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Association of dipeptidyl peptidase IV polymorphism, serum lipid profile, and coronary artery stenosis in patients with coronary artery disease and type 2 diabetes

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Abstract

Cardiovascular disease (CAD) is a devastating illness, but to date there are limited means of predicting a person's coronary stenosis severity and their prognosis. The study was performed to investigate the relationship between dipeptidyl peptidase 4(*DPP4*) gene polymorphisms and serum lipid profiles, as well as the severity of coronary artery stenosis in patients with CAD and type 2 diabetes (T2DM) for the first time.

Herein, 201 patients with CAD and T2DM were enrolled in the Department of Cardiology, Shandong Provincial Qianfoshan Hospital. *DPP4* rs3788979 and rs7608798 single nucleotide polymorphisms (SNPs) were genotyped. The general information of all patients was collected, and the associations between DPP4 SNPs and lipid profiles were detected. At the same time, association between SNP polymorphisms and the degree of coronary artery stenosis were analyzed.

There was a significant difference in apolipoprotein B (ApoB) levels ($P = .011$) for the rs3788979 polymorphism, while no difference was identified in other blood lipids or with other mutations. SNP mutation of A to G in rs3788979 was associated with a reduced percentage of severe coronary artery stenosis in female patients ($P = .023$) as well as those with nosmoking ($P = .030$), nodrinking ($P = 0.007$), and nocardiovascular family history ($P = 0.015$).

G allele of rs3788979 is associated with a reduced ApoB level. Besides, we suggest that G allele in rs3788979 may have a cardioprotective effect and prove to be a useful and specific measure when predicting a patient's coronary stenosis severity if diagnosed with CAD and T2DM.

Keywords: coronary artery disease, coronary artery stenosis, dipeptidyl peptidase IV polymorphism, serum lipid profile, type 2 diabetes

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1. Introduction

Coronary artery disease (CAD) is one of the leading causes of disability and death all over the world.[1,2] It is a multifaceted disease of the circulatory system that results from both genetic and environmental factors.[3] It has been reported that gene polymorphisms are strongly associated with CAD pathogenesis,[4,5] contributing to approximately 40% to 60% of all occurrences of CAD development.[6] Type 2 diabetes mellitus (T2DM) is considered to compound the health risks of CAD, and is an independent predictor of adverse outcomes and mortality in patients with CAD.[7,8] Previous studies confirmed that patients with CAD and T2DM showed significantly higher rates of major adverse cardiac events (MACE), non-fatal myocardial infarction (MI), and all-cause death, than non-diabetic patients.[9] CAD and T2DM often lead to premature disability and mortality, contributing substantially to the health care burden.[10,11] Therefore, predictors of coronary stenosis severity and cardiovascular events in patients with CAD and T2DM will have a great impact on the identification, prognosis, and treatment of high-risk patients.

Dipeptidyl peptidase 4 (DPP4) is a multifunctional protein. It is not only important in pancreatic β-cell regulation but also responsible for signal transduction, cell–cell interaction, immunomodulation, and peptide regulation.[12] The influence of *DPP4* gene variants have been studied in monocytes and animal models,

where *DPP4* deletion in single cardiomyocytes was shown to improve the tolerance of cells to oxidative stress and have a protective effect against chemical injury sustained by H_2O_2 exposure.[13]*DPP4* gene deficiency can lead to an increase in glucagon-like peptide-1(GLP-1) levels in vivo, which results in decreased cardiac function caused by endotoxemia and MI.[12] In addition, *DPP4* knockout or inhibition can reduce the incidence of central vascular events in mice with MI.[14]

DPP4 has been reported to be involved in the neovascularization of human atherosclerotic plaques, and in regulating lipid metabolism.[15,16] We studied the *DPP4* allelic distributions as well as their association with dyslipidemia in Chinese T2DM patients in a previous study and concluded that polymorphisms in the defined *DPP4* loci were associated with serum lipid levels.[17] Xing et al[18] studied *DPP4* gene polymorphism in a Caucasian patient population and found that polymorphism in the *DPP4* gene in patients with known CAD may increase the risk of MI. However, the results have not been generalized to patients of different ethnic backgrounds, and the polymorphisms are not well studied in patients with other diseases. Polymorphisms of the *DPP4* gene in Chinese patients with CAD and T2DM have never been reported before but are speculated to be associated with coronary artery stenosis.[16] The relationship between *DPP4* polymorphism and serum lipid profiles, as well as the severity of coronary artery stenosis is unclear. Therefore, this study was performed to investigate *DPP4* single nucleotide polymorphisms (SNPs) in patients with CAD and T2DM. The relationships between *DPP4* SNPs and lipid profile as well as coronary stenosis severity were also explored.

2. Methods

2.1. Study population and definition

Patients with CAD and T2DM were enrolled between January 2016 and December 2018 from the Department of Cardiology, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, Shandong Province, China.

The following criteria were applied for selecting participants: all participants were ≤70 years old with CAD diagnosed through coronary angiography (CAG).

The diagnostic criteria for patients with CAD were as follows: according to the criteria of the World Health Organization and/or CAG, at least 1 of the 3 major coronary arteries or major branches has stenosis ≥50%.[19]

Diagnosis of T2DM was made if participants experienced one or more of the following: symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L; fasting plasma glucose ≥7.0 mmol/L; 2-hour post load glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT).[20] Participants need also to have not consumed any lipid-lowering drugs in the previous 3 months.

Patients with severe kidney disease and eGFR ≤30 mL/min/1.73 or with elevated liver transaminase were excluded. Patients with drug or alcohol abuse[21] were also excluded.

Ethics approval was granted by the Clinical Research Ethics Committee of Shandong Provincial Qianfoshan Hospital (approval number [2015] (S004)). Informed consent was obtained from all participants before inclusion.

2.2. SNP selection and Genotyping

Four *DPP4* SNPs (rs4664443(C>T), rs7608798 (T>C), rs1558957 (C>T), and rs3788979 (A>G)) have been reported to be associated with lipid metabolism and cardiovascular disease.[17] As the minor alleles of rs1558957 and rs4664443 were present at very low frequencies, only rs3788979 (A>G) and rs7608798 (T>C) will be studied in this study.

Venous blood (3 mL) was extracted and stored at −80 °C. The Relax Gene blood DNA system (Tiangen Biotech, Beijing, China) was used to extract genetic material. Extracted DNA was isolated and stored at −20 °C. Polymerase chain reactions (PCR) was performed on the extracted material using 25 μL mixture of 5× PCR Dye plus Master Mix (GM bio lab, Taichung, Taiwan), 0.1 μM of forward and reverse primers, and 0.1 μg genomic DNA. (PCR was carried out with the Gene Pro PCR system TC-E [Bioer Technology, Hangzhou, China]) as follows: pre-denaturation at 94 °C for 3 minutes, followed by 35 cycles of denaturation for 30 seconds at 94 °C, annealing for 30 seconds and extension at 72 °C for 60 seconds, ending with a 5 minutes re-extension at 72 °C. Primers were designed using Primer 5.0 software. The details of the primers used are listed in Supplementary Table 1, http://links.lww.com/MD/F940.

2.3. Physiological and biochemical information

Physiological and biochemical parameters were collected for each patient, including sex, age, body mass index (BMI), left ventricular ejection fraction (LVEF), smoking history, drinking history, family history of CAD, hypertension history, the medications of the patients at enrollment. Besides, blood serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein a (Lpa), apolipoprotein A1(ApoA1), and apolipoprotein B (ApoB) levels, were collected if available. The CAG results were all analyzed.

2.4. Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics 24 software. Continuous data are presented as the mean ± standard deviation (mean ± SD) and the paired Student *t* test was used to compare means between 2 groups. 95% confidence intervals were calculated for all observed allelic frequencies. ANOVA was applied for comparisons between >2 groups. Categorical variables were compared using the Chi-square test. Multivariate logistic stepwise regression was performed to identify predictors related to the severity of coronary artery stenosis, and diagnostic accuracy was assessed based on the receiver operating characteristics (ROC) curve. A *P* value of <.05 was considered statistically significant.

3. Results

3.1. Basic data of patients

A total of 201 CAD patients with T2DM were enrolled, of which 117 were men and 84 were women. The clinical and biochemical data are shown in Table 1. The treatments received by the participants are also listed and there was no statistical difference between the mutant and non-mutant groups (Supplementary Table 2, http://links.lww.com/MD/F941). The BMI of the enrolled patients was 25.96 ± 3.81.

3.2. Distribution of DPP4 gene polymorphism

The *DPP4* rs3788979 and rs7608798 SNP distribution and allele frequency are shown in Table 2. In the 201 enrolled patients, the

Table 1

Clinical and biochemical characteristics of study population.

Baseline characteristics Clinical characteristics	Mean ± SD
Age, y	59.671 ± 7.26
Gender (Male/Female)	117/84
HbA1c (%)	7.41 ± 0.32
FPG, mmol/L	7.87 ± 0.46
TG, mmol/L	2.20 ± 1.94
TC, mmol/L	5.12 ± 1.87
HDL-C, mmol/L	1.18 ± 0.24
LDL-C, mmol/L	3.10 ± 0.88
LPa, mg/L	229.72 ± 302.35
ApoA1, g/L	1.24 ± 0.88
ApoB, g/L	1.01 ± 0.26
BMI, kg/m^2	25.96 ± 3.81
Medication	n (%)
Antiplatelet drugs	40 (19.90)
Statin	0 (0)
β-Blockers	41 (20.40)
ACEi and/or ARB	68 (33.83)
Calcium channel blockers	72 (35.82)
Diuretics	8 (3.98)
Exogenous Insulin	51 (25.37)
Alpha glucosidase inhibitors	86 (42.79)
Biguanides	109 (54.23)
Thiazolidinediones	5 (2.49)
Insulin secretagogues	59 (29.35)

Values are mean ± SD or numbers (percentages). ACEi and/or ARB: Angiotensin I converting enzyme inhibitors, Angiotensin II type 1 receptor blockers.
ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lpa = lipoprotein a; TG = triglyceride; TC = total cholesterol.

rs3788979 and rs7608798 gene polymorphisms were in accordance with Hardy–Weinberg equilibrium: $\chi^2 = 0.0051$, $P = .94$ and $\chi^2 = 0.2799$, $P = .5968$, respectively.

3.3. Relationship of serum lipid profiles and DPP4 polymorphism

The relationship between *DPP4* polymorphisms and the serum lipid profiles of the enrolled patients was investigated. For rs3788979, the difference of serum TG, TC, HDL-C, LDL-C, Lpa, ApoA1, and ApoB levels between the AA and AG/GG group were investigated separately. We found that there was a significant difference in ApoB between G carriers and non-carriers of *DPP4* ($P = .011$). Carriers of the allele G had lower ApoB levels compared with non-carriers, however, no differences were confirmed for the other indices. The results are shown in Table 3. The data for rs7608798 is shown in Table 4 and no significant differences were found.

Table 2

Allelic frequencies of rs3788979 and rs7608798.

SNP	Genotype	N (%)	Allele	Frequencies
rs3788979	A/A	61 (30.35)	A	54.98%
	A/G	99 (49.25)	G	45.02%
	G/G	41 (19.90)		
rs7608798	T/T	91 (45.27)	T	66.67%
	C/T	86 (42.79)	C	33.33%
	C/C	24 (11.94)		

Values are numbers (percentages).
Chi-square test was used to analyze gene frequency with Hardy–Weinberg equilibrium.
rs3788979: $P = .9426$, $\chi^2 = 0.0051$; rs7608798: $P = .5968$, $\chi^2 = 0.2799$.
SNP = single nucleotide polymorphism.

Table 3

Relationship between gene polymorphism of rs3788979 and serum lipid levels.

Lipid levels	SNP	n	Mean ± SD	*P* value
TG	0	45	2.13 ± 1.31	.684
	1	111	2.24 ± 2.15	
TC	0	45	5.18 ± 1.13	.662
	1	109	5.09 ± 1.21	
HDL-C	0	39	1.18 ± 0.20	.994
	1	96	1.18 ± 0.25	
LDL-C	0	43	3.21 ± 0.75	.290
	1	102	3.05 ± 0.92	
LPa	0	33	207.33 ± 242.75	.574
	1	88	238.11 ± 322.73	
ApoA1	0	33	1.16 ± 0.16	.323
	1	87	1.27 ± 1.03	
ApoB	0	33	1.10 ± 0.03	.011*
	1	87	0.98 ± 0.27	

AA was defined as 0, while AG and GG was 1. Values are Mean ± SD. *t* test was used.
ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lpa = lipoprotein a, SNP = single nucleotide polymorphism, TC = total cholesterol, TG = triglyceride.

3.4. DPP4 gene polymorphism and coronary artery stenosis

The association between *DPP4* SNPs and the severity of coronary artery stenosis was also investigated. All diagnoses of CAD were confirmed through CAG. Following the CAG analysis, the CAD patients were divided into 2 groups based on the grade of diagnosed coronary stenosis: one group with stenosis <70% and the other with stenosis ≥70%. Coronary stenosis ≥70% was considered to be severe stenosis. For rs3788979, no difference was found between the AG/GG and AA in the coronary artery

Table 4

Relationship between gene polymorphism of rs7608798 and serum lipid levels.

Lipid levels	SNP	n	Mean ± SD	*P* value
TG	0	69	2.06 ± 1.27	.402
	1	87	2.31 ± 2.34	
TC	0	69	5.05 ± 1.12	.515
	1	85	5.18 ± 1.24	
HDL-C	0	60	1.17 ± 0.20	.658
	1	75	1.19 ± 0.26	
LDL-C	0	65	3.13 ± 0.83	.751
	1	80	3.08 ± 0.92	
LPa	0	52	194.46 ± 234.58	.243
	1	69	256.29 ± 344.07	
ApoA1	0	53	1.31 ± 1.31	.490
	1	67	1.18 ± 0.20	
ApoB	0	53	1.15 ± 0.025	.111
	1	67	0.98 ± 0.25	

TT was defined as 0, CT and CC was 1 for rs7608798. Values are Mean ± SD. T test was used.
ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, HDL-C = high-density ipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, Lpa = lipoprotein a, SNP = single nucleotide polymorphism, TC = total cholesterol, TG = triglyceride.

Table 5

DPP4 polymorphism and the coronary artery stenosis.

rs3788979	Coronary artery stenosis		
	<70% (n)	≥70% (n)	*P* value
AG/GG	44	96	.123
AA	12	49	
rs7608798			
CT/CC	33	77	0.528
TT	23	68	

Values are numbers of patients and *P* values of chi-squared test.

stenosis severity ($P=.123$), the same result was also observed for rs7608798 ($P=.528$) (Table 5).

We performed subgroup analyses and discovered that for the smoking patients, there is no difference between AA group and AG/GG group in the degree of coronary artery stenosis ($P>.999$). When we analyzed the data after excluding smokers, we observed significant differences between the AG/GG and AA groups on the presence of severe coronary stenosis ($P=.03$). For allele G carriers, the percentage of those with severe stenosis was lower. Similar analyses were performed based on drinking history, with no significant differences discovered between the AG/GG and AA groups ($P=.592$) for drinking patients. As with the smoking excluded result, when alcohol consumers were excluded, the degree of coronary artery stenosis was relatively alleviated ($P=.007$) for those expressing the G allele. In the male group, there was no significant difference between the AG/GG and AA groups ($P>.999$). However, for women, the coronary artery stenosis was less severe ($P=.023$) in the AG/GG group. Analysis was also performed according to family history. For those with a clear family history of cardiovascular disease, there was no difference between the AG/GG and AA groups, but for those with no cardiovascular family history, a significant difference was identified ($P=.015$) (Table 6).

The association between DPP4 rs7608798 SNPs and the severity of coronary artery stenosis was also studied. Generally, no significant difference was confirmed between the rs7608798 SNPs and coronary artery stenosis ($P=.528$). There were no significant differences observed between CT/CC and TT when smoking, drinking, and family history were considered, nor between sexes (Table 7).

Multivariate logistic regression analysis results identified that *DPP4* rs3788979 SNP is effective to predict the severity of

Table 6

Rs3788979 polymorphism and the coronary artery stenosis in different groups.

Smoking history	Smoking			No smoking		
	<70% (n)	≥70% (n)	*P* value	<70% (n)	≥70% (n)	*P* value
AG/GG	11	48	>.999	33	48	.030*
AA	6	23		6	26	
Drinking history	Drinking			No drinking		
	<70% (n)	≥70% (n)	*P* value	<70%(n)	≥70%(n)	*P* value
AG/GG	13	47	.592	31	49	.007*
AA	8	20		4	29	
Gender	Male			Female		
	<70% (n)	≥70% (n)	*P* value	<70% (n)	≥70% (n)	*P* value
AG/GG	16	63	>.999	28	33	.023*
AA	8	30		4	19	
Family history	With family history			With no family history		
	<70% (n)	≥70% (n)	*P* value	<70% (n)	≥70% (n)	*P* value
AG/GG	15	49	0.794	29	47	0.015*
AA	7	20		5	29	

Values are numbers of patients and *P* values of chi-squared test.

Table 7

Rs7608798 polymorphism and the coronary artery stenosis in different groups.

