

# High Apolipoprotein B/Apolipoprotein A1 is Associated with Vitamin D Deficiency Among Type 2 Diabetes Patients

Shuqi Wang<sup>1,2</sup>, Haina Gao<sup>3</sup>, Mengmeng Zhang<sup>1,2</sup>, Shuchun Chen<sup>1,2</sup>

<sup>1</sup>Department of Internal Medicine, Hebei Medical University, Shijiazhuang, People's Republic of China; <sup>2</sup>Department of Endocrinology, Hebei General Hospital, Shijiazhuang, People's Republic of China; <sup>3</sup>Department of Internal Medicine, The Second Hospital of Shijiazhuang, Shijiazhuang, People's Republic of China

Correspondence: Shuchun Chen, Department of Endocrinology, Hebei General Hospital, Shijiazhuang, People's Republic of China, Tel/Fax +86 311 85988406, Email chenshuc2014@163.com

**Purpose:** To explore the relationship between vitamin D (VitD) deficiency and the apolipoprotein B/apolipoprotein A1 (apo B/A1) in type 2 diabetes mellitus (T2DM) patients.

**Methods:** This was a retrospective study that lasted 2 years and 6 months, collecting information and laboratory data from 784 patients with T2DM. Patients were divided into VitD deficiency group (n = 433) and non-VitD deficiency group (n = 351) based on VitD levels. Calculated apo B/A1 ratio, and patients were further divided into high-apo B/A1 group (n = 392) and low-apo B/A1 group (n = 392) based on the median of the apo B/A1. All data were analyzed using Prism 8.0.1 and R version 4.3.1 software.

**Results:** Apo B/A1 levels of T2DM patients combined with VitD deficiency was significantly higher than that of non-VitD deficiency patients, and the VitD levels of patients with high apo B/A1 was significantly lower than that patients with low apo B/A1 (all  $P < 0.001$ ). Spearman correlation analysis showed that VitD levels were negatively correlated with apo B/A1 ( $r = -0.238$ ,  $P < 0.001$ ). Multiple linear regression analysis revealed after adjusting other factors, VitD levels were significantly negatively associated with apo B/A1 ( $\beta = -0.123$ ,  $P = 0.001$ ). Binary logistic regression analysis showed apoB/A1 was an independent risk factor for VitD deficiency in T2DM patients. Restrictive cubic spline indicated a significant linear relationship between apoB/A1 and VitD deficiency ( $P$  general trend  $< 0.0001$ ,  $P$  nonlinear = 0.0896), after stratification of gender, the results showed that apo B/A1 was more susceptible to VitD deficiency in female patients. The receiver operating characteristic (ROC) curve analysis showed that the area under the curve, sensitivity and specificity of the apo B/A1 for VitD deficiency were 0.654, 66.3% and 59.8%, respectively.

**Conclusion:** The apo B/A1 was significantly negatively associated with VitD levels and an independent risk factor for VitD deficiency in patients with T2DM.

**Keywords:** type 2 diabetes mellitus, vitamin D deficiency, apolipoprotein B/apolipoprotein A1

## Introduction

Due to population aging, obesity, lack of exercise and other factors, the global incidence of diabetes has increased rapidly and is expected to increase to 629 million by 2040. Among them, the vast majority of diabetics show type 2 diabetes mellitus (T2DM).<sup>1</sup> T2DM seriously damages the physical and mental health of patients and poses huge challenges to global healthcare systems. Studies have shown that the cost of T2DM treatment and care is 3.2 times higher than the average per capita healthcare expenditure, increasing to 6.4 times in the presence of cardiovascular disease (CVD) complications.<sup>2</sup> Therefore, identifying more treatment targets for T2DM is particularly important for patient prognosis. Recently, numerous studies have extensively explored the relationship between vitamin D (VitD) levels and islet beta cell function in T2DM patients, reporting a strong correlation between the two variables.<sup>3-5</sup> A recent meta-analysis summarizing three clinical randomized trials found that VitD reduced the risk of T2DM in patients with prediabetes by 15% (risk ratio: 0.85; 95% confidence interval (CI): 0.75–0.96), with an absolute risk reduction of 3.3% within 3 years

(95% CI: 0.6–6.0%).<sup>5</sup> In addition, low VitD levels in T2DM patients are often accompanied by a higher incidence of CVD in diabetes.<sup>6,7</sup> A prospective study by Wan et al pointed out that compared with VitD deficiency, the CVD risk ratio in T2DM patients without VitD deficiency was 0.75 (95% CI: 0.64, 0.88).<sup>7</sup> Thus, maintaining sufficient levels of VitD in T2DM patients is of great significance in preventing the occurrence of CVD.

Dyslipidemia in patients with T2DM is an important risk factor for diabetic CVD, especially low-density lipoprotein cholesterol (LDL-C) in blood lipids. When the vascular endothelium is damaged, foam cells engulf the oxidized LDL-C to form lipid stripes, which is the main pathological basis of atherosclerosis.<sup>8</sup> In recent years, the apolipoprotein family has gradually attracted substantial attention in blood lipid metabolism-related biochemical examination. Apolipoprotein, a protein connected to the lipids in lipoprotein particles, binds and transports lipids to the target organs. Among them, apolipoprotein A1 (apo A1) mainly exists on the surface of high-density lipoprotein (HDL), while apolipoprotein B (apo B) is the main structural protein of all other lipoproteins but HDL.<sup>9</sup> Studies have shown that the apolipoprotein B/apolipoprotein A1 (apo B/A1) can more accurately reflect the degree of arterial stiffness in patients, which is a better indicator for predicting atherosclerosis and coronary heart disease outside conventional lipid parameters.<sup>10,11</sup> Therefore, clinical monitoring of the apo B/A1 can more effectively prevent the occurrence of adverse cardiovascular events.

With the global epidemic status of T2DM, VitD deficiency and lipid metabolic disorders have also been continuously discovered. Considering that VitD deficiency and apo B/A1 are both risk factors for CVD in patients with T2DM, the present study endeavored to explore the intrinsic relationship between VitD deficiency and apo B/A1 in T2DM patients, to provide new treatment ideas and more data for T2DM patients.

## Methods

### Moral Statement

This study strictly adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital. Since this was a cross-sectional, retrospective, non-interventional study, and the patient's information was anonymous and confidential, signed informed consent was waived.

### Experimental Design

A total of 784 patients diagnosed with T2DM at Hebei General Hospital from January 2021 to June 2023 were recruited. The inclusion criteria were as follows: 1) aged 18–80 years old; 2) T2DM patients diagnosed according to the 2011 World Health Organization Diagnostic Standards for Diabetes.<sup>12</sup> The exclusion criteria were as follows: The exclusion criteria were as follows: 1) patients with acute complications and acute stress of diabetes; 2) those with persistent diabetic feet or ulcers; 3) those with severe heart, liver and kidney insufficiency and cancer; 4) T2DM patients combined with thyroid disease or those using drugs that affect VitD levels; 5) other types of diabetes.

Based on the diagnostic criteria for VitD deficiency recommended by the 2011 clinical practice guidelines of the European Endocrine Society,<sup>13</sup> patients with VitD levels <20 ng/mL were included in the VitD deficiency group and those with VitD levels >20 ng/mL were included in the non-VitD deficiency group. Then, the apo B/A1 was calculated, and patients were further divided into high-apo B/A1 group (n = 392) and low-apo B/A1 group (n = 392) based on the median of apo B/A1.

### Data Collection and Laboratory Analysis

The baseline data of the patients were collected, including age, gender, course of T2DM, smoking history, drinking history, systolic blood pressure (SBP), diastolic blood pressure (DBP), height and weight. Laboratory examinations included aspartate aminotransferase (AST), alanine transaminase (ALT), albumin (ALB), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), fasting insulin (FINS), total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), LDL-C, apo A1, apo B, VitD. The body mass index (BMI) was determined by dividing body weight by the square of height ( $\text{kg}/\text{m}^2$ ). The insulin resistance index (homeostatic model assessment for insulin resistance [HOMA-IR]) was calculated by multiplying FBG by FINS and dividing by 22.5.<sup>14</sup> The apo B/A1 was calculated by dividing the apo B by the apo A1.

## Statistical Analysis

Statistical analysis of patients used Prism 8.0.1 and R version 4.3.1 software. Normally distributed measurement data were expressed as mean  $\pm$  standard deviation (SD) and compared using two independent samples *t*-tests; Non-normally distributed measurement data were presented as median and quartile spacing (M [P25%, P75%]) and compared using the Mann–Whitney *U*-test. Count data were compared using the chi-square test. Spearman correlation analysis was used to assess the relationship between VitD and the apo B/A1. Multiple linear regression was used to analyze the dependence between VitD levels and the apo B/A1. Logistic regression was used to analyze independent risk factors for VitD deficiency in T2DM patients. The restricted cubic spline was utilized to analyze the nonlinear relationship between VitD levels and the apo B/A1. The receiver operating characteristic curve (ROC) and the area under the curve (AUC) were used to determine the diagnostic value of the apo B/A1 for VitD deficiency in patients with T2DM. The bilateral difference and  $P < 0.05$  were considered statistically significant.

## Results

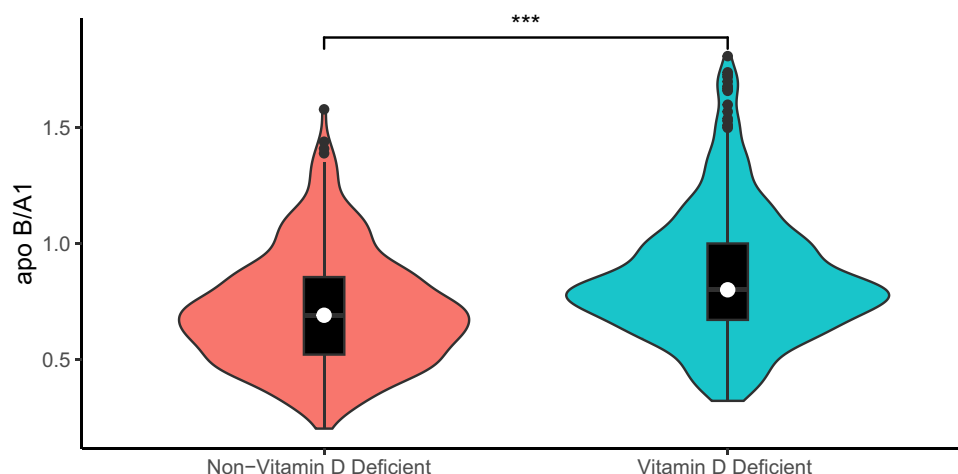
### Comparison of Baseline Characteristics and Laboratory-Related Indicators Between T2DM Patients with and Without VitD Deficiency

The apo B/A1 was significantly higher in the VitD deficiency group than in the non-VitD deficiency group ( $P < 0.001$ ) (Table 1 and Figure 1). The incidence of male patients was lower in the VitD deficiency group than in the non-VitD deficiency group ( $P < 0.001$ ). Compared with the non-VitD deficiency group, patients with VitD deficiency had significantly higher levels of DBP, BMI, HbA1c, TC, TG, LDL-C and apoB, and significantly lower of ALB, HDL-C, apo A1 levels, age and disease course (all  $P < 0.05$ ). However, no significant difference was found between the two groups in terms of smoking history, drinking history, SBP, FBG, HOMA-IR, ALT and AST (Table 1).

**Table 1** Comparison of Baseline Characteristics and Laboratory-Related Indicators Between T2DM Patients with and without Vitamin D Deficiency

Variable	Non-Vitamin D Deficiency (n = 351)	Vitamin D Deficiency (n = 433)	Statistics	P-value
Gender (male)	245 (68.8%)	246 (56.81%)	13.971	<0.001
Age (years)	60 (53, 67)	56 (46, 64)	-5.984	<0.001
Diabetes course (years)	10 (4, 17)	7 (1, 13)	-5.111	<0.001
History of smoking (yes)	93 (26.5%)	116 (26.79%)	0.009	0.926
History of drinking (yes)	102 (29.06%)	116 (26.79%)	0.498	0.481
SBP (mmHg)	131.15 $\pm$ 17.93	132 (121.5, 145)	-1.744	0.081
DBP (mmHg)	80.09 $\pm$ 11.28	82 (75, 90)	-3.080	0.002
BMI (Kg/m <sup>2</sup> )	25.8 (23.63, 27.73)	26.51 (24.12, 29.01)	-2.962	0.003
HbA1c (%)	8.5 (7.1, 10.2)	9.1 (7.5, 10.7)	-3.254	0.001
FBG (mmol/L)	7.88 (6.08, 10.28)	8.35 (6.39, 11.09)	-1.768	0.077
HOMA-IR	3.07 (1.42, 5.26)	2.9 (1.46, 5.27)	-0.485	0.627
ALT (U/L)	19.2 (14.6, 26.6)	20.6 (14.15, 28.2)	-0.728	0.467
AST (U/L)	20.1 (17.3, 24.3)	19.6 (16.1, 24)	-1.461	0.144
ALB (g/L)	42.32 $\pm$ 3.47	41.6 (39, 44.4)	-2.590	0.01
TC (mmol/L)	4.49 (3.78, 5.21)	4.89 (4.11, 5.67)	-4.662	<0.001
TG (mmol/L)	1.29 (0.91, 1.82)	1.65 (1.14, 2.33)	-5.847	<0.001
HDL-C (mmol/L)	1.1 (0.95, 1.3)	1.04 (0.89, 1.21)	-3.580	<0.001
LDL-C (mmol/L)	2.93 (2.28, 3.48)	3.23 (2.63, 3.76)	-4.824	<0.001
Apo A1	1.21 (1.06, 1.41)	1.14 (0.98, 1.31)	-4.472	<0.001
Apo B	0.81 (0.66, 1.00)	0.94 (0.76, 1.11)	-5.497	<0.001
Apo B/A1	0.69 (0.52, 0.86)	0.80 (0.67, 1.0)	-7.441	<0.001

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo B/A1, apolipoprotein B/apolipoprotein A1.



**Figure 1** Comparison of apo B/A1 between T2DM patients with and without vitamin D deficiency.

**Note:** \*\*\*Denotes significance at a P value of <0.001.

**Abbreviation:** apo B/A1, apolipoprotein B/apolipoprotein A1.

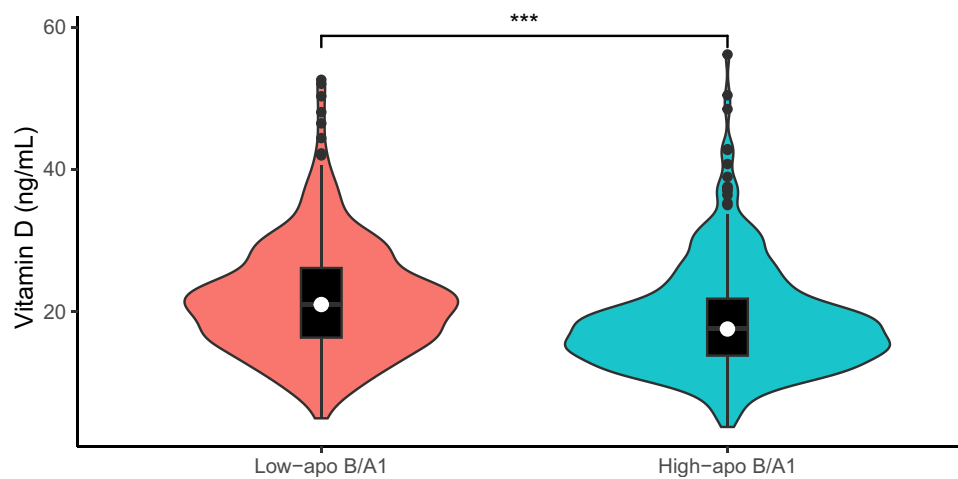
## Comparison of Baseline Characteristics and Laboratory-Related Indicators Between High- apo B/A1 and Low-apo B/A1 Groups

VitD levels were significantly lower in the high-apo B/A1 group than in the low-apo B/A1 group ( $P < 0.001$ ) (Table 2 and Figure 2). Compared with the low-apo B/A1 group, the high-apo B/A1 group had significantly higher levels of DBP, BMI, HbA1c, FBG, HOMA-IR, TC, TG and LDL-C and significantly lower age, disease course and HDL-C level (all

**Table 2** Comparison of Baseline Characteristics and Laboratory-Related Indicators Between High-and Low-apo B/A1 Groups

Variable	Low-apo B/A1 (n = 392)	High-apo B/A1 (n = 392)	Statistics	P-value
Gender (male)	255 (65.05%)	236 (60.20%)	1.967	0.161
Age (years)	60 (52,66.75)	56 (46.25,64)	-4.621	<0.001
Diabetes course (years)	10 (5,16)	7 (1,13)	-6.039	<0.001
History of smoking (yes)	99 (25.26%)	110 (28.06%)	0.789	0.374
History of drinking (yes)	108 (27.55%)	110 (28.06%)	0.025	0.873
SBP (mmHg)	131 (119, 143)	132 (122, 144)	-1.422	0.155
DBP (mmHg)	80.34 ± 10.93	82.57 ± 11.39	-2.803	0.005
BMI (Kg/m <sup>2</sup> )	25.91 (23.65, 28.03)	26.16 (24.18,28.84)	-2.140	0.032
VitD (Ng/mL)	20.95 (16.26, 26.09)	17.5 (13.71, 21.79)	-6.038	<0.001
HbA1c (%)	8.3 (6.9, 9.88)	9.3 (7.73, 10.88)	-5.814	<0.001
FBG (mmol/L)	7.49 (5.92, 10.61)	8.67 (6.61, 10.97)	-3.595	<0.001
HOMA-IR	2.63 (1.40, 4.61)	3.15 (1.54, 5.76)	-1.995	0.046
ALT (U/L)	19.2 (14.33, 26.58)	20.8 (14.5, 28.28)	-1.144	0.253
AST (U/L)	20.1 (16.7, 24)	19.75 (16.6, 24.4)	-0.225	0.822
ALB (g/L)	42.15 (39.8, 44.5)	41.75 (39, 44.5)	-1.256	0.209
TC (mmol/L)	4.18 (3.53, 4.90)	5.17 (4.61, 5.98)	-12.751	<0.001
TG (mmol/L)	1.19 (0.86, 1.79)	1.70 (1.24, 2.40)	-8.323	<0.001
HDL-C (mmol/L)	1.1 (0.95, 1.29)	1.03 (0.88, 1.21)	-4.181	<0.001
LDL-C (mmol/L)	2.62 (2.09, 3.19)	3.48 (3.02, 4.03)	-13.921	<0.001

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; VitD, vitamin D; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.



**Figure 2** Comparison of VitD levels between high- and low-apo B/A1 groups.

**Note:** \*\*\*Denotes significance at a P value of <0.001.

**Abbreviation:** apo B/A1, apolipoprotein B/apolipoprotein A1.

$P < 0.05$ ). No significant difference was detected between the two groups in terms of gender, smoking history, drinking history, SBP, ALT, AST and ALB (Table 2).

### Correlation Between VitD and Various Indicators

Spearman correlation analysis results showed that VitD levels were significantly positively correlated with age ( $r = 0.198$ ), diabetes course ( $r = 0.169$ ), AST ( $r = 0.084$ ), ALB ( $r = 0.145$ ), HDL-C ( $r = 0.150$ ) and apo A1 ( $r = 0.160$ ) in T2DM patients, the difference was statistically significant ( $P < 0.05$ ). Meanwhile, VitD levels were significantly negatively correlated with the apo B/A1 ( $r = -0.238$ ), SBP ( $r = -0.089$ ), DBP ( $r = -0.121$ ), BMI ( $r = -0.145$ ), HbA1c ( $r = -0.124$ ), FBG ( $r = -0.079$ ), TC ( $r = -0.150$ ), TG ( $r = -0.231$ ), LDL-C ( $r = -0.153$ ) and apo B ( $r = -0.140$ ), the difference was statistically significant ( $P < 0.05$ ) (Table 3).

### Correlation Between apo B/A1 and Various Indicators

Spearman correlation analysis results revealed that the apo B/A1 was significantly positively correlated with DBP ( $r = 0.106$ ), BMI ( $r = 0.109$ ), HbA1c ( $r = 0.267$ ), FBG ( $r = 0.164$ ), HOMA-IR ( $r = 0.102$ ), TC ( $r = 0.533$ ), TG ( $r = 0.367$ ) and LDL-C ( $r = 0.597$ ) in T2DM patients, the difference is statistically significant ( $P < 0.05$ ). However, the apo B/A1 was significantly negatively correlated with VitD ( $r = -0.238$ ), age ( $r = -0.195$ ), diabetes course ( $r = -0.253$ ) and HDL-C ( $r = -0.218$ ), the difference is statistically significant ( $P < 0.05$ ) (Table 4).

**Table 3** Correlation Between VitD and Various Indicators

Variable	R-value	P-value
Age (years)	0.198	<0.001
Diabetes course (years)	0.169	<0.001
SBP (mmHg)	-0.089	0.013
DBP (mmHg)	-0.121	0.001
BMI (Kg/m <sup>2</sup> )	-0.145	<0.001
HbA1c (%)	-0.124	0.001
FBG (mmol/L)	-0.079	0.027
HOMA-IR	0.019	0.597

(Continued)

**Table 3** (Continued).

Variable	R-value	P-value
ALT (U/L)	0.02	0.579
AST (U/L)	0.084	0.019
ALB (g/L)	0.145	<0.001
TC (mmol/L)	-0.150	<0.001
TG (mmol/L)	-0.231	<0.001
HDL-C (mmol/L)	0.150	<0.001
LDL-C (mmol/L)	-0.153	<0.001
Apo A1	0.160	<0.001
Apo B	-0.140	<0.001
Apo B/A1	-0.238	<0.001

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo B/A1, apolipoprotein B/apolipoprotein A1.

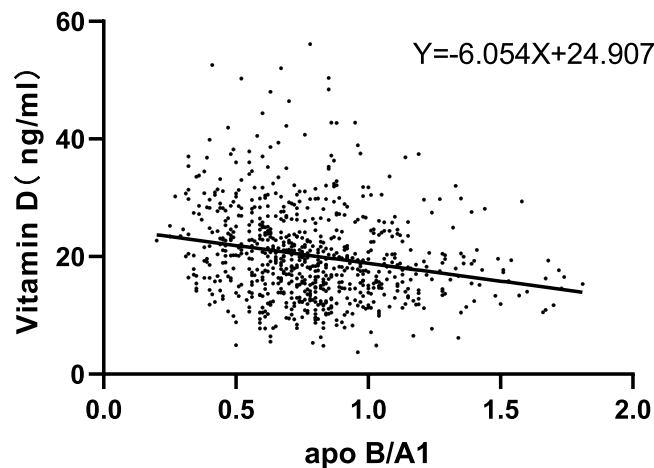
**Table 4** Correlation Between apo B/A1 and Various Indicators

Variable	R-value	P-value
Age (years)	-0.195	<0.001
Diabetes course (years)	-0.253	<0.001
SBP (mmHg)	0.065	0.067
DBP (mmHg)	0.106	0.003
BMI (Kg/m <sup>2</sup> )	0.109	0.002
HbA1c (%)	0.267	<0.001
FBG (mmol/L)	0.164	<0.001
HOMA-IR	0.102	0.004
ALT (U/L)	0.025	0.476
AST (U/L)	-0.030	0.404
ALB (g/L)	-0.069	0.054
TC (mmol/L)	0.533	<0.001
TG (mmol/L)	0.367	<0.001
HDL-C (mmol/L)	-0.218	<0.001
LDL-C (mmol/L)	0.597	<0.001
VitD (Ng/mL)	-0.238	<0.001

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VitD, vitamin D.

## Linear Regression Analysis of apo B/A1 and VitD

A regression model 1 was constructed with VitD as the dependent variable and apo B/A1 as the independent variable. The results showed that the apo B/A1 was significantly negatively correlated with VitD levels in T2DM patients ( $\beta = -0.212$ ,  $P < 0.001$ ,  $R^2 = 0.044$ ) (Figure 3). Variables were screened from the baseline data of patients, and candidate



**Figure 3** Linear regression analysis of apo B/A1 and VitD.

**Abbreviation:** apo B/A1, apolipoprotein B/apolipoprotein A1.

variables with  $P < 0.1$ , including gender, age, disease course, SBP and DBP, were included in the linear regression equation, and a regression model 2 was constructed. The results revealed that the apo B/A1 was significantly negatively correlated with VitD levels in T2DM patients ( $\beta = -0.142$ ,  $P < 0.001$ ,  $R^2 = 0.118$ ). Further laboratory-related indicators with  $P < 0.1$  and non-colinearity with the apo B/A1, including HbA1c, FBG and ALB, were incorporated into the linear regression equation, and a regression model 3 was constructed. The results showed a significant negative correlation between the apo B/A1 and VitD levels in T2DM patients ( $\beta = -0.123$ ,  $P = 0.001$ ,  $R^2 = 0.136$ ) (Table 5).

Model 3 adjusted for gender, age, course of T2DM, SBP, DBP, BMI, HbA1c, FBG and ALB, and the results showed that the regression equation was significant ( $F = 13.319$ ,  $P < 0.001$ ). Among them, apo B/A1 ( $\beta = -0.123$ ,  $P = 0.001$ ), SBP ( $\beta = -0.129$ ,  $P = 0.009$ ), BMI ( $\beta = -0.093$ ,  $P = 0.007$ ) were significantly negatively correlated with VitD levels in patients with T2DM, whereas age ( $\beta = 0.249$ ,  $P < 0.001$ ) and ALB ( $\beta = 0.149$ ,  $P < 0.001$ ) were significantly positively correlated with T2DM patients. Compared with male patients, female patients had low VitD levels ( $\beta = -0.151$ ,  $P < 0.001$ ). These variables explain the variation of 13.6% in VitD (Table 6).

