

Very low-density lipoprotein cholesterol is associated with extent and severity of coronary artery disease in patients with type 2 diabetes mellitus

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Abstract

Objective: Patients with type 2 diabetes mellitus usually have multiple cardiovascular disease risk factors. The objective of this study was to examine the severity and associated risk factors in coronary artery disease patients with type 2 diabetes mellitus.

Methods: Two hundred and five coronary artery disease patients with type 2 diabetes mellitus and 205 age-, gender- and smoking-matched coronary artery disease patients without type 2 diabetes mellitus were recruited from the Department of Cardiology of our hospital. Demographic and clinical data were collected for all participants. Severity of coronary artery disease was assessed using Gensini scoring system, the number of diseased coronary arteries, and the extent of coronary stenosis.

Results: Coronary artery disease patients with type 2 diabetes mellitus had higher Gensini scores ($p < 0.01$), more numbers of diseased coronary arteries ($p < 0.001$), and higher degrees of coronary stenosis ($p = 0.05$) than coronary artery disease patients without type 2 diabetes mellitus. The plasma levels of very low-density lipoprotein cholesterol ($p < 0.001$) and triglycerides ($p < 0.001$) were also higher in coronary artery disease patients with type 2 diabetes mellitus than in coronary artery disease patients without type 2 diabetes mellitus. In coronary artery disease patients with type 2 diabetes mellitus, very low-density lipoprotein cholesterol was positively correlated with Gensini scores ($r = 0.15$, $p = 0.03$), the number of diseased coronary arteries ($r = 0.15$, $p = 0.04$), and the extent of coronary stenosis ($r = 0.14$, $p = 0.05$) by partial correlation analysis after controlling for other lipid parameters, and independently associated with Gensini scores ($\beta = 0.18$, $p = 0.02$) and the number of diseased coronary arteries (odds ratio = 2.09, $p = 0.05$) after adjusting for other cardiovascular risk factors in the following multiple regression analysis.

Conclusion: Very low-density lipoprotein cholesterol may represent a marker for the severity of coronary artery disease and be a target for the treatment in diabetic patients. Further research is needed to determine whether very low-density lipoprotein cholesterol plays a causal role of coronary artery disease in diabetic patients.

Keywords

Coronary artery disease, type 2 diabetes mellitus, very low-density lipoprotein cholesterol, severity, Gensini score

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Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality all over the world. Types of CAD include stable angina pectoris, unstable angina pectoris, and myocardial infarction. Common symptoms of CAD include discomfort and chest pain which may travel into the shoulder, arm, and back. Traditional risk factors for CAD include obesity, type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, smoking, and so on. Hyperuricemia,¹ hyperhomocysteinemia,² meta-inflammation,³ and oxidative stress⁴ are the emerging non-traditional risk factors for CAD.

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Diabetes mellitus has become a major public health problem in China, with an estimated prevalence of 11.6% for diabetes and 50.1% for prediabetes.⁵ Except for hyperglycemia and insulin resistance, the patients with T2DM are often accompanied by a number of severe metabolic disorders, such as hypertriglyceridemia,⁶ hypercholesterolemia,⁷ hyperuricemia,⁸ and hyperhomocysteinemia,⁹ all of which have been recognized as important risk factors for CAD. The aggregation of cardiovascular risk factors in diabetic patients makes these patients be at high risk of CAD and more severe than those without T2DM. This study used Gensini score, the number of diseased coronary arteries, and the extent of coronary stenosis to evaluate the severity of CAD, compared the severity of CAD between the patients with and without T2DM, and examined the risk factors for severity of CAD in patients with T2DM. The results of this study can provide diagnostic markers and therapeutic targets for patients with CAD and T2DM.

Patients and methods

Patients

A total of 410 consecutive unrelated patients who underwent coronary angiography for suspected CAD were enrolled in the retrospective case-control study between September 2016 and January 2019. Among them, there were 205 CAD patients with T2DM and 205 CAD patients without T2DM, matched for age, gender, and smoking. The patients had an age range from 36 to 88 years (64.62 ± 9.54 years). There were 131 men (64%) and 74 women (36%), 112 smokers (55%), and 93 non-smokers (45%) in each group. The body mass index (BMI) of the CAD patients with T2DM ranged from 17.80 to 34.85 kg/m² and that of the CAD patients without T2DM ranged from 16.65 to 37.46 kg/m². CAD was diagnosed according to the angiographic evidence of stenosis greater than 50% in at least one major coronary artery. T2DM was diagnosed according to 1999 World Health Organization (WHO) criteria for diabetes.¹⁰ Patients referred with renal or hepatic dysfunction, significant valvular disease, myocarditis malignant disease, or any diabetes-related complications such as ketoacidosis, hypoglycemia, and coma were not included in the study. Patients taking lipid-lowering drugs or the drugs that may affect the results of the study were also excluded. All patients provided written informed consent prior to participation in the study. This study was approved by the ethics committee of North Sichuan Medical College (2017008).

Coronary angiography

Coronary angiography was evaluated by two experienced cardiologists who were unaware of the patients' biochemical status. Standard coronary angiography with at least two

views of right coronary artery and four views of left coronary system was performed using Judkins technique by Allura Xper FD20 (Philips Medical Systems Nederland B.V., Netherlands). Atherosclerotic CAD was diagnosed in patients who had angiographic evidence of stenosis greater than 50% in at least one major coronary artery. Those with normal coronary arteries or minimal stenosis (less than 50%) in any of the major coronary arteries were excluded from the study. Gensini scoring system was used to assess the severity of CAD.¹¹ In this system, lumen narrowing of coronary artery is graded as 1 point for 1%–25% stenosis, 2 points for 26%–50% stenosis, 4 points for 51%–75% stenosis, 8 points for 76%–90% stenosis, 16 points for 91%–99% stenosis, and 32 points for complete occlusion. Each score is then multiplied by a factor that takes into account the importance of lesion's position in the coronary arterial tree, for example, 5 points for left main coronary artery, 2.5 points for proximal left anterior descending branch (LAD) or proximal left circumflex branch (LCX), 1.5 points for middle LAD or middle LCX, and 1 point for distal LAD, distal LCX, or right coronary arteries. Gensini score is calculated by the sum of the scores from all coronary arteries.

Anthropometric and biochemical measurement

BMI is calculated by dividing weight by height squared (kg/m²). Smokