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The ApoB/A-1 Ratio is Independently Associated with Subclinical Arteriosclerosis and Arterial Stiffness in Type 2 Diabetes Patients

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Keywords:

Type 2 diabetes; ApoB/A-1 ratio; carotid atherosclerosis; ABI; baPWVa

Abbreviations:

CAD: Cardiovascular Disease; T2D: Type 2 Diabetes, baPWV: brachial-ankle Pulse Wave Velocity; W: Waist Circumference; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ApoB: apolipoprotein B; ApoA1: Apolipoprotein A1; ApoB/A1: ApoB/ApoA-1 Ratio; HbA1c: glycosylated hemoglobin A1c; VLDL: Very Low-Density Lipoprotein; sd-LDL: small dense Low-Density Lipoprotein; TC: Total Cholesterol; TG: Triglyceride; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; ABI: Ankle Brachial Index; AIP: Atherogenic Index of Plasma; ANOVA: One-Way Analysis Of Variance; C-pep0h: C-peptide at 0 min; C-pep2h: C-peptide at 2 h; G0: glucose at 0 min; G2h: glucose at 2 h; DPP-4Is: Dipeptidyl Peptidase-4 inhibitors; SGL-2Is: Sodium Glucose Cotransporter-2 Inhibitors

1. Abstract

1.1. Background: The ApoB/ApoA-1 (ApoB/A1) ratio is a predictor of atherosclerotic vascular disease. In this study, we aimed to explore whether ApoB/A1 ratio is related to arteriosclerosis parameters, including subclinical atherosclerosis and arterial stiffness, in type 2 diabetic patients.

1.2. Methods: In this cross-sectional study, 256 type 2 diabetic (T2D) patients, including 152 patients with carotid atherosclerosis, were recruited. Traditional fasting lipid profiles and ApoB and ApoA-1 levels were measured. Arterial stiffness was assessed by brachial ankle pulse wave velocity (baPWV), and subclinical arteriosclerosis was assessed by Ankle Brachial Index (ABI) and carotid atherosclerosis.

1.3. Results: The ApoB/A1 ratio in T2D patients with no carotid atherosclerosis was significantly higher than that in T2D patients with carotid atherosclerosis ($p < 0.05$). The arterial stiffness parameters baPWV and ABI were significantly lower among T2D patients with no carotid atherosclerosis (all $p < 0.05$). Moreover, the baPWV and ABI were significantly decreased across the ApoB/A1 ratio quartiles (all p for trend < 0.05). Additionally, baPWV and ABI were both inversely related to ApoB/A1 ratio ($r = –0.223$ and $–0.224$, respectively, $p < 0.001$). Using univariate logistic regression analyses, ApoB/A1 ratio, sex, age, duration, baPWV, HbA1c, and statin use were found to be independent contributors to carotid atherosclerosis, and the corresponding odds ratios (95% confidence intervals) were 0.242 (0.090–0.646), 0.326 (0.178–0.599), 2.730 (1.619–4.603), 6.833 (3.024–15.44), 1.204 (1.103-1.314), 0.842 (0.745-0.953), and 2.704 (1.228, 5.954), respectively. After adjusting for clinical covariates by multiple logistic regression analyses, the corresponding odds ratio (OR) for the ApoB/A1 ratio of carotid atherosclerosis was 0.216 (0.062-0.759).

1.4. Conclusions: The ApoB/A1 ratio was independently and inversely associated with baPWV and ABI and independently contributed to carotid atherosclerosis

2. Background

Type 2 Diabetes (T2D) patients with arteriosclerosis have a high risk of cardiovascular disease (CAD) [1]. Traditional atherogenic dyslipidemia is characterized by high Triglycerides (TGs), low serum High-Density Lipoprotein Cholesterol (HDL-C) and elevated or normal low-density lipoprotein cholesterol (LDL-C) [2]. However, there is growing interest in the fact that serum apolipoproteins, which are important proteins attached to lipoprotein, are better predictors of CAD [3-5]. Apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1) are two of the most well-investigated predictors. ApoB is attached to the surface of proatherogenic lipoproteins, including Very Low-Density Lipoprotein (VLDL), small dense low-density lipoprotein (sd-LDL) and LDL-C [6,7]. ApoA1 is attached to the surface of the antiatherogenic lipoprotein HDL-C. Thus, the ApoB/ApoA-1 ratio (ApoB/A1) is considered to be an ideal predictor of cardiovascular risk [8,9].

The Ankle Brachial Index (ABI) [10], carotid atherosclerosis [11] and brachial ankle Pulse Wave Velocity (baPWV) [12,13] have been widely developed as simple, noninvasive surrogate measures to evaluate subclinical arteriosclerosis and arterial stiffness. Moreover, atherosis and sclerosis, a structural process and a function process, respectively, are two steps in the development of atherosclerosis [14]. The report suggested that ABI and carotid atherosclerosis participate in the atherosis process, while baPWV participates in the sclerosis process [15]. Although many clinical and basic studies have suggested that ABI, carotid atherosclerosis and baPWV are independent predictors of CAD and are related to the incidence and mortality of CAD [13,16,17], there are few reports on the relationship between these parameters and atherogenic dyslipidemia, especially the ApoB/A1. Previous studies found that ApoB/A1 ratio may be an indicator in predicting T2D [18] and that this ratio was obviously related to carotid atherosclerosis in T2D patients with normal LDL-C levels [11]. However, when taking arteriosclerosis risk factors into account, the association of ApoB/A1 with carotid atherosclerosis and arterial stiffness has not been adequately explored.

Therefore, in the present study, we explored whether ApoB/A1 ratio was related to arteriosclerosis parameters, including subclinical atherosclerosis assessed by ABI and carotid atherosclerosis and arterial stiffness assessed by baPWV in T2D patients.

3. Methods

3.1. Study Subjects

In this cross-sectional study, 256 T2D patients (females, 99, males, 157) who were admitted as inpatients and followed up in the Department of Endocrinology, the Affiliated Zhangjiagang Hospital of Soochow University, were recruited. Patients between 20 and 73 years old with a diagnosis of type 2 diabetes [19] and who underwent baPWV, ABI and carotid B-ultrasonography were enrolled to participate. A well-trained examiner collected the information of the patients via their clinal records, including sex, age, sex, duration, waist circumference, blood pressure, body mass index (BMI: weight (kg)/height (m) squared), history of cardiovascular events, dyslipidemia [20], hypertension [17], medical history (statin use), antidiabetic treatment (lifestyle alone, insulin treatment, insulin secretagogues, insulin sensitizers, metformin, glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4Is), and sodium-glucose cotransporter-2 inhibitors (SGL-2Is)). These patients were excluded if they had a history of CAD, abnormal liver function, severe renal disease, previous tumor, or acute diabetic complications (diabetic ketoacidosis). Written informed consent was waived in this retrospective study, and the study was approved by the Ethics Committee of Affiliated Zhangjiagang Hospital of Soochow University.

3.2. Measurement of Clinical Variables, baPWV, ABI, and Carotid Atherosclerosis

Overnight fasting blood samples were collected, and the serum was separated. Sera were stored at -70°C. High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), Triglyceride (TG), Total Cholesterol (TC), Apolipoprotein B (ApoB), and apolipoprotein A1 (ApoA1) were measured with an automated biochemical instrument (Model 7600, Hitachi). Glycated hemoglobin (HbA1c) and blood glucose concentrations were determined via standard laboratory procedures [21, 22]. After a minimum 5 min rest, the brachial-ankle pulse wave velocity (baPWV) and ankle brachial index (ABI) were calculated via a noninvasive vascular screening device (BP-203RPE III device, Omron Healthcare, Kyoto, Japan). Both carotid arteries of all subjects were scanned using high-resolution mode B ultrasonography (SonoAce 9900, Medison, Korea) with an electrical linear array transducer (7.5 MHz) by physicians. Carotid atherosclerosis was defined as carotid plaque, which was considered a protrusion into the arterial lumen that was 100% thicker than the nearest area [23].

3.3. Statistical Analyses

Clinical variables were calculated for all subjects and across the quartiles of the ApoB/A1. The mean ± standard deviation, median and interquartile range, and frequency (percentage) are used to present normally distributed data, skewed continuous data and categorical data, respectively. One-way analysis of variance (ANOVA) or the Mann–Whitney U test was used to explore the differences in continuous variables, and the chi square test was used to explore the differences in categorical variables between groups. The correlations of ApoB/A1 with baPWV, ABI and other clinical variables were analyzed by Spearman's bivariate correlation analysis. Considering that antidiabetic treatment and statins may affect the values of ApoB/A1, two partial correlation analyses were used to analyze the associations of the ApoB/A1 with baPWV and ABI, adjusting for antidiabetic treatment and statins. Finally, univariate and multivariate logistic regression analyses were conducted to analyze the impact of ApoB/A1 and other factors on carotid

atherosclerosis. SPSS 25.0 (Inc., Chicago, IL) statistical software was used, and $p < 0.05$ was considered significant.

4. Results

4.1. Baseline Characteristics of Patients

The general and biochemical characteristics of all T2D patients and those with or without carotid atherosclerosis are shown in Table 1. The T2D patients with carotid atherosclerosis were older, were less likely to be female, had a higher waist circumference, had a longer disease duration and had higher Systolic Blood Pressure (SBP). The proportions of patients with hypertension and statin use were significantly higher in the carotid atherosclerosis group. Furthermore, the ABI and ba-PWV were also increased. Interestingly, HbA1c and ApoB/A1 ratio (Figure 1) were decreased significantly in the carotid atherosclerosis group, while ApoA-1 was increased. There was no remarkable difference in HOMA-IR, TG, TC, HDL-C, LDL-C, AIP, or ApoB between the two groups.