**Table 5** Linear Regression Analysis of apo B/A1 and VitD

	B	$\beta$	t	P	F-value	Adjust $R^2$
Model 1	-6.054	-0.212	-6.059	<0.001	36.712	0.044
Model 2	-4.063	-0.142	-4.028	<0.001	15.976	0.118
Model 3	-3.531	-0.123	-3.442	0.001	13.319	0.136

**Table 6** Linear Regression Analysis of Multiple Factors and VitD

	B	$\beta$	t	P	F-value	Adjust $R^2$
Apo B/A1	-3.531	-0.123	-3.442	0.001	13.319	0.136
Female	-2.429	-0.151	-4.419	<0.001		
Age	0.170	0.249	5.882	<0.001		
Diabetes course	0.010	0.010	0.257	0.797		
SBP	-0.055	-0.129	-2.610	0.009		
DBP	0.032	0.046	0.943	0.346		
BMI	-0.202	-0.093	-2.683	0.007		
HbA1c	0.008	0.002	0.054	0.957		
FBG	0.023	0.010	0.251	0.802		
ALB	0.308	0.149	4.128	<0.001		

**Abbreviations:** Apo B/A1, apolipoprotein B/apolipoprotein A1; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; ALB, albumin.

## Binary Logistic Regression Analysis of VitD Deficiency in Patients with T2DM

With VitD as the dependent variable, the independent variables were screened in order, and candidate variables with  $P < 0.1$ , including apo B/A1, gender, age, disease course, SBP, DBP, BMI, HbA1c, FBG, ALB, TC, TG, HDL-C and LDL-C, were included in the binary logistic regression equation. The Hosmer-Lemeshow test indicates the goodness of fit for the logistic regression model ( $X^2 = 6.384$ ,  $P = 0.604$ ). Regression analysis revealed that gender, age, SBP, ALB and apo B/A1 were independent risk factors for VitD deficiency in T2DM patients. For each additional unit of apo B/A1, T2DM patients were 2.027 times more likely to have VitD deficiency (Table 7).

## Nonlinear Relationship Between VitD Deficiency and apo B/A1 in T2DM Patients

After adjusting for gender, age, SBP and ALB confounding factors, we analyzed the nonlinear relationship between VitD deficiency and apo B/A1 in T2DM patients by restricted cubic spline, and a significant linear relationship was found between the two ( $P$  for trend  $< 0.0001$ ,  $P$  for nonlinear = 0.0896). The incidence of VitD deficiency increased significantly at apo B/A1  $> 0.763$ , and the incidence of VitD deficiency increased linearly with an increase in the apo B/A1 (Figure 4). After gender stratification, the results showed that the apo B/A1 was more susceptible to VitD deficiency in female patients (Figure 5).

## Diagnostic Value of apo B/A1 in VitD Deficiency Patients with T2DM

The ROC curve analysis showed that when using apo B/A1 to evaluate VitD deficiency, the area under the curve is 0.654, a sensitivity of 66.3% and a specificity of 59.8% (Table 8 and Figure 6).

## Discussion

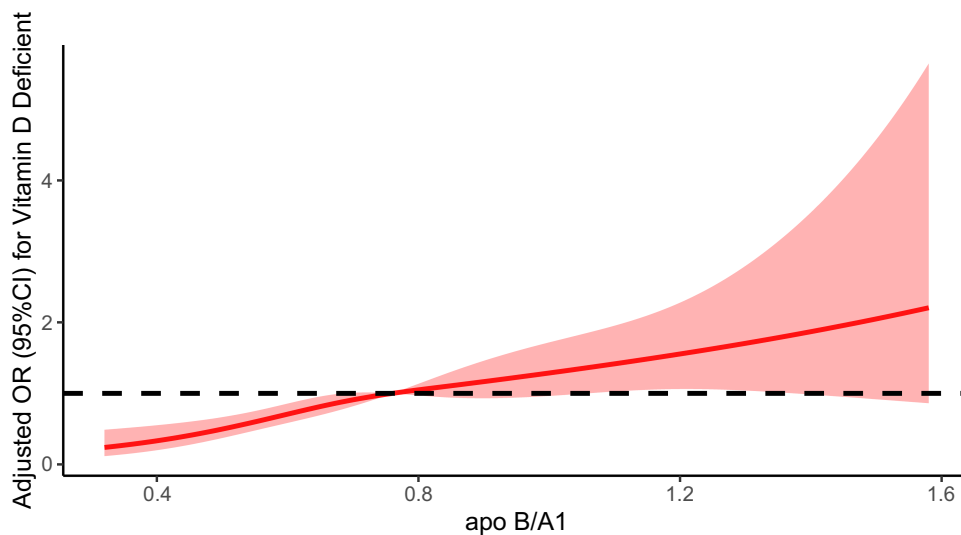
VitD has always been regarded as an important bone health marker, mainly regulating the metabolism of bone minerals in the body such as calcium and phosphorus. The three sources of VitD are ultraviolet rays, diet and supplements. VitD, obtained from the conversion of 7-dehydrocholesterol in the skin by solar ultraviolet B radiation, can meet 90% of the needs of the human body.<sup>15</sup> The continuous in-depth research on VitD has deepened our understanding of VitD deficiency. Several clinical studies have confirmed that VitD levels are negatively correlated with the incidence of cancer, hypertension, CVD and diabetes.<sup>16–21</sup> Michael et al found that VitD can slow down the occurrence of diabetes by maintaining the protein kinase signaling pathway activated by Wnt/ $\beta$ -catenin and filamentogen to inhibit the