Smoking history	Smoking			No smoking		
	<70% (n)	≥70% (n)	*P* value	<70%(n)	≥70%(n)	*P* value
CT/CC	9	40	>.999	24	37	.321
TT	8	31		15	37	
Drinking history	Drinking			No drinking		
	<70% (n)	≥70% (n)	*P* value	<70% (n)	≥70% (n)	*P* value
CT/CC	10	37	.620	23	40	.219
TT	11	30		12	38	
Gender	Male			Female		
	<70% (n)	≥70% (n)	*P* value	<70% (n)	≥70% (n)	*P* value
CT/CC	12	46	>.999	21	31	.648
TT	12	47		11	21	
Family history	With family history			With no family history		
	<70% (n)	≥70% (n)	*P* value	<70%(n)	≥70%(n)	*P* value
CT/CC	11	38	.807	22	39	.218
TT	11	31		12	37	

Values are numbers of patients and *P* values of chi-squared test.

coronary artery stenosis in women and those without history of smoking, drinking, and cardiovascular disease in the family (Supplementary Table 3, http://links.lww.com/MD/F942). Diagnostic accuracy was assessed using the area under the ROC curve. From the ROC curve, it showed a good or very good diagnostic accuracy, with an AUC of 0.854 in women, 0.840 in non-smoking participants, 0.866 in non-drinking participants, and 0.929 in those without cardiovascular disease family history (Fig. 1).

4. Discussion

CAD is caused by an interaction between genetic and environmental factors.[3,22] Epidemiology studies have suggested that smoking, hyperlipidemia, hypertension, DM, obesity, family history of early CAD, and age are major risk factors for CAD.[23,24] The accumulation of these risk factors accelerates the progression of atherosclerosis.[23,25] Evidence suggests that compared with those without T2DM or CAD, patients with CAD and T2DM have a 4-fold increased risk of cardiovascular events; 4-fold, myocardial infarction; 10-fold, cardiovascular death; and 8-fold, vascular interventions.[26] CAD and T2DM impose a huge burden on the social health care system.[10,11,27] Clinically, traditional risk factors for patients with CAD and T2DM cannot successfully predict the severity of coronary stenosis and risk of cardiovascular events. Therefore, it is of great importance to confirm a predictor for high-risk patients with CAD and T2DM.