The characteristics of the four subgroups according to ApoB/A1 quartiles are shown in Table 2. From the first quartile to the fourth quartile of ApoB/A1, the age, diabetes duration, HDL-C, ApoA-1, ABI, and ba-PWV levels decreased significantly (all p for trend < 0.05). While BMI, C-peptide at 2 h (C-pep2h) levels, HbA1c, TC, LDL-C and ApoB significantly increased across the quartiles (all p for trend < 0.05).

4.2. Relationship between ApoB/A1 and baPWV and ABI

The correlation of ApoB/A1 with baPWV and ABI in T2D patients was assessed by Spearman's bivariate correlation analysis. As shown in Figure 2, ApoB/A1 was negatively associated with baPWV and ABI ($r = -0.223$, $p < 0.001$; $r = -0.224$, $p < 0.001$, respectively). Moreover, the correlations were still significant even after adjustment for antidiabetic treatment ($r = -0.193$, $p = 0.002$; $r = -0.191$, $p = 0.002$, respectively) and statins ($r = -0.212$, $p < 0.001$; $r = -0.223$, $p < 0.001$, respectively). Additionally, ApoB/A1 was negatively related to diabetes duration and HDL-C and was positively related to HbA1c, TC, and LDL-C (Figure 3, all $p < 0.05$).

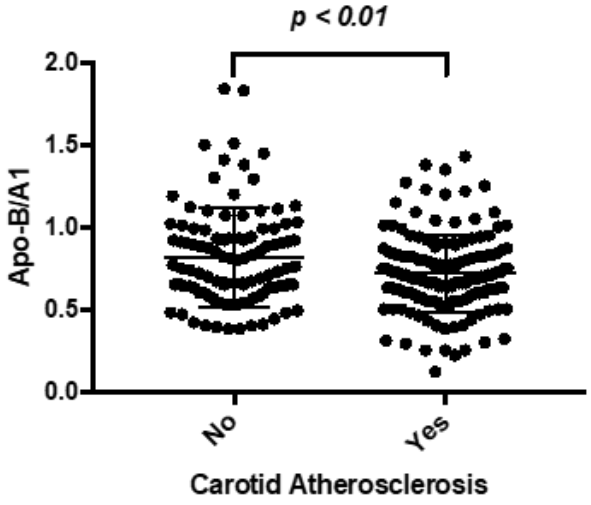

Figure 1: Comparison of Apo-B/A1 ratio between the carotid atherosclerosis groups

Table 1: Characteristics of the study participants based on the prevalence of carotid atherosclerosis.

Variable	Total	Carotid Atherosclerosis		$t/Z/x^2$ value	*p* value
		No	Yes		
n	256	104	152		
Female n (%)	99(38.7)	51(49.0)	48(31.6)	7.04	<0.01**
Age (years)	53.36±9.97	48.74±11.10	56.78±7.30	-6.57	<0.01**
BMI (kg/m^2)	25.32±3.34	24.98±3.47	25.55±3.23	-1.36	0.18
W (cm)	91.45±9.45	89.59±9.38	92.73±9.31	-2.66	<0.01**
Duration(months)	84.89(24.0-120.0)	58.13(6.0-99.0)	103.31(60.0-133.0)	-5.65	<0.01**
SBP (mmHg)	128.46±17.02	125.58±16.25	130.44±17.30	-2.28	<0.05*
DBP (mmHg)	76.63±10.13	77.13±10.65	76.29±9.77	0.66	0.51
Antidiabetic treatment					
Lifestyle alone, n (%)	4(1.6)	1(1.0)	3(2.0)	0.42	0.52