**Table 7** Binary Logistic Regression Model

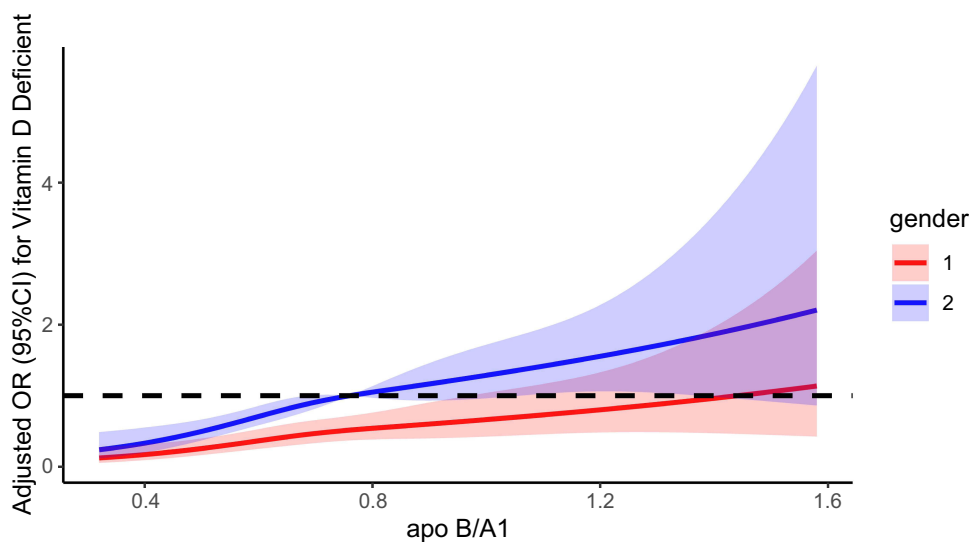
	B	SE	Wals	P	OR	95% CI
Gender	-0.638	0.174	13.527	<0.001	0.528	0.376–0.742
Age	-0.049	0.009	27.647	<0.001	0.952	0.935–0.970
SBP	0.014	0.006	4.769	0.029	1.014	1.001–1.027
ALB	-0.073	0.025	8.865	0.003	0.930	0.886–0.975
Apo B/A1	1.107	0.479	5.350	0.021	3.027	1.184–7.736
Diabetes course	-0.009	0.012	0.607	0.436	0.991	0.969–1.014
DBP	-0.010	0.010	0.849	0.357	0.990	0.971–1.011
BMI	0.022	0.024	0.841	0.359	1.022	0.975–1.071
HbA1c	0.029	0.043	0.474	0.491	1.030	0.947–1.120
FBG	-0.019	0.028	0.427	0.513	0.982	0.928–1.038
TC	0.047	0.355	0.018	0.895	1.048	0.523–2.100
TG	0.116	0.093	1.546	0.214	1.123	0.935–1.349
HDL-C	-0.515	0.607	0.719	0.396	0.598	0.182–1.964
LDL-C	0.110	0.389	0.080	0.777	1.117	0.521–2.392

**Abbreviations:** SBP, systolic blood pressure; ALB, albumin; apo B/A1, apolipoprotein B/apolipoprotein A1; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.





**Figure 4** Nonlinear relationship between vitamin D deficiency and apo B/A1 in T2DM patients.  
**Abbreviation:** apo B/A1, apolipoprotein B/apolipoprotein A1.



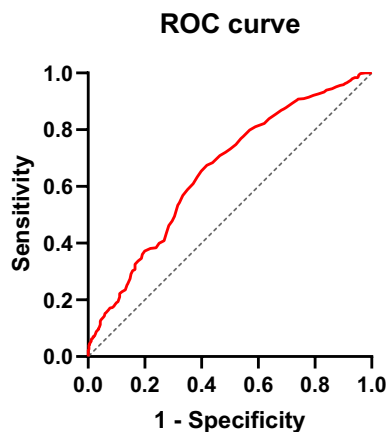
**Figure 5** Nonlinear relationship between vitamin D deficiency and apo B/A1 after gender stratification in T2DM patients.  
**Note:** 1 for male and 2 for female.  
**Abbreviation:** apo B/A1, apolipoprotein B/apolipoprotein A1.

differentiation of fat cells, upregulating the insulin receptor to maintain the insulin signaling pathway, reducing the expression of mitochondrial uncoupling protein 2 (UCP2) to prevent apoptosis of islet beta cells, regulating leptin formation and reducing inflammatory reactions.<sup>21</sup> However, the current study found that VitD deficiency occurred in over 60% of T2DM patients. VitD deficiency is associated with microvascular and macrovascular complications, abnormal blood pressure and blood lipids, increased risk of obesity, neuro-oxidative damage, musculoskeletal-related

**Table 8** Diagnostic Value of apo B/A1 in Vitamin D Deficiency Patients with T2DM

	AUC 95% CI	P-value	Cutoff	Sensitivity (%)	Specificity (%)
Apo B/A1	0.654 (0.616,0.693)	<0.001	0.261	66.3%	59.8%

**Abbreviation:** Apo B/A1, apolipoprotein B/apolipoprotein A1.



**Figure 6** ROC curve of apo B/A1.

complications and adverse mental health conditions, affecting the prognosis of T2DM patients.<sup>22</sup> Monica et al found that VitD deficiency was related to the metabolic characteristics of atherosclerosis and enhanced pro-inflammatory state but not to a glucose steady state.<sup>23</sup> Wan et al pointed out that compared with T2DM patients with VitD deficiency, the CVD risk ratio of T2DM patients without VitD deficiency was 0.75 (95% CI: 0.64, 0.88).<sup>7</sup> Said et al also found through animal experiments that the serum levels of asymmetric dimethylarginine, aortic malondialdehyde and endothelin 1 (ET-1) and induced nitric oxide synthase (iNOS) activity decreased after oral administration of VitD in diabetic rats, whereas aortic superoxide dismutase and structural nitric oxide synthase activities and nitric oxide level increased. Oral VitD can prevent diabetic vascular complications associated with vascular endothelial dysfunction by reducing oxidative stress.<sup>24</sup> Therefore, the natural pharmacological effect of VitD makes the clinical monitoring of VitD particularly important. Maintaining sufficient VitD levels in T2DM patients is of great significance to prevent the occurrence of diabetes complications, reduce unconscious vascular events and improve the prognosis and quality of life of patients with T2DM.

Accumulating evidence has demonstrated that although apolipoproteins have often been ignored in the biochemical detection of blood lipids, their contribution to the pathogenesis of early atherosclerosis may exceed our imagination.<sup>25–28</sup> As a communicator of lipoprotein, apolipoprotein can mediate the activation of vascular endothelial cells (ECs), and the activated vascular ECs produce interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and other cytokines. These factors stimulate the recruitment of monocytes and adhesion to ECs, prompting monocytes to pass through endothelial tissues and transform into macrophages.<sup>25</sup> Apo B in apolipoprotein acts as a ligand-mediated LDL to bind to the LDL receptor (LDLR) to promote cholesterol uptake in peripheral tissues. Meanwhile, apo B causes excessive LDL to accumulate under the vascular endothelial by interacting with proteoglycan in the extracellular matrix, initiating the formation of atherosclerosis.<sup>26</sup> A large prospective US cohort study showed that only apo B was associated with myocardial infarction in the primary and secondary prevention cohorts of coronary heart disease, and apo B may be the only driver of the risk of blood lipid-related myocardial infarction.<sup>27</sup> Contrarily, as the main protein component of HDL, apo A1 not only participates in the reverse transport of cholesterol but also has anti-inflammatory and immunomodulatory effects.<sup>28,29</sup> In addition, animal studies on rats demonstrated that apo A1 can reduce the inflammatory response of pregnant rats and improve insulin sensitivity of adipose tissue and skeletal muscle, making it a potential target for reducing the occurrence of gestational diabetes.<sup>30</sup> Previous studies found that apo B/A1 was independently correlated with the incidence of T2DM, coronary heart disease, ischemic stroke, metabolic-associated fatty liver, cancer, etc., with a better risk prediction ability of the disease than the conventional clinical blood lipid index.<sup>31–35</sup> Apo B/A1 has gradually shown its unique advantages and has broad development prospects in clinical practice.