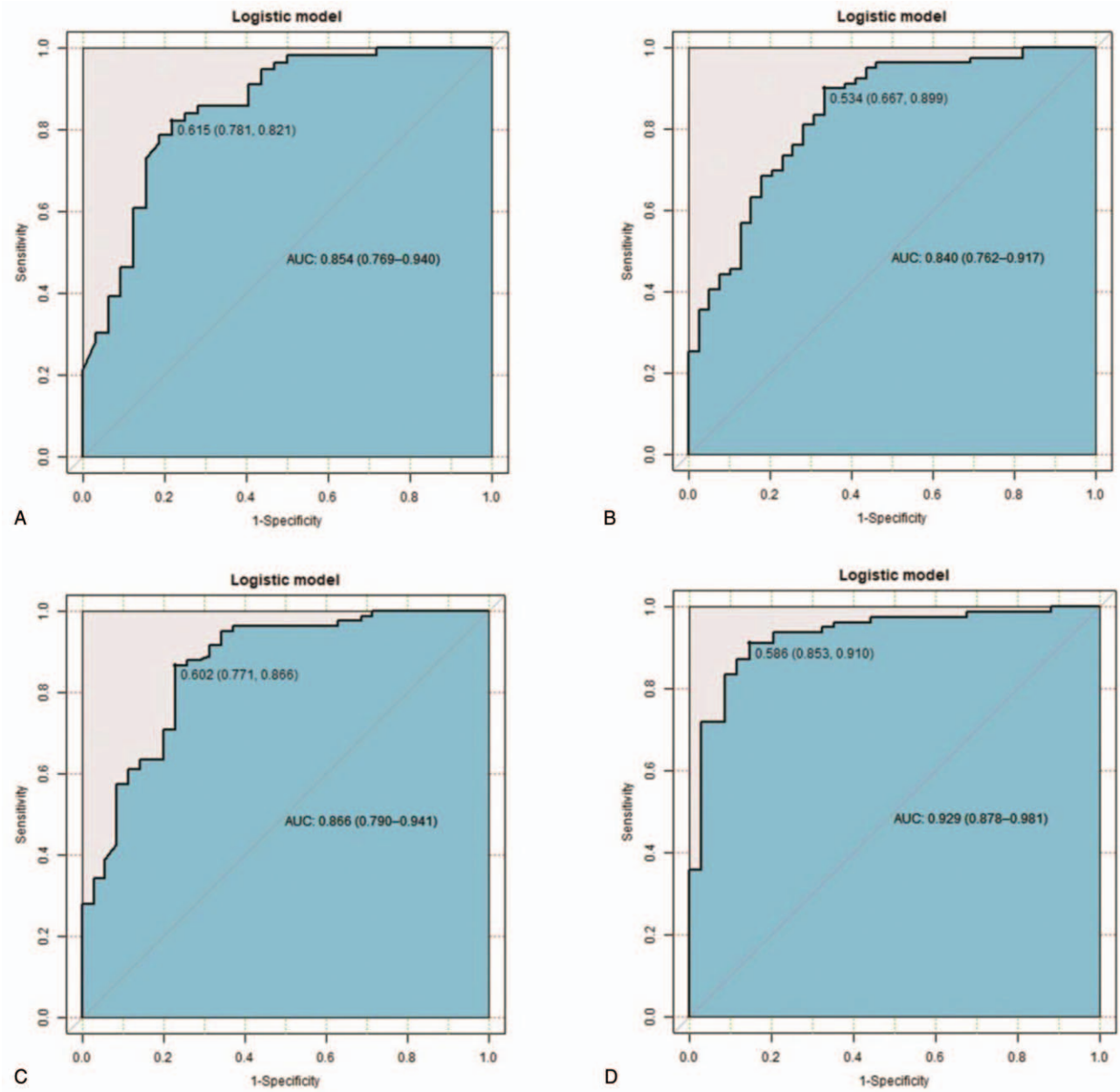

Figure 1. The receiver operating characteristic curve (ROC) for DPP4 SNPs predicting the severity of coronary artery stenosis in CAD patients with T2DM. A = ROC curve with female; B = ROC curve with no smoking; C = ROC curve with no drinking; D = ROC curve with no family history. Numbers in parentheses are the 95% confidence intervals.

Our study is the first to verify the *DPP4* gene polymorphism in patients with CAD and T2DM in Chinese Han population. We found that the allele frequencies of *DPP4* rs3788979 and rs7608898 were in accordance with a previous study performed on Japanese men.[28] However, the allele frequencies of polymorphic *DPP4* rs3788979 in Chinese were significantly different from those in a Caucasian population (allele frequency was 45.02% for G and 54.98% for A vs 85.8% for G and 14.2% for A),[18] confirming an ethnic difference in *DPP4* rs3788979 distribution. These findings may partly explain the significant differences in cardiovascular outcomes between Chinese Han and Caucasian patients with CAD.

In recent years, much attention has been devoted to the association of the *DPP4* SNPs with lipid metabolism and the pathogenesis of CAD.[17,18,22] ApoB was considered a useful predictor for evaluating the severity of coronary stenosis in patients with CAD.[29]*DPP4* SNPs and their relationship with ApoB have already been studied, and evidence suggests that ApoB48 may be reduced by pharmaceutical inhibition of DPP4.[30] The *DPP4* rs4664443 SNP was shown to be associated with ApoB metabolism in a South Asian cohort.[31] Our previous study has reported that *DPP4* rs4664443 minor allele T carriers have higher plasma ApoB levels.[17] However, the association between *DPP4* rs3788979 SNP and ApoB has not been detailed before. We discovered low serum ApoB in the AG/GG groups of *DPP4* rs3788979 in this study. In other words, an increase in the frequency of the rs3788979 G allele is associated with significantly lower levels of ApoB. We speculated that allele G influences the occurrence and development of atherosclerosis through regulation of ApoB metabolism and thus may have a cardioprotective effect. It was the first time the relationship between ApoB levels and the *DPP4* polymorphism was studied in patients with CAD and T2DM with a Chinese cohort. Considering the limitations of the sample size in this study, further investigation is required to confirm the relationship between the *DPP4* SNPs and the lipid profiles.

DPP4 is pleiotropic; in addition to regulating glucose homeostasis, DPP4 regulates inflammation, oxidative stress, lipid metabolism, and insulin resistance.[32–35] Inflammation plays a pivotal role in the pathogenesis of coronary artery atherosclerosis in T2DM and CAD,[36,37] and it could be the link between the two.[38] Oxidative stress is crucial in developing atherosclerotic plaque.[39] It was reported that in T2DM, reactive oxygen species (ROS) levels were found to be increased and that the elevation is more pronounced in obese patients with T2DM.[40] Further, dyslipidemia was reported to be a trigger for CAD in patients with diabetes in a Romanian population, as it is an initiation factor of the dyslipidemia-inflammation-T2DM-cardiovascular signaling pathway.[41] The patients enrolled in our study were overweight (with a mean BMI of 25.96) and had CAD and T2DM; therefore, their levels of inflammation and ROS were elevated. Theoretically, patients with CAD and T2DM will suffer from severe coronary stenosis and have an increased risk of MACE. Given the pleiotropic effects mentioned above, *DPP4* SNPs influences the severity of coronary artery stenosis. However, no relationship was found between *DPP4* rs3788979 or rs7608898 alleles and the severity of coronary artery stenosis in our study. We found that their impact on the pathogenesis of CAD is such that the presence of the traditional risk factors decreases the prediction value of *DPP4* polymorphism for coronary artery stenosis, obscuring any effect of *DPP4* polymorphism. To circumvent the influence of these risk factors, we further analyzed the data including only the women, no-smoking, no-drinking, and no-family history participants. We discovered that A>G changes in rs3788979 were associated with a reduction in the proportion of severe coronary artery stenosis in women, those with no-drinking, no-smoking, or no cardiovascular family history. In conjunction with the logistic stepwise regression, we concluded that *DPP4* rs3788979 was a predictor of coronary artery stenosis and hypothesized that G allele may have a cardioprotective effect and thereby lead to only moderate coronary artery stenosis.