Insulin treatments, n (%)	191(74.6)	74(71.2)	117(77.0)	0.8	0.37
Insulin-secretagogues, n (%)	90(35.2)	43(41.3)	47(30.9)	2.1	0.15
Insulin-sensitisers, n (%)	38(14.8)	12(11.5)	26(17.1)	1.9	0.17
Metformin, n (%)	151(59.0)	65(62.5)	86(56.6)	0.86	0.35
Glucosidase inhibitors, n (%)	70(27.0)	27(26.0)	42(27.6)	0.02	0.88
DPP-4, n (%)	66(25.8)	31(29.8)	35(23.0)	1.83	0.18
SGL-2, n (%)	25(9.8)	14(13.5)	11(7.2)	2.66	0.1
Hypertension, n (%)	119(46.5)	36(34.6)	83(54.6)	9.73	<0.01**
Statins, n (%)	40(15.6)	9(8.7)	31(20.4)	6.43	0.01**
G0 (mmol/L)	6.92±2.41	6.95±2.99	6.91±1.91	0.12	0.9
G2h (mmol/L)	16.24±4.05	16.11±4.18	16.34±3.96	-0.42	0.67
C-pept0 (nmol/L)	0.52(0.30-0.67)	0.53(0.30-0.70)	0.51(0.32-0.65)	-0.43	0.67
C-pept2h (nmol/L)	1.85(1.18-2.35)	1.89(1.20-2.57)	1.82(1.17-2.30)	-0.64	0.52
HbA1c (%)	8.99±2.12	9.45±2.36	8.68±1.88	2.8	<0.01**
HOMA-IR	97.83(34.53-108.26)	74.13(29.72-92.87)	114.69(35.99-116.13)	-1.29	0.2
TG (mmol/L)	2.11(1.05-2.20)	2.19(1.08-2.37)	2.06(1.04-2.19)	-0.92	0.36
TC (mmol/L)	4.79±1.07	4.90±1.06	4.72±1.08	1.34	0.18
HDL-C (mmol/L)	1.23±0.32	1.20±0.31	1.24±0.33	-1.02	0.31
LDL-C (mmol/L)	2.73±0.90	2.81±0.93	2.68±0.89	1.06	0.29
ApoA-1 (g/L)	1.28±0.26	1.25±0.25	1.31±0.27	-1.99	<0.05*
ApoB (g/L)	0.93±0.27	0.95±0.25	0.92±0.27	0.98	0.33
ApoB/A1	0.76±0.27	0.81±0.30	0.72±0.23	2.81	<0.01**
ABI	1.11±0.09	1.09±0.09	1.11±0.08	-2.05	<0.05*
ba-PWV (m/s)	16.06±3.36	14.93±2.94	16.85±3.42	-4.65	<0.01**
AIP	2.13(0.81-2.13)	2.09(0.79-2.45)	2.15(0.81-1.95)	-1.08	0.28

Categorical variables are frequency (percentage), normally distributed values in the table are mean ± SD and non-normally distributed values are median (25 and 75% interquartiles).

baPWV brachial-ankle pulse wave velocity, W waist, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, ApoB apolipoprotein B, ApoA1 apolipoprotein A1, ApoB/A1 ApoB/ApoA-1 ratio, HbA1c glycosylated haemoglobin A1c, VLDL very low-density lipoprotein, sd-LDL small dense low-density lipoprotein, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, ABI ankle brachial lndex, AIP atherogenic index of plasma, DPP-4Is dipeptidyl peptidase-4 inhibitors, SGL-2Is sodiumglucose cotransporter-2 inhibitors, G0 glucose at 0min, G2h glucose at 2 hour, C-pep0h C-peptide at 0min, C-pep2h C-peptide at 2h, HOMA-IR homeostatic model assessment for insulin resistance.

Carotid atherosclerosis is defined as carotid intima-media thickness ≥ 1.0 mm or presence of plaque.

p values for continuous variables and categorical variables were determined by ANOVA and the Chi squared test, respectively.

* $P < 0.05$, ** $P < 0.01$

Table 2: Characteristics of the study participants based on the quartiles of apolipoprotein B/apolipoprotein A-I ratio

Variable	ApoB/A1				*p for trend*
	Q1 (0.12-0.59)	Q2 (0.60-0.71)	Q3 (0.72-0.90)	Q4 (0.91-1.84)	
n	63	62	69	62	
Female n (%)	24(38.1)	24(38.7)	26(37.7)	25(40.3)	0.84
Age (years)	55.85±9.02	54.39±7.63	54.68±8.73	48.41±12.36	<0.01**
BMI (kg/m^2)	24.74±3.20	24.97±2.94	25.59±3.35	25.94±3.73	<0.05*
W (cm)	90.51±8.94	90.68±9.83	91.70±9.59	92.91±9.45	0.12