Given that VitD and apo B/A1 are risk factors for cardiovascular complications of diabetes, the present study evaluated the relationship between VitD levels and apo B/A1 in T2DM patients. It was found that apo B/A1 was

significantly higher in the VitD deficiency group than in the non-VitD deficiency group, and VitD levels were significantly lower in the high-apo B/A1 group than in the low-apo B/A1 group. Meanwhile, VitD levels in patients with T2DM were significantly negatively associated with apo B/A1. It has been previously proven that VitD deficiency is associated with dyslipidemia. Some studies reported that VitD levels were negatively correlated with TC, TG, LDL-C, apo B, and apo B/A1, and positively correlated with HDL-C and apo A1,<sup>36,37</sup> consistent with the results of the present study. Our further analysis of the T2DM population showed that after correcting multiple mixed factors, the apo B/A1 was still significantly negatively correlated with VitD levels. Apo B/A1 was an independent risk factor for VitD deficiency in T2DM patients. When the apo B/A1 was  $>0.763$ , the incidence of VitD deficiency increased significantly. After gender stratification, it was found that apo B/A1 was more susceptible to VitD deficiency in female patients, perhaps because male patients may spend more time outdoors, which may slightly reduce the incidence of VitD deficiency compared with their female counterparts. Therefore, special attention should be paid to monitoring the ratio of apo B/A1 among female T2DM patients. Moreover, the accuracy of using apo B/A1 to evaluate VitD deficiency was 65.4%, further highlighting the close relationship between VitD deficiency and the apo B/A1. Taken together, our findings suggest that the increase in apo B/A1 levels may be one of the pathological bases for high cardiovascular risk in patients with T2DM combined with VitD deficiency, which warrants further investigation.

Nonetheless, this study has several limitations. Firstly, due to the retrospective nature of this study, we could not determine the causal relationship between VitD levels and the apo B/A1. Secondly, since VitD levels are greatly affected by exposure to ultraviolet during outdoor activities, the subjects' movements and whether they were treated with lipid-lowering drugs have not been considered in this study, which requires further exploration. Finally, since this is a single-center study, the results cannot be generalized to other populations. Therefore, the correlation between VitD levels and apo B/A1 in T2DM patients should be validated in large-scale, multicenter clinical trials.

## Conclusion

In summary, this study demonstrated that apo B/A1 was significantly negatively associated with VitD levels in patients with T2DM, and apo B/A1 was an independent risk factor for VitD deficiency in patients with T2DM. The increase in apo B/A1 levels may be one of the pathological bases for high cardiovascular risk in patients with T2DM combined with VitD deficiency. Therefore, focusing on the apo B/A1 levels can effectively monitor the occurrence of VitD deficiency in T2DM patients.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabet Res Clin Pract.* 2018;138:271–281. PMID: 29496507. doi:10.1016/j.diabres.2018.02.023
2. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J Epidemiol Glob Health.* 2020;10(1):107–111. PMID: 32175717; PMCID: PMC7310804. doi:10.2991/jeqh.k.191028.001
3. Zhao H, Zheng C, Zhang M, Chen S. The relationship between vitamin D status and islet function in patients with type 2 diabetes mellitus. *BMC Endocr Disord.* 2021;21(1):203. PMID: 34663294; PMCID: PMC8522231. doi:10.1186/s12902-021-00862-y
4. Hussain Gilani SY, Bibi S, Siddiqui A, Ali Shah SR, Akram F, Rehman MU. Obesity and diabetes as determinants of vitamin D deficiency. *J Ayub Med Coll Abbottabad.* 2019;31(3):432–435. PMID: 31535522.
5. Pittas AG, Kawahara T, Jorde R, et al. Vitamin D and risk for type 2 diabetes in people with prediabetes: a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. *Ann Intern Med.* 2023;176(3):355–363. PMID: 36745886. doi:10.7326/M22-3018
6. Renke G, Starling-Soares B, Baesso T, Petronio R, Aguiar D, Paes R. Effects of vitamin D on cardiovascular risk and oxidative stress. *Nutrients.* 2023;15(3):769. PMID: 36771474; PMCID: PMC9920542. doi:10.3390/nu15030769
7. Wan Z, Geng T, Li R, et al. Vitamin D status, genetic factors, and risks of cardiovascular disease among individuals with type 2 diabetes: a prospective study. *Am J Clin Nutr.* 2022;116(5):1389–1399. PMID: 35771998. doi:10.1093/ajcn/nqac183
8. Khatana C, Saini NK, Chakrabarti S, et al. Mechanistic Insights into the oxidized low-density lipoprotein-induced atherosclerosis. *Oxid Med Cell Longev.* 2020;2020:5245308. PMID: 33014272; PMCID: PMC7512065. doi:10.1155/2020/5245308
9. Wolkowicz P, White CR, Anantharamaiah GM. Apolipoprotein mimetic peptides: an emerging therapy against diabetic inflammation and dyslipidemia. *Biomolecules.* 2021;11(5):627. PMID: 33922449; PMCID: PMC8146922. doi:10.3390/biom11050627
10. Kim MK, Ahn CW, Kang S, et al. Association between Apolipoprotein B/Apolipoprotein A-1 and arterial stiffness in metabolic syndrome. *Clin Chim Acta.* 2014;437:115–119. PMID: 25025299. doi:10.1016/j.cca.2014.07.005