We observed that the majority of the women groups were neither alcohol consumers nor smokers, and perhaps there is a common mechanism behind the 3 groups, which could explain the cardioprotective effect of allele G. Further explorations are needed. Studies on plasma DPP4 levels in patients with CAD and T2DM in Chinese are also urgently needed in the near future to further verify the effect of allele G.

Some study limitations should be taken into consideration. First, the sample size was relatively small. Only 201 patients were enrolled over a study period of 3 years, and the lipid levels of many of those patients could not be obtained. Second, DPP4 concentration and activity were not detected, and further studies need to be performed to determine the plasma DPP4 levels.

5. Conclusion

The allele frequencies of *DPP4* rs3788979 SNP in patients with CAD and T2DM were significantly different from those found in a Caucasian patient population, verifying an ethnic difference. Allele mutation of A to G in rs3788979 is associated with reduced ApoB level. In the female group as well as those groups with no smoking, drinking, and cardiovascular family history, *DPP4* rs3788979 may be a predictor of coronary stenosis severity and allele G may have a cardioprotective effect; however, the underlying mechanism is unclear, and further studies are needed.

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Correction

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Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, PR China." and have since been corrected to "a Department of Cardiology, Shandong Qianfoshan Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, PR China. b Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, PR China c Department of Pharmacy, Shandong Qianfoshan Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, PR China. d Department of Cardiology, Tengzhou Central People's Hospital, Shandong Province, PR China."

References

[1] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 2014;129:e28–92.

[2] Mack M, Gopal A. Epidemiology traditional and novel risk factors in coronary artery disease. Heart Fail Clin 2016;12:1–10.

[3] O'Donnell CJ, Nabel EG. Genomics of cardiovascular disease. N Engl J Med 2011;365:2098–109.

[4] Roberts R, Marian AJ, Dandona S, et al. Genomics in cardiovascular disease. J Am Coll Cardiol 2013;61:2029–37.

[5] Nordlie MA, Wold LE, Kloner RA. Genetic contributors toward increased risk for ischemic heart disease. J Mol Cell Cardiol 2005; 39:667–79.

[6] Roberts R, Stewart AF. Genes and coronary artery disease: where are we? J Am Coll Cardiol 2012;60:1715–21.

[7] Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000;102: 1014–9.

[8] Rivas Rios JR, Franchi F, Rollini F, et al. Diabetes and antiplatelet therapy: from bench to bedside. Cardiovasc Diagn Ther 2018;8:594–609.

[9] Mangiacapra F, Bressi E, Colaiori I, et al. Interaction between diabetes mellitus and platelet reactivity in determining long-term outcomes following percutaneous coronary intervention. J Cardiovasc Transl Res 2020;13:668–75.

[10] Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008;88: 1254–64.

[11] Lin CC, Liu CS, Li CI, et al. Dietary macronutrient intakes and mortality among patients with type 2 diabetes. Nutrients 2020;12:1665.

[12] Aghili N, Devaney JM, Alderman LO, et al. Polymorphisms in dipeptidyl peptidase IV gene are associated with the risk of myocardial infarction in patients with atherosclerosis. Neuropeptides 2012;46:367–71.

[13] Sato Y, Koshioka S, Kirino Y, et al. Role of dipeptidyl peptidase IV (DPP4) in the development of dyslipidemia: DPP4 contributes to the steroid metabolism pathway. Life Sci 2011;88:43–9.

[14] Ansorge S, Bank U, Heimburg A, et al. Recent insights into the role of dipeptidyl aminopeptidase IV (DPIV) and aminopeptidase N (APN) families in immune functions. Clin Chem Lab Med 2009;47:253–61.

[15] Ku HC, Chen WP, Su MJ. DPP4 deficiency exerts protective effect against H2O2 induced oxidative stress in isolated cardiomyocytes. PLoS One 2013;8:e54518.