Duration(months)	102.87(54.0-144.0)	95.88(48.0-120.0)	88.21(24.0-128.0)	52.41(1.0-93.0)	<0.01**
SBP (mmHg)	128.62±16.30	127.29±18.10	127.90±14.39	130.03±19.38	0.61
DBP (mmHg)	75.52±10.12	74.85±11.63	78.30±8.77	77.67±9.76	0.08
Antidiabetic treatment					
Lifestyle alone, n (%)	2(3.2)	0	1(1.4)	1(1.6)	0.64
Insulin treatments, n (%)	46(73.0)	47(75.8)	49(71.0)	49(79.0)	0.6
Insulin-secretagogues, n (%)	18(28.6)	23(37.1)	23(33.3)	26(41.9)	0.18
Insulin-sensitisers, n (%)	7(11.1)	11(17.7)	14(20.3)	6(9.7)	0.96
Metformin, n (%)	35(55.6)	33(53.2)	41(59.4)	42(67.7)	0.13
Glucosidase inhibitors, n (%)	19(30.2)	20(32.3)	16(23.2)	14(22.6)	0.2
DPP-4Is, n (%)	7(11.1)	12(19.4)	22(31.9)	25(40.3)	<0.01**
SGL-2Is, n (%)	3(4.8)	9(14.5)	4(5.8)	9(14.5)	0.23
Hypertension, n (%)	32(50.8)	28(45.2)	36(52.2)	23(37.1)	0.24
Statins, n (%)	9(14.3)	13(21.0)	9(13.0)	9(14.5)	0.72
G0 (mmol/L)	6.95±1.69	6.74±1.79	6.73±1.62	7.28±3.82	0.47
G2h (mmol/L)	16.05±4.59	16.70±3.98	15.79±3.65	16.55±3.97	0.81
C-pep0 (nmol/L)	0.50(0.34-0.67)	0.46(0.26-0.62)	0.56(0.31-0.75)	0.55(0.32-0.72)	0.09
C-pep2h (nmol/L)	1.79(1.14-2.45)	1.72(1.11-2.20)	1.88(1.22-2.31)	2.00(1.36-2.46)	<0.05*
HbA1c (%)	8.54±2.07	8.94±2.23	8.86±1.88	9.64±2.19	<0.01**
HOMA-IR	114.3(30.56-139.9)	82.03(29.59-104.7)	85.27(35.88-106.1)	109.1(36.65-100.3)	0.64
TG (mmol/L)	2.14(0.89-2.02)	1.82(0.89-1.72)	2.32(1.09-2.47)	2.13(1.25-2.52)	0.06
TC (mmol/L)	4.31±1.08	4.69±1.09	5.02±0.85	5.12±1.09	<0.01**
HDL-C (mmol/L)	1.34±0.43	1.28±0.29	1.21±0.25	1.09±0.22	<0.01**
LDL-C (mmol/L)	2.10±0.80	2.64±0.72	2.96±0.78	3.23±0.94	<0.01**
ApoA-1 (g/L)	1.46±0.29	1.33±0.21	1.26±0.20	1.08±0.18	<0.01**
ApoB (g/L)	0.66±0.18	0.86±0.14	1.00±0.15	1.21±0.22	<0.01**
ABI	1.13±0.09	1.11±0.09	1.10±0.09	1.08±0.07	<0.01**
ba-PWV (m/s)	16.23±3.17	16.61±3.23	16.40±3.40	14.99±3.47	<0.05*
AIP	2.03(0.66-1.73)	1.61(0.76-1.38)	2.70(0.80-2.49)	2.10(1.12-2.51)	<0.01**

Categorical variables are frequency (percentage), normally distributed values in the table are mean ± SD and non-normally distributed values are median (25 and 75% interquartiles).

baPWV brachial-ankle pulse wave velocity, W waist, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, ApoB apolipoprotein B, ApoA1 apolipoprotein A1, ApoB/A1 ApoB/ApoA-1 ratio, HbA1c glycosylated haemoglobin A1c, VLDL very low-density lipoprotein, sd-LDL small dense low-density lipoprotein, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, ABI ankle brachial lndex, AIP atherogenic index of plasma, DPP-4Is dipeptidyl peptidase-4 inhibitors, SGL-2Is sodiumglucose cotransporter-2 inhibitors, G0 glucose at 0min, G2h glucose at 2 hour, C-pep0h C-peptide at 0min, C-pep2h C-peptide at 2h, HOMA-IR homeostatic model assessment for insulin resistance.

p values for continuous variables and categorical variables were determined by ANOVA and the Chi squared test, respectively.

