared to the patients with the normal plasma lipid. Additionally, in the Chi-square test (linear-by-linear association), the prevalence rates of dyslipidemia, high cholesterol, high LDL-C, hypertriglyceridemia and mixed type hyperlipidemia rates exhibited decline trend in the vitamin D deficiency, insufficiency and sufficiency groups. After further controlling the confounding factors, the partial correlation matrix showed that there was still a significant negative correlation between TC, LDL-C, TG and 25OHD, and the logistical regression study also demonstrated that low 25OHD levels were associated with the risk of onset of dyslipidemia.

Table 3. Chi-square test (linear-by-linear association) of the association between vitamin D nutritional status and dyslipidemia

	Deficiency (n=7545)	Insufficiency (n=2266)	Sufficiency (n=227)	Chi-Square value (linear-by-linear association)	*p* value
Dyslipidemia	3422 (45.4)	942 (41.6)	88 (38.8)	12.979	<0.001
High cholesterol	459 (6.1)	102 (4.5)	7 (3.1)	11.047	0.001
High LDL-C	245 (3.2)	61 (2.7)	1 (0.4)	5.640	0.018
Hypertriglyceridemia	1587 (21.0)	433 (19.1)	33 (14.5)	8.281	0.004
Mixed type hyperlipidemia	227 (3.0)	40 (1.8)	4 (1.8)	10.103	0.001
Low HDL-C	1775 (23.5)	508 (22.4)	56 (24.7)	0.437	0.508

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 4. Partial correlation analysis of the associations between vitamin D concentration and lipid parameters

	Lipid parameters	Partial correlation coefficient	*p* value
Model 1	TC (mmol/L)	-0.035	<0.001
	LDL-C (mmol/L)	-0.024	0.016
	TG (mmol/L)	-0.055	<0.001
	HDL-C (mmol/L)	0.009	0.378
Model 2	TC (mmol/L)	-0.033	0.001
	LDL-C (mmol/L)	-0.022	0.031
	TG (mmol/L)	-0.047	<0.001
	HDL-C (mmol/L)	-0.001	0.942
Model 3	TC (mmol/L)	-0.033	0.001
	LDL-C (mmol/L)	-0.022	0.030
	TG (mmol/L)	-0.044	<0.001
	HDL-C (mmol/L)	-0.003	0.773

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol.
Model 1: controlling for age, gender and examination month;
Model 2: as in model 1 plus BMI and HbA1c;
Model 3: as in model 2 plus sociodemographic factor (education), lifestyle behaviours (tea, coffee, alcohol, and smoking), dietary habits (aquatic products, organ meats, and nutrients supplement), dyslipidemia history.

Table 5. Multiple logistic regression analysis of the associations between vitamin D nutritional status and dyslipidemia

Vitamin D nutritional status	OR	95% CI	*p* value
Model 1			
Q1	1.241	(1.102, 1.398)	<0.001
Q2	1.121	(0.998, 1.259)	0.054
Q3	1.179	(1.051, 1.322)	0.005
Q4	1	—	—
Model 2			
Q1	1.207	(1.069, 1.363)	0.002
Q2	1.089	(0.968, 1.226)	0.156
Q3	1.169	(1.040, 1.314)	0.009
Q4	1	—	—
Model 3			
Q1	1.225	(1.075, 1.397)	0.002
Q2	1.062	(0.934, 1.208)	0.357
Q3	1.170	(1.031, 1.327)	0.015
Q4	1	—	—

Q: quartile.
Model 1: adjusted for age, gender and examination month;
Model 2: as in model 1 plus BMI and HbA1c;
Model 3: as in model 2 plus sociodemographic factor (education), lifestyle behaviours (tea, coffee, alcohol, and smoking), dietary habits (aquatic products, organ meats, and nutrients supplement), dyslipidemia history.