[16] Zhong J, Rao X, Rajagopalan S. An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: potential implications in cardiovascular disease. Atherosclerosis 2013;226:305–14.

[17] Sauvé M, Ban K, Momen MA, et al. Genetic deletion or pharmacological inhibition of dipeptidyl peptidase-4 improves cardiovascular outcomes after myocardial infarction in mice. Diabetes 2010;59:1063–73.

[18] Xing X, Han Y, Zhou X, et al. Association between DPP4 gene polymorphism and serum lipid levels in Chinese type 2 diabetes individuals. Neuropeptides 2016;60:1–6.

[19] Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation 1979;59:607–9.

[20] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26(suppl):S5–20.

[21] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th text revision. Washington, DC; 2000.

[22] Wu Y, Wang W, Li XY, et al. Strong association between the interleukin-8-251A/T polymorphism and coronary artery disease risk. Medicine (Baltimore) 2019;98:e14715.

[23] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.

[24] Sevinç S, Akyol AD. Cardiac risk factors and quality of life in patients with coronary artery disease. J Clin Nurs 2010;19:1315–25.

[25] Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791–8.

[26] Engelen SE, van der Graaf Y, Stam-Slob MC, et al. Incidence of cardiovascular events and vascular interventions in patients with type 2 diabetes. Int J Cardiol 2017;248:301–7.

[27] Wittbrodt E, Bhalla N, Andersson Sundell K, et al. Assessment of the high risk and unmet need in patients with CAD and type 2 diabetes (ATHENA): US healthcare resource utilization, cost and burden of illness in the Diabetes Collaborative Registry. Endocrinol Diabetes Metab 2020;3:e00133.

[28] Higashibata T, Naito M, Mori A, et al. DPP4 genetic variants influence baseline prostate-specific antigen levels: the J-MICC study. Nagoya J Med Sci 2013;75:73–80.

[29] Song Y, Yang Y, Zhang J, et al. The apoB100/apoAI ratio is independently associated with the severity of coronary heart disease: a cross sectional study in patients undergoing coronary angiography. Lipids Health Dis 2015;14:150.

[30] Tremblay AJ, Lamarche B, Deacon CF, et al. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. Diabetes Obes Metab 2011;13:366–73.

[31] Bailey SD, Xie C, Paré G, et al. Variation at the DPP4 locus influences apolipoprotein B levels in South Asians and exhibits heterogeneity in Europeans related to BMI. Diabetologia 2014;57:738–45.

[32] Bassendine MF, Bridge SH, McCaughan GW, et al. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? J Diabetes 2020;12:649–58.

[33] Cheng XW, Narisawa M, Jin E, et al. Dose rectification of an imbalance between DPP4 and GLP-1 ameliorates chronic stress-related vascular aging and atherosclerosis? Clin Exp Pharmacol Physiol 2018;45:467–70.

[34] Zheng T, Liu H, Qin L, et al. Oxidative stress-mediated influence of plasma DPP4 activity to BDNF ratio on mild cognitive impairment in elderly type 2 diabetic patients: results from the GDMD study in China. Metabolism 2018;87:105–12.

[35] Ottobelli Chielle E, de Souza WM, da Silva TP, et al. Adipocytokines, inflammatory and oxidative stress markers of clinical relevance altered in young overweight/obese subjects. Clin Biochem 2016;49:548–53.

[36] Emamalipour M, Seidi K, Jahanban-Esfahlan A, et al. Implications of resistin in type 2 diabetes mellitus and coronary artery disease: impairing insulin function and inducing pro-inflammatory cytokines. J Cell Physiol 2019;234:21758–69.

[37] Fargnoli JL, Sun Q, Olenczuk D, et al. Resistin is associated with biomarkers of inflammation while total and high-molecular weight adiponectin are associated with biomarkers of inflammation, insulin resistance, and endothelial function [published correction appears in Eur J Endocrinol. 2010 Aug;163(2):359]. Eur J Endocrinol 2010;162:281–8.

[38] Adela R, Reddy PNC, Ghosh TS, et al. Serum protein signature of coronary artery disease in type 2 diabetes mellitus. J Transl Med 2019;17:17.

[39] Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 2004;24:816–23.

[40] Pourrajab B, Fatahi S, Sohouli MH, et al. The effects of probiotic/synbiotic supplementation compared to placebo on biomarkers of oxidative stress in adults: a systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr 2020;1–8.

[41] Găman MA, Cozma MA, Dobrică EC, et al. Dyslipidemia: a trigger for coronary heart disease in Romanian patients with diabetes. Metabolites 2020;10:195.