* $P < 0.05$, ** $P < 0.01$

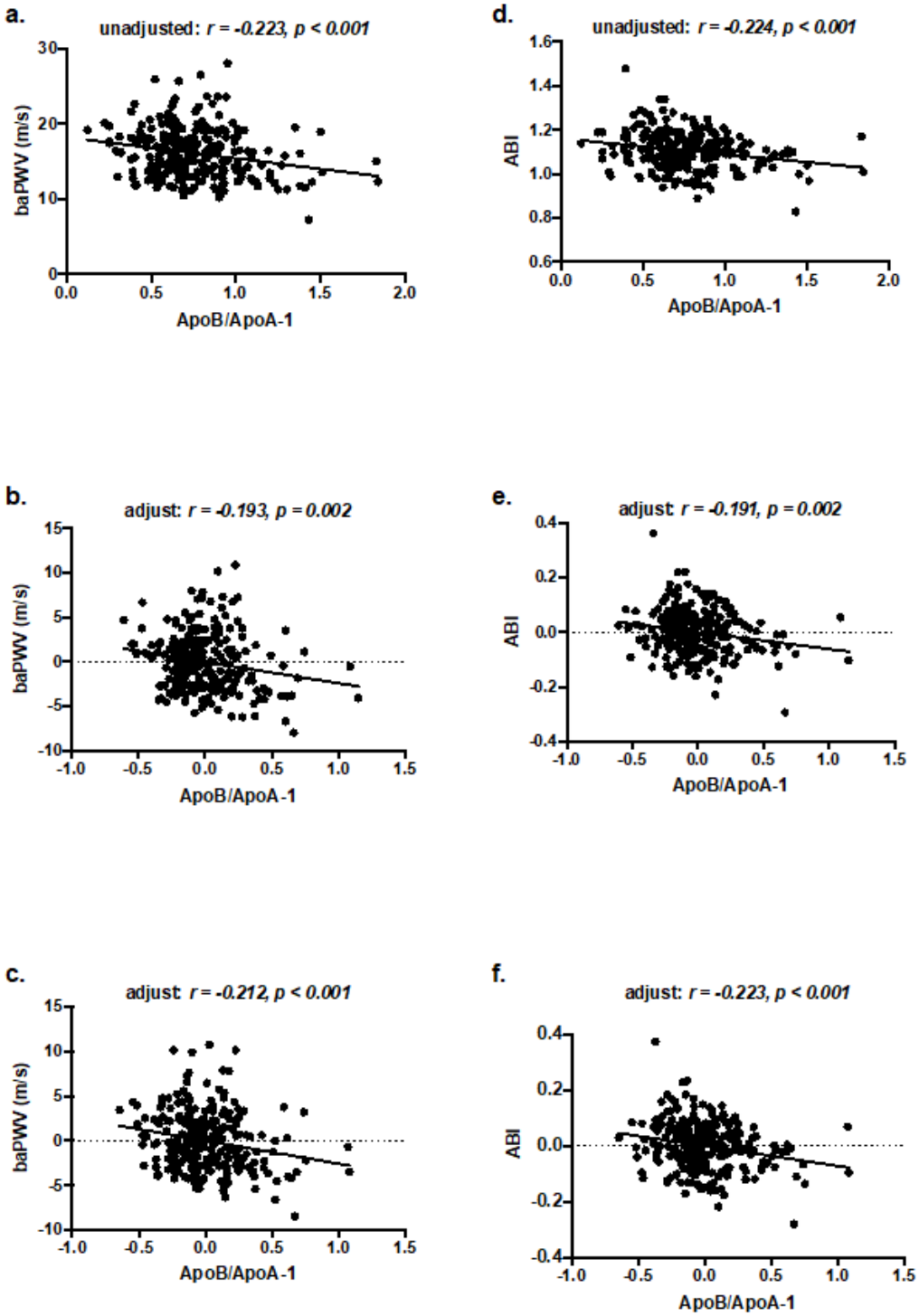

Figure 2: Relationships between ApoB/ApoA-1 and baPWV, ABI ((a.d unadjusted b.e adjust for antidiabetic treatment c.f adjust for statins)).

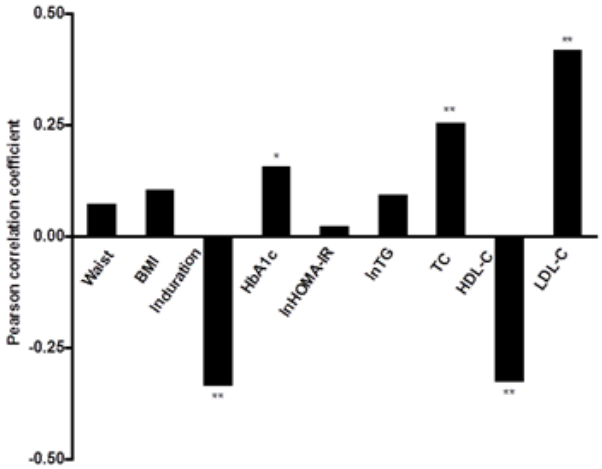

Figure 3: Correlations between ApoB/ApoA-1 and variables. *correlation is significant at the 0.05 level; ** correlation is significant at the 0.01 level. ApoB/ApoA-1, ratio of ApoB and ApoA1; BMI, body mass index; HbA1c, Glycosylated
Hemoglobin; TG, triglycerides; TC, total cholesterol; HDL-C, highdensity lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

4.3. Univariate and Multivariate Logistic Regression Analyses Explored the Impact of Apob/A1 and Other Factors on Carotid Atherosclerosis

In Figure 4, the univariate logistic regression analysis showed that ApoB/A1 [OR (95% CI), 0.242 (0.090-0.646)], baPWV [OR (95% CI), 1.204 (1.103-1.314)], HbA1c [OR (95% CI), 0.842 (0.745-0.953)], statins [OR (95% CI), 2.704 (1.288-5.954)], male sex [OR (95% CI), 0.326 (0.178-0.599)], age >55 [OR (95% CI), 2.730 (1.619-4.603)], and diabetes duration >24 [OR (95% CI), 2.786 (1.387-5.959)] were independently correlated with carotid atherosclerosis. Furthermore, multivariate logistic regression analysis was performed, and as shown in Table 3, in the basal unadjusted Model 0, ApoB/A1 was independently associated with carotid atherosclerosis [OR (95% CI), 0.242 (0.090-0.646)]. Based on Model 0, Model 1 was adjusted for HOMA-IR, BMI, SBP, and DBP; in Model 2, HbA1c and antidiabetic treatments were additionally included; and in Model 3, statin medications and antihypertensive treatments were additionally included. ApoB/A1 remained independently related to carotid atherosclerosis [OR (95% CI), 0.246 (0.080-0.760), 0.193 (0.056-0.658), and 0.216 (0.062-0.759), respectively].

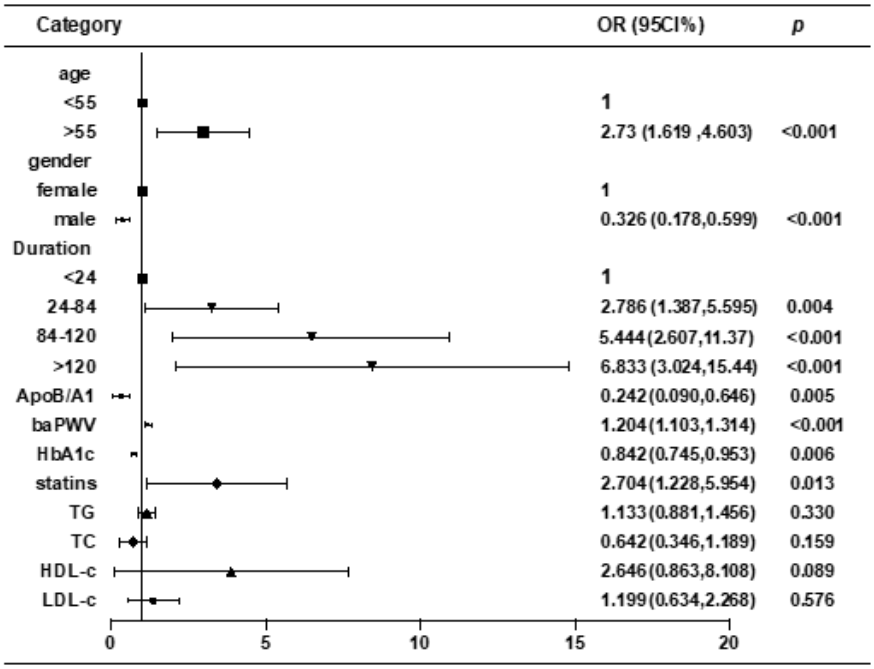

Figure 4: Forest plot for the associations of ApoB/A1 and other factors with carotid atherosclerosis.

Table 3: Multivariate logistic regression analysis to identify the association of ApoB/A1 with carotid atherosclerosis

Models	*B*	SE	Wald	*p*	OR	95%CI
Model 0	-1.421	0.502	8.013	0.005	0.242	0.090-0.646
Model 1	-1.4	0.575	5.94	0.015	0.246	0.080-0.760
Model 2	-1.648	0.627	6.9	0.009	0.193	0.056-0.658
Model 3	-1.531	0.64	5.717	0.017	0.216	0.062-0.759

Model 0: unadjusted model

Model 1: adjusted for HOMA-IR, BMI, SBP, DBP

Model 2: additionally adjusted for HbA1c, antidiabetic treatments

Model 3: additionally adjusted for statins medications, antihypertensive treatments

5. Discussion

In this medium-sized cohort study, we explored whether ApoB/A1 was related to arteriosclerosis parameters, including subclinical atherosclerosis and arterial stiffness, in type 2 diabetes patients. The main findings are as follows: The ApoB/A1 was significantly lower in T2D patients with carotid atherosclerosis than in T2D patients without carotid atherosclerosis; ApoB/A1 was negatively related to baPWV and ABI regardless of antidiabetic treatment and statins; and ApoB/A1 and baPWV were independent contributors to carotid atherosclerosis. After adjusting for HOMA-IR, BMI, SBP, DBP, HbA1c, antidiabetic treatments, statin medications, and antihypertensive treatments via multivariate logistic regression analysis, ApoB/A1 was still independently related to carotid atherosclerosis; each 1-unit increase in ApoB/A1 may lead to a 0.216-fold decreased mean risk of carotid atherosclerosis, with a 95% CI of 0.062-0.759.

ApoB surrounds atherogenic lipoproteins and attaches to the surface of VDLD, sd-LDL and LDL-C. ApoB is responsible for transporting lipids from the liver and gut to the surrounding tissues and trapping lipids on the arterial wall [24]. ApoA1 makes up the main proportion of HDL-C and initiates the reverse transport of cholesterol. ApoA1 attaches to the surface of HDL-C and removes cholesterol via Lecithin Cholesterol Acyltransferase (LCAT) and Cholesteryl Ester Transfer Protein (CETP) [25]. Thus, ApoB/A1 represents the balance of antiatherogenic lipoprotein and proatherogenic lipoprotein.

Several large clinical studies have revealed that ApoB/A1 is a better predictor of cardiovascular diseases. The AMORIS (Apolipoprotein-related MOrtality RISk) study, which recruited 175553 Swedish men and women, revealed that ApoB/A1 was an important factor for fatal myocardial infarction even after adjustment for age, TC and TG [3]. In the INTERHEART study, which enrolled 9345 patients and 12,120 controls from 52 countries, ApoB/A1 was more valuable for assessing cardiovascular diseases than any other cholesterol ratio [26]. In the Scandinavian Simvastatin Survival Study (4S) study, the changed ApoB levels were highly related to a reduction in coronary events among coronary heart disease patients treated with simvastatin for one year [27]. Moreover, UM Jadhav et al. showed that when ApoB/A1 exceeded one, Intima-Media Thickness (IMT) showed a 2.27-fold increase, and the prevalence of CAD had a 2.50-fold increase after adjustment for sex, smoking, BMI and other lipid parameters [28]. In middle-aged T2D patients, ApoB/A1 was shown to be an important indicator of subclinical atherosclerosis as assessed by the IMT of the carotid arteries [29]. Consistent with these studies, the current study revealed that ApoB/A1 was significantly and independently associated with carotid atherosclerosis even after adjustment for other clinical parameters. Previous studies showed that a high level of ApoB/ApoA-I was significantly correlated with carotid atherosclerosis in T2D patients with normal LDL-C levels and associated with the occurrence of artery stenosis and carotid plaque [11,30]. Inconsistent with this, we found that ApoB/A1 was lower in patients with carotid atherosclerosis and that the decrease could be caused by the use of statins. The ApoB levels decreased by 15%, and ApoA1 increased by 5%-15% after treatment with statins. This was perhaps due to the increased degradation of ApoB-containing lipoproteins, which reduced the production of ApoB attached to LDL-C and inhibited cholesteryl transfer from HDL [31,32].

The ABI [10], carotid atherosclerosis [11] and baPWV [12,13] are considered noninvasive techniques for evaluating subclinical arteriosclerosis and arterial stiffness. The ABI and carotid atherosclerosis participate in the atherosis process, while baPWV participates in the sclerosis process [15]. Previous studies revealed that baPWV, ABI and carotid atherosclerosis are widely used in Chinese clinics [33]. baPWV was related to HbA1c [34], BP, the status of diabetes [35], obesity [36] and arteriosclerosis [17]. The ABI is a useful tool for identifying peripheral arterial disease [37], macroangiopathy including CAD, arteriosclerosis obliterans and stoke [38]. Subclinical arteriosclerosis assessed by carotid atherosclerosis was referred to as atherosclerosis [39]. A recent study strongly suggested that ApoB/A1 was significantly and negatively correlated with baPWV and ABI, even after adjustment for antidiabetic treatment and statins. Furthermore, univariate logistic regression analysis also showed that ApoB/A1 and baPWV were independently related to carotid atherosclerosis. ApoB/A1 was a meaningful indicator of carotid atherosclerosis in the fully adjusted Model 3 [(OR (95% CI), 0.216 (0.062-0.759)].

Serum lipid deposition, leukocyte infiltration and intimal thickening are the main steps in the progression of atherosclerosis [40]. ApoB is the main component of LDL and reflected the level of

LDL. ApoB internalizes LDL and enters blood vessels, improving the absorption of cholesterol, promoting macrophage transformation into foam cells and finally triggering the atherogenic process [41]. sd-LDL can easily enter the subintimal space when LDL-C is at low or normal levels and is then oxidized, promoting inflammation and atherogenic effects [9]. ApoA1 is attached to the surface of HDL-C and removes cholesterol via lecithin cholesterol acyltransferase (LCAT) and Cholesteryl Ester Transfer Protein (CETP) [25]. ApoA1 can also inhibit the oxidation of LDL-C, block the connection of inflammatory cells, reduce inflammation and finally promote cholesterol efflux from arteries, inhibiting atherogenesis [9]. Moreover, high levels of ApoA1 could reduce endothelial injury and inflammation, stabilize plaques and protect nerve function [42]. Although we revealed that ApoB/ApoA1 was lower in T2D with carotid atherosclerosis patients, ApoB/A1 was independently correlated with ABI and baPWV and was an indicator of carotid atherosclerosis as assessed by carotid plaque.

This study also had a few limitations. First, the results of this cross-sectional study with a medium-sized cohort could not be used to identify causation. Second, all subjects were recruited from China, and the global diabetic population was not represented. Third, several cofounding factors that affect atherogenesis, including alcohol and smoking history, treatment with antiplatelet agents, and health behavior, were not assessed completely. Last, there was no normal control group in our study, and the T2D patients with carotid atherosclerosis mostly had a history of statin use. Therefore, a larger follow-up study should be conducted to investigate the relationship of ApoB/ApoA1 and subclinical arteriosclerosis.

6. Conclusions

The ApoB/A1 ratio was independently and inversely associated with baPWV and ABI and independently contributed to carotid atherosclerosis in T2D patients.

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