As seen in our study, Jorde et al[13] and Karhapaa et al[14] found the serum 25OHD concentration to be negatively correlated with the TG, LDL-C, LDL-C/HDL-C and ApoB levels, but not the HDL-C or ApoA-1 levels in adults after taking into account BMI and waist circumference. Ponda et al reported subjects with the optimal levels (25OHD ≥30 ng/mL) had lower mean TC, LDL-C, TG and higher HDL-C compared with vitamin D deficient patients (25OHD <20 ng/mL).[11] Wang et al reported that the serum 25OHD levels were inversely associated with TG and LDL-C in 1475 Chinese men after adjusting for age and BMI.[19] One study was conducted in a total of 3788 adults in northern China during their routine health examinations.[20] When the highest quintile of the 25OHD level was set as reference, the risk of having dyslipidemia increased progressively across the highest to the lowest 25OHD after adjustment for age. Lupton JR et al used the Very Large Database of Lipids, which includes 20,360 subjects.[21] In multivariable adjusted linear regression, deficient serum 25OHD was associated with significantly lower serum HDL-C (-5.1%) and higher TC (+9.4%), non-HDL-C (+15.4%), directly measured LDL-C (+13.5%), and TG (+26.4%) when compared with the optimal group. Moreover, Carbone et al. found the serum 25OHD concentration to be positively correlated with the HDL-C and ApoA-1 levels, but not the TG, LDL-C, ApoB or ApoB/ApoA-1 levels, without considering factors of obesity in middle-aged adults.[22] Ooi examined lipoprotein levels in 85,868 white, Danish individuals and 25OHD levels in 31,435, resulting that elevated nonfasting remnant cholesterol is associated with low 25OHD levels, whereas reduced HDL-C is not associated with low 25OHD levels.[23] Vitamin D deficiency is found to be inversely associated with dyslipidemia in these most cross sectional epidemiological studies generally.

One study aimed to examine the effects of daily consumption of vitamin D3-supplemented yogurt (VDY) drink on lipid profiles in pregnant gestational diabetes mellitus patients.[24] After 16 weeks of intervention, levels of TG, TC and LDL had significantly decreased in the VDY group. Hirschler et al. compared the prevalence and the distribution of lipid levels among vitamin D supplemented children with a nonsupplemented population group.[25] There was a significantly higher prevalence of high TG and low HDL-C in vitamin D supplemented children. A total of 104 postmenopausal women with type 2 diabetes were randomly assigned in a double-blind manner to 1 of 2 groups taking a daily tablet for 6 months: a group consuming 4000 IU tablets of vitamin D supplement or a group consuming placebo tablets. The finding revealed no significant changes in LDL, HDL and TC concentrations, but did identify a greater decrease in serum TG in the vitamin D group.[26] Xia assessed the association of vitamin D receptor gene Fok I and Bsm I polymorphisms.[27] They found Fok I polymorphisms may be a risk factor for dyslipidemia in elderly male patients with type 2 diabetes among Chinese Han population, where Bsm I polymorphisms are not associated with diabetic dyslipdiemia.

The mechanisms by which vitamin D could affect lipid profiles are not clear. The observed association between them may be confounded by shared metabolic risk factors rather than a causal mechanism. Serum 25OHD has been shown to be decreased in obese patients.[28] Suggested mechanisms include vitamin D stimulated intestinal calcium absorption leading to reduced formation of calcium-fatty soaps in the gut and thereby increased absorption of fat.[29] Meanwhile vitamin D and statins have synergistic effects on serum cholesterol concentrations.[30] This phenomenon results in an inverse association between BMI and 25OHD. BMI is also associated with dyslipidemia and the presence of obesity may explain the observed association of 25OHD with dyslipidemia. Fortunately, we did have BMI available in our data set to adjust for this potentially confounding variable. There also appears to be an association between lipid lowering and increases in 25OHD, suggesting that the observed association between low 25OHD levels and dyslipidemia may be due to other

mechanisms. Thus, specifically designed, new clinical studies are needed to be conducted in well-defined populations, following normalizing the serum vitamin D levels in vitamin D deficient subjects, to test the hypothesis that hypovitaminosis D worsens these disorders and correction would alleviate it.

The present study is associated with several limitations. First, we used a cross-sectional design and therefore cannot provide causal evidence regarding the association between the serum 25OHD concentration and lipid profiles. Second, the study population included only Chinese Han population. It remains unknown whether the same associations exist in people of other ethnicities, as vitamin D metabolism and the circulating 25OHD concentration vary substantially by race. Further understanding of this issue in other populations is therefore needed. Despite these limitations, the present analysis is the first large study to focus on the relationship between the 25OHD concentration and lipid profiles among middle aged and elderly Chinese individuals.

Conclusions

Deficient serum 25OHD is associated with significantly higher directly measured TC, LDL-C, and TG in middle aged and elderly Chinese individuals. These findings suggest that low 25OHD levels observationally is simple a marker for elevated atherogenic lipoproteins and question a role for vitamin D supplementation in the prevention of cardiovascular disease.

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AUTHOR DISCLOSURES

The authors declare that there are no conflicts of interest exist in relation to the publication of this paper.

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