11. Galal H, Samir A, Shehata M. Assessment of apolipoprotein B/apolipoprotein A-I ratio in non-ST segment elevation acute coronary syndrome patients. *Egypt Heart J.* 2020;72(1):27. PMID: 32449038; PMCID: PMC7246270. doi:10.1186/s43044-020-00057-1
12. Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L; European Diabetes Working Party for Older People. European diabetes working party for older people 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab.* 2011;37(Suppl 3):S27–S38. PMID: 22183418. doi:10.1016/S1262-3636(11)70962-4
13. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(7):1911–1930. Erratum in: *J Clin Endocrinol Metab.* 2011;96(12):3908. PMID: 21646368. doi:10.1210/jc.2011-0385
14. Gayoso-Diz P, Otero-González A, Rodríguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord.* 2013;13(1):47. PMID: 24131857; PMCID: PMC4016563. doi:10.1186/1472-6823-13-47
15. Aguilar-Shea AL. Vitamin D, the natural way. *Clin Nutr ESPEN.* 2021;41:10–12. PMID: 33487250. doi:10.1016/j.clnesp.2020.12.001
16. Zhang X, Fang YJ, Feng XL, et al. Interactions between vitamin D and calcium intake, vitamin D receptor genetic polymorphisms, and colorectal cancer risk. *Dig Dis Sci.* 2021;66(6):1895–1905. PMID: 32627088. doi:10.1007/s10620-020-06455-4
17. Chakraborty M, Arora M, Ramteke A, et al. FokI polymorphism of vitamin D receptor gene and deficiency of serum vitamin D increases the risk of breast cancer in north Indian women. *Endocrine.* 2023;81(1):168–174. PMID: 36854857. doi:10.1007/s12020-023-03334-6
18. Luchi WM, Crajoinas RO, Martins FL, et al. High blood pressure induced by vitamin D deficiency is associated with renal overexpression and hyperphosphorylation of Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter type 2. *J Hypertens.* 2021;39(5):880–891. PMID: 33337598. doi:10.1097/HJH.0000000000002745
19. Agarwal P, Agarwal Y, Hameed M. Recent advances in association between vitamin D levels and cardiovascular disorders. *Curr Hypertens Rep.* 2023;25(8):185–209. PMID: 37256476. doi:10.1007/s11906-023-01246-4
20. Niroomand M, Fotouhi A, Irannejad N, Hosseinpanah F. Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with pre-diabetes? A double-blind randomized clinical trial. *Diabet Res Clin Pract.* 2019;148:1–9. PMID: 30583032. doi:10.1016/j.diabres.2018.12.008
21. Berridge MJ. Vitamin D deficiency and diabetes. *Biochem J.* 2017;474(8):1321–1332. PMID: 28341729. doi:10.1042/BCJ20170042
22. Md Isa Z, Amsah N, Ahmad N. The impact of vitamin D deficiency and insufficiency on the outcome of type 2 diabetes mellitus patients: a systematic review. *Nutrients.* 2023;15(10):2310. PMID: 37242192; PMCID: PMC10223393. doi:10.3390/nu15102310
23. Verdoia M, Nardin M, Rolla R, et al; Novara Atherosclerosis Study Group (NAS). Association of lower vitamin D levels with inflammation and leucocytes parameters in patients with and without diabetes mellitus undergoing coronary angiography. *Eur J Clin Invest.* 2021;51(4):e13439. PMID: 33112413. doi:10.1111/eci.13439
24. Said MA. Vitamin D attenuates endothelial dysfunction in streptozotocin induced diabetic rats by reducing oxidative stress. *Arch Physiol Biochem.* 2022;128(4):959–963. PMID: 32233807. doi:10.1080/13813455.2020.1741645
25. Li Y, Luo X, Hua Z, et al. Apolipoproteins as potential communicators play an essential role in the pathogenesis and treatment of early atherosclerosis. *Int J Biol Sci.* 2023;19(14):4493–4510. PMID: 37781031; PMCID: PMC10535700. doi:10.7150/ijbs.86475
26. Wilkins JT, Gidding SS, Robinson JG. Can atherosclerosis be cured?. *Curr Opin Lipidol.* 2019;30(6):477–484. PMID: 31592794; PMCID: PMC7375463. doi:10.1097/MOL.0000000000000644
27. Marston NA, Giugliano RP, Melloni GEM, et al. Association of apolipoprotein B-containing lipoproteins and risk of myocardial infarction in individuals with and without Atherosclerosis: distinguishing between particle concentration, type, and content. *JAMA Cardiol.* 2022;7(3):250–256. PMID: 34773460; PMCID: PMC8590731. doi:10.1001/jamacardio.2021.5083
28. Georgila K, Vyrla D, Drakos E. Apolipoprotein A-I (ApoA-I), immunity, inflammation and cancer. *Cancers.* 2019;11(8):1097. PMID: 31374929; PMCID: PMC6721368. doi:10.3390/cancers11081097
29. Olofsson SO, Wiklund O, Borén J. Apolipoproteins A-I and B: biosynthesis, role in the development of atherosclerosis and targets for intervention against cardiovascular disease. *Vasc Health Risk Manag.* 2007;3(4):491–502. PMID: 17969379; PMCID: PMC2291326.
30. Wu BJ, Sun Y, Ong KL, et al. Apolipoprotein A-I protects against pregnancy-induced insulin resistance in rats. *Arterioscler Thromb Vasc Biol.* 2019;39(6):1160–1171. PMID: 31018664. doi:10.1161/ATVBAHA.118.312282
31. Gao L, Zhang Y, Wang X, Dong H. Association of apolipoproteins A1 and B with type 2 diabetes and fasting blood glucose: a cross-sectional study. *BMC Endocr Disord.* 2021;21(1):59. PMID: 33794863; PMCID: PMC8017773. doi:10.1186/s12902-021-00726-5
32. Tian M, Li R, Shan Z, Wang DW, Jiang J, Cui G. Comparison of apolipoprotein B/A1 ratio, Framingham risk score and TC/HDL-c for predicting clinical outcomes in patients undergoing percutaneous coronary intervention. *Lipids Health Dis.* 2019;18(1):202. PMID: 31744496; PMCID: PMC6864950. doi:10.1186/s12944-019-1144-y
33. Chou YC, Chan PC, Yang T, You SL, Bai CH, Sun CA. Apolipoprotein B Level and the Apolipoprotein B/Apolipoprotein A-I ratio as a Harbinger of Ischemic stroke: a prospective observation in Taiwan. *Cerebrovasc Dis.* 2020;49(5):487–494. PMID: 32950994. doi:10.1159/000509452
34. Zhao Y. Association between apolipoprotein B/A1 and the risk of metabolic dysfunction associated fatty liver disease according to different lipid profiles in a Chinese population: a cross-sectional study. *Clin Chim Acta.* 2022;534:138–145. PMID: 35905837. doi:10.1016/j.cca.2022.07.014
35. Zhang F, Xie Y, Ma X, et al. Preoperative apolipoprotein B/A1 ratio is an independent prognostic factor in metastatic renal cell carcinoma. *Urol Oncol.* 2019;37(3):184.e9–184.e17. PMID: 30509867. doi:10.1016/j.urolonc.2018.11.010
36. Elmi C, Fan MM, Le M, Cheng G, Khalighi K. Association of serum 25-Hydroxy Vitamin D level with lipid, lipoprotein, and apolipoprotein level. *J Community Hosp Intern Med Perspect.* 2021;11(6):812–816. PMID: 34804396; PMCID: PMC8604514. doi:10.1080/20009666.2021.1968571
37. Lee Y, Yoon JW, Kim YA, Choi HJ, Yoon BW, Seo JH. A genome-wide association study of genetic variants of apolipoprotein A1 levels and their association with vitamin D in Korean cohorts. *Genes.* 2022;13(9):1553. PMID: 36140721; PMCID: PMC9498618. doi:10.3390/genes13091553

Diabetes, Metabolic Syndrome and Obesity

Dovepress

### Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal>