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Association between serum 25-hydroxyvitamin D and carotid atherosclerotic plaque in Chinese type 2 diabetic patients

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Abstract

In this study, we investigated the distribution of vitamin D and its association with carotid atherosclerotic plaque (CP) in Chinese type 2 diabetic (T2D) patients. We performed a cross-sectional study in 210 T2D and 94 age- and gender-matched nondiabetic patients during winter months, by determining serum 25-hydroxyvitamin D (25(OH)D) levels in both diabetic and nondiabetic controls. We carried out measurements of B-mode ultrasonography of carotid arteries in each T2D patient. The 25(OH)D concentration was 26.25 nmol/L among the T2D patients. About 93.3% T2D patients suffered from hypovitaminosis D. First, we found a clear inverse correlation between the 25(OH)D concentration and CP ($P<0.001$). Second, an association between 25(OH)D and macrovascular disease was significant ($P=0.005$). In multivariate logistic regression analysis, decreasing 25(OH)D concentration was markedly associated with CP in T2D patients. Third, after adjusting for the confounding factors, we also observed a positive correlation between low levels of 25(OH)D in T2D patients with CP, when the following parameters were measured: old age (odds ratio [OR] = 2.533, $P=0.013$); smoking (OR = 3.872, $P=0.001$); and high level of low-density lipoprotein (LDL) cholesterol (OR = 2.776, $P=0.009$). Thus, we concluded that high prevalence of hypovitaminosis D exists in Chinese T2D patients. Further, we found a significant association between low concentration of serum 25(OH)D and the existence of high body mass index, and high circulating LDL to be substantially positive predictors of patients with CP in T2D.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, BDR = background diabetic retinopathy, BMI = body mass index, BP = blood pressure, CI = confidence interval, CP = carotid atherosclerotic plaque, CVD = cardiovascular disease, CYP = 24-hydroxylase, CYP27B1 = 1-alpha-hydroxylase, DBP = diastolic blood pressure, DR = diabetic retinopathy, FIB = fibrinogen, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, hsCRP = high-sensitivity C-reactive protein, IMT = intima-media thickness, LDL = low-density lipoprotein, OR = odds ratio, PDR = proliferative diabetic retinopathy, SBP = systolic blood pressure, T2D = type 2 diabetic.

Keywords: 25-hydroxyvitamin D, carotid atherosclerotic plaque, Chinese, type 2 diabetes

1. Introduction

Atherosclerosis or hardening of arteries is a progressive and inflammatory systemic disease confirmed to be the primary cause of myocardial infarction and ischemic strokes,[1] resulting in increasing morbidity, disability, and mortality, especially in diabetic population.[2,3]

Vitamin D deficiency is a risk factor linked with muscle weakness, bone pain, and fragility fractures.[4] Additionally, low circulating concentrations of 25-hydroxyvitamin D (25(OH)D) were found to be associated with cardiovascular events in the Framingham Offspring Study[5] of causes, patients' follow-up studies, and determination of mortality rates in cardiovascular diseases, including myocardial infarction and acute coronary syndrome[6] by Health Professionals. Accelerated atherosclerosis may play a critical role in the associations of vitamin D deficiency with cardiovascular disease and associated mortality. Vitamin D influence on vascular function has been implicated in the development and progression of atherosclerosis. Recently, studies involving Amish, European–American, and Italian participants revealed that 25(OH)D concentrations are inversely correlated with subclinical atherosclerosis, as measured by carotid atherosclerotic plaque (CP) or carotid intima-media thickness (IMT).[6–9] However, it remains unclear whether circulating vitamin D levels relate to the development or progression of atherosclerosis in Chinese populations.

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In light of these premises, we sought to estimate the prevalence of hypovitaminosis D via measurements of plasma 25(OH)D concentrations and to determine the relationship with type 2 diabetic (T2D) patients who also have CP, measured by B-mode ultrasonography in representative samples from 210 patients.

2. Materials and methods

2.1. Subjects

We conducted a cross-sectional study among Chinese individuals in Lishui (latitude 28° north), Zhejiang, China. A total of 210 T2D patients who attended our clinic during the winter months (November–March) were included in this study. We considered the following exclusion criteria: acute illness (diabetic ketoacidosis, diabetic hyperosmolar coma, and lactic acidosis); advanced chronic liver or renal disease; taking any medications known to affect vitamin D metabolism; and abnormal thyroid and parathyroid hormone. Ninety-four age- and sex-matched nondiabetic volunteers were recruited in the control group. Informed consent was obtained from each participant. The research followed the assumption of the Declaration of Helsinki and approved by the Sciences Ethics Committee of the First Affiliated Hospital of Wenzhou Medical College.

2.2. Measurement of carotid plaque

Bilateral carotid B-mode ultrasonography was performed for every patient using an ultrasonogram (Acuson Sequoia 512; Siemens) with a linear array 7.5-MHz transducer. The acoustic shadow in hard plaque detection was at the levels of the common carotid and internal carotid arteries and bifurcation indicated the presence of calcified plaque. The study included carrying out scans in transverse and longitudinal views. All scans were performed by a single experienced ultrasonographer blinded to the clinical characteristics of the participants. We used the results of the ultrasound examination to categorize patients into the CP and non-CP groups.

2.3. Physical and laboratory measurements

All the patients were evaluated using the following criteria: interviewed for medical histories; their current medications were verified; carried out measurements of their body mass indexes (BMIs), calculated by dividing weight in kilograms by height in meters squared; determined their resting blood pressure (BP); electrocardiogram; and fundus photography. After an overnight fasting, venous blood was drawn from each patient and placed into tubes protected from sunlight. Plasma from each blood sample was separated and stored at −70°C within 30 minutes of collection.

We performed laboratory assays, including the following: hemoglobin A1c (HbA1c); total cholesterol; triglycerides; low-density lipoprotein; high-density lipoprotein; high-sensitivity C-reactive protein (hsCRP); fibrinogen (FIB); uric acid; creatinine; albuminuria; intact parathyroid hormone (PTH); calcium; and 25(OH)D. Serum 25(OH)D level is the best marker of whole-body vitamin D status.[10,11] Thus, we determined the 25(OH)D using electrochemiluminescence immunoassay (Modular Analytics E170, Roche Diagnosis). We assessed vitamin D nutritional status as "sufficiency" (≥75 nmol/L), "insufficiency" [50 ≤ 25 (OH)D < 75 nmol/L], or "deficiency" (<50 nmol/L).[12] Vitamin D intoxication was observed when serum levels of 25(OH)D were >150 ng/mL (374 nmol/L).[11]

2.4. Definition of hypertension, diabetes, and dyslipidemia

Diabetes definition was according to the American Diabetes Association criteria.[13] Subjects were diagnosed with hypertension if their BP was ≥140/≥90 mm Hg or if they use antihypertensive agents as recommended by the Joint National Committee VII. Dyslipidemia diagnosis was according to the 2004 update of National Cholesterol Education Program guidelines.[14]

2.5. Statistical analyses

Data were expressed as mean ± SD for continuous variables and categorical variables percentages. Because of skewness and kurtosis of the distributions, 25(OH)D, hsCRP, and FIB were described by median values with interquartile ranges (25th and 75th). Univariate analyses included unpaired *t*-test, Mann–-Whitney *U* test, and χ^2 test. The logistic regression analysis was used for multivariate analysis. *P* values <0.05 were considered statistically significant. Statistical evaluation was performed using SPSS software version 13.0.

3. Results

A total of 210 patients who fulfilled the eligibility criteria were recruited for this study (mean age 57 ± 12 years, 48.8% male). Table 1 displays the baseline characteristics of the study

Table 1

Baseline characteristics of selected covariates with and without CP in type 2 diabetic group.

	CP	Non-CP	*P* value
n	82	128	
Age, y	59.90 ± 11.60	55.51 ± 12.61	0.012
Gender (male)	40 (48.8%)	63 (49.2%)	1.000
diabetic duration, y	11.07 ± 6.65	6.20 ± 5.38	<0.001
Smoking	45 (54.9%)	35 (27.3%)	0.001
Macrovascular diseases	21 (25.6%)	12 (9.4%)	0.003
History of hypertension	57 (69.5%)	70 (54.7%)	0.043
Antiplatelet use (%)	57 (69.5%)	59 (46.1%)	0.001
Statins use (%)	56 (68.3%)	51 (39.8%)	<0.001
BMI, kg/m^2	23.18 ± 2.52	21.62 ± 3.41	<0.001
Systolic BP, mm Hg	148.27 ± 20.76	145.09 ± 21.34	0.288
Diastolic BP, mm Hg	81.82 ± 11.70	81.83 ± 9.87	0.994
HbA1c (%)	9.39 ± 2.19	9.15 ± 2.15	0.450
Total cholesterol, mmol/L	4.94 ± 0.97	4.61 ± 1.01	0.019
Triglyceride, mmol/L	2.07 ± 1.34	1.72 ± 0.87	0.020
HDL, mmol/L	1.31 ± 0.40	1.31 ± 0.41	0.973
LDL, mmol/L	3.17 ± 1.00	2.75 ± 0.95	0.002
Uric acid, μmol/L	328.20 ± 112.43	292.52 ± 97.45	0.016
Creatinine, μmol/L	60.55 ± 16.18	58.34 ± 15.11	0.315
PTH	38.38 ± 21.15	39.77 ± 27.90	0.701
Calcium, mmol/L	2.22 ± 0.23	2.20 ± 0.15	0.437
hsCRP, mg/L	12.50 (6.00–17.25)	10.00 (5.00–14.75)	0.036
FIB, g/L	3.80 (3.30–4.56)	3.46 (3.00–4.20)	0.002
25 (OH)D, nmol/L	18.15 (14.00–26.13)	39.75 (22.38–59.15)	<0.001
Albuminuria (%)	21 (25.6%)	14 (10.9%)	0.008
DR			0.003
NDR	34 (41.5%)	67 (52.3%)	
BDR	30 (36.6%)	53 (41.4%)	
PDR	18 (22.0%)	8 (6.3%)	

Data are presented as the mean value ± SD, median values with interquartile ranges (25th to 75th) or the number (%) of patients.

BDR = background diabetic retinopathy, BMI = body mass index, BP = blood pressure, CP = carotid atherosclerotic plaque, DR = diabetic retinopathy (detected by Fundus photography), FIB = fibrinogen, HbA1c = hemoglobin A1c; HDL = high-density lipoprotein, hsCRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, NDR = nondiabetic retinopathy, PDR = proliferative diabetic retinopathy, PTH = parathyroid hormone, SD = standard deviation.

population. Patients who developed CP were significantly older and had had a longer duration of diabetes. Additionally, they scored higher levels of BMI, cholesterol, triglycerides, LDL, uric acid, hsCRP, and FIB than patients of the non-CP group. We observed significant trends in the outcomes of these measurements indicating positive correlations with smoking, albuminuria, histories of macrovascular diseases, hypertension, diabetic retinopathy, the use of antiplatelet, and the use of a statin. There were no significant gender differences among male and female groups for the following evaluations: HbA1c, BP, high-density lipoprotein, creatinine, PTH, and calcium.

For all 210 diabetic participants, the concentration of 25(OH)D was mean 26.25 nmol/L (range = 16.78–48.60 nmol/L). In diabetic patients, the percentages of vitamin D deficiency, insufficiency, and sufficiency were 76.67%, 16.67%, and 6.66%, respectively. In 94 nondiabetic subjects, the concentration of 25(OH)D was 36.25 (24.48–49.65) nmol/L, which was significantly higher than that of people living with diabetes ($P = 0.003$). In controls, the percentages of vitamin D deficiency, insufficiency, and sufficiency were 75.53%, 18.09%, and 6.38%, respectively.

Macrovascular diseases, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease, were observed in the present study. Diabetic patients with macrovascular diseases had a lower concentration of 25(OH)D [19 (14–37) nmol/L] than those without macrovascular diseases [28.10 (18.05–51.10) nmol/L] ($P = 0.005$).

Among the diabetic patients, the concentration of 25(OH)D in the CP group was significantly lower compared with the non-CP group; 18.25 (14.75–25.70) nmol/L versus 41.75 (22.50–60.25) nmol/L, $P < 0.001$, respectively. In addition, we classified the 25(OH)D concentration obtained among the diabetic patients into three levels: Level 1: 39.00–92.10 nmol/L (n = 70); Level 2: 19.20–38.70 nmol/L (n = 70); and Level 3: <19.00 nmol/L (n = 70). The proportions of CP were significantly different among the three levels of 25(OH)D ($P < 0.001$; Fig. 1).

Furthermore, a multivariate logistic regression model was fit in a forward method with all related covariates of the 25(OH)D concentrations obtained in each of the above-mentioned categories. The results showed that the levels of 25(OH)D concentration varied significantly among the different classes of CP patients. Table 2 shows that the odds ratio (OR) for Levels 2 and 3 are 2.283 (95% confidence interval [CI] = 1.074, 4.852, $P = 0.012$), whereas for Level 1 is 32.734 (95% CI = 9.607, 111.532, $P < 0.001$), respectively. We adjusted for gender, age, smoking, BP, HbA1c, LDL cholesterol, hsCRP, and FIB in our statistical analysis. The OR for Levels 3 to 2 was 10.333 (95% CI = 3.709, 28.789, $P < 0.001$), after adjustment (Table 2 not show). We adjusted for potential confounding factors in our analysis. Our results show that old age (OR = 2.533, $P = 0.013$), smoking (OR = 3.872, $P = 0.001$), and increased level of LDL (OR = 2.776, $P = 0.009$) had marked association with T2D patients with CP. By contrast, there were no significant differences for gender, BP, HbA1c, hsCRP, and FIB.

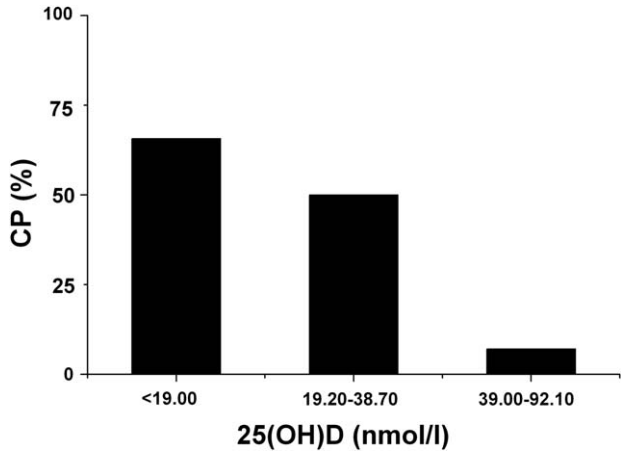

Figure 1. The relationship between T2D with CP and different 25(OH)D concentration measurements. The percent of CP prevalence determined by 25(OH)D concentration measurements ($P < 0.001$) in three assigned categories were 65.7%, 44.3%, and 7.1%, for Levels 1, 2, and 3, respectively. 25(OH)D = 25-hydroxyvitamin D CP = carotid atherosclerotic plaque, T2D = type 2 diabetes.

4. Discussion

In our present study, we obtained a 25(OH)D median concentration of 36.25 nmol/L for the nondiabetic subjects. The percentage of vitamin D deficiency was 75.53%. A recent study by Ling and colleagues indicated an association of age with differences in vitamin D deficiency. They categorized serum vitamin D levels as follows: deficiency [25(OH)D <50 nmol/L] and insufficiency [50≤ 25(OH)D <75 nmol/L]. We obtained vitamin D concentrations of 69.2% and 24.4% for the middle-aged and elderly Chinese population in Beijing and Shanghai, respectively,[15] which fall in the insufficiency and deficiency categories. Wenzhou, the city of Zhejiang, as well as Beijing and Shanghai are in temperate zones (23.5°–66.5°) where people lack sufficient ultraviolet B radiation from the sun for 1 month in a year. They have 11 months for their body to synthesize vitamin D. However, our study indicates that the nutritional status of hypovitaminosis D is still popular.

Moreover, the status of vitamin D was worse in T2D patients. We obtained a 25(OH)D concentration of 26.25 (16.78–48.60) nmol/L in T2D patients. Notably, only 6.66% diabetic patients had the typical nutritional status of vitamin D. So, we confirmed that hypovitaminosis D was more prevalent in diabetic than in the healthy Chinese population. Multiple studies have shown that hypovitaminosis D may inversely affect glycemia, whereas glucose metabolism might ameliorate combined supplementation with vitamin D and calcium. Thus, induction of hypovitaminosis D might influence impair pancreatic beta cell function with subsequent insulin insensitivity and systemic inflammation, with the ultimate development and acceleration of diabetes.[16]

Our present study indicates that a negative association prevails between serum 25(OH)D concentrations and CP in Chinese population living with diabetics. After adjusting for potential confounding factors, the negative association still existed. The inverse correlation between 25(OH)D and CP found in our study is consistent with those from three previous reports in Amish, European–American, and Italian participants.[6–9] However, the association of serum levels of 25(OH)D metabolites with subclinical vascular disease, such as CP, is still controversial. Freedman et al[17] reported that positive associations existed between 25(OH)D and carotid artery CP in African–Americans. The most likely explanations for this contradiction are as follows: firstly, different imaging technologies, such as multislice computed tomography and B-mode ultrasonography, were used to evaluate the carotid artery CP or IMT and both of these conditions might coexist in different diabetic stages to result in inconsistent findings. Secondly, 25(OH)D nutritional status is

Table 2

Multivariate-adjusted odds ratios from logistic regression analysis for CP and variables in patients with type 2 diabetes.

Variables	N = 210	Number of CP (%)	Crude OR (% CI)	*P* value	Adjusted OR (% CI)	*P* value
Gender						
Men	103	40 (38.8%)	1.00 (reference)		1.00 (reference)	
Women	107	42 (39.3%)	1.018 (0.584–1.772)	0.951	1.682 (0.776–3.644)	0.187
Age, y						
<60	109	32 (29.4%)	1.00 (reference)		1.00 (reference)	
≥60	101	50 (49.5%)	2.359 (1.337–4.161)	0.003	2.533 (1.218–5.271)	0.013
Smoking						
No	130	37 (28.5%)	1.00 (reference)		1.00 (reference)	
Yes	80	45 (56.3%)	2.232 (1.803–5.791)	<0.001	3.872 (1.780–8.420)	0.001
SBP, mm Hg						
<140	81	28 (34.6%)	1.00 (reference)		1.00 (reference)	
≥140	129	54 (41.9%)	1.363 (0.766–2.425)	0.292	1.015 (0.481–2.141)	0.97
DBP, mm Hg						
<90	153	57 (37.3%)	1.00 (reference)		1.00 (reference)	
≥90	57	25 (43.9%)	1.316 (0.710–2.439)	0.384	1.748 (0.764–4.002)	0.186
HbA1c (%)						
<7	33	14 (42.4%)	1.00 (reference)		1.00 (reference)	
≥7	177	68 (38.4%)	0.847 (0.398–1.799)	0.665	1.139 (0.444–2.919)	0.787
LDL, mmol/L						
<2.6	78	21 (26.9%)	1.00 (reference)		1.00 (reference)	
≥2.6	132	61 (46.2%)	2.332 (1.272–4.275)	0.006	2.776 (1.290–5.973)	0.009
hsCRP, mg/L						
<10	101	34 (33.7%)	1.00 (reference)		1.00 (reference)	
≥10	109	48 (44.0%)	1.551 (0.886–2.714)	0.125	0.953 (0.471–1.928)	0.892
FIB, g/L						
<4	140	49 (35.0%)	1.00 (reference)		1.00 (reference)	
≥4	70	33 (47.1%)	1.656 (0.924–2.970)	0.09	1.746 (0.825–3.695)	0.145
25 (OH)D, nmol/L						
11.00–19.00	70	46 (65.7%)	1.00 (reference)		1.00 (reference)	
19.20–38.70	70	31 (44.3%)	2.411 (1.218–4.772)	0.012	2.283 (1.074–4.852)	0.032
39.00–92.10	70	5 (7.1%)	24.917 (8.852–70.134)	<0.001	32.734 (9.607–111.532)	<0.001

CI = confidence interval, CP = carotid atherosclerotic plaque, DBP = diastolic blood pressure, LDL = low-density lipoprotein, FIB = fibrinogen, HbA1c = hemoglobin A1c, hsCRP = high-sensitivity C-reactive protein, OR = odds ratio, SBP = systolic blood pressure.

Logistic regression analysis was performed for the associations between variables and carotid atherosclerotic plaque, adjusted for potential confounding factors such gender, age, smoking, blood pressure, HbA1c, LDL, hsCRP, FIB, and different levels of 25 (OH)D.

influenced by environmental factors, include differences in latitudes and the degree of sunshine, and also vitamin D supplements from food or medicine in different regions. Thirdly, the association between 25(OH)D status and atherosclerosis may vary in different ethnicities. Fourthly, whether genetic factors are involved with increasing the predisposition of CP to hypovitaminosis D in some populations is an important consideration.[10] Further, prospective studies are needed to focus on the association between carotid atherosclerosis in diabetes and variations in vitamin D metabolic pathway genes. These variants should include polymorphisms in vitamin D pathway genes such as vitamin D receptor, 1-alpha-hydroxylase (CYP27B1) enzyme, vitamin D-binding protein, and 24-hydroxylase (CYP24).

Recent reports provided evidence which suggested an association between low serum 25(OH)D concentrations and macrovascular diseases, including coronary artery disease, cerebrovascular disease,[18] and peripheral arterial disease.[19] Our present study shows that the 25(OH)D inversely associates with macrovascular diseases. Our results are consistent with that of Kendrick et al[20] and Michos et al.[21] In contrast, another study has found no correlation between serum $1,25(OH)_2D$ levels and coronary calcification among 50 patients undergoing coronary angiography.[22] Hence, we speculated that macrovascular diseases mainly correlated with the instability of CP, except for ethnic variations and differences in measuring methods. Thus, characteristics of the plaques, such as distinct components and structural morphology, should be considered during evaluation.

The plausible mechanisms through which 25(OH)D deficiency can contribute to the pathogenesis of atherosclerosis, including CP, have been previously reported. 25(OH)D influences multiple known mechanisms responsible for the decreased vascular inflammation, thrombus formation, vascular smooth muscle cell proliferation,[23] arterial calcification, and the renin–angiotensin system. Recent in vitro studies suggested that low 25(OH)D influence the activity/expression of macrophages and lymphocytes in atherosclerotic plaques, thus promoting chronic inflammation in the arterial wall.[24–26] It has also been postulated that vitamin D supplementation in humans also favors cardiovascular health.[27] However, opinions on this claim are conflicting. Although animal models show that atherosclerosis is accelerated when on vitamin D and cholesterol-rich diet,[28] the mechanisms underlying 25(OH)D-associated atherosclerosis is unclear, which allows for more speculation.

The limitations we encountered in this study are as follows: first, the cross-sectional study could not explain the causal relationship between 25(OH)D and CP in diabetes, thus a follow-up study is needed to be carried out for better insight. Second, the evaluation of macrovascular diseases was done through interviewing patients who lack precision. More reliable methods

such as measuring creatinine levels in the patients, using spot urine test, or dilated eye examination (fundus photography) could have been carried out. Despite these limitations, this study is still valuable in that it is the first to investigate the distribution and association of 25(OH)D levels, evaluated by B-mode ultrasonography, in Chinese diabetic patients with CP.

5. Conclusion

Our present study showed that hypovitaminosis D, measured by determination of 25(OH)D deficiency and sufficiency status, was common among type 2 diabetic patients in Lishui, Zhejiang, China. Low concentrations of 25(OH)D are markedly associated with the existence of CP in T2D. Besides, old age, smoking, and high level of LDL were also independently associated with CP in T2D. Perspective and large-scale studies are required to further establish the relationship between 25(OH)D and CP and to determine whether vitamin D interventions could prevent the formation or acceleration of carotid atherosclerosis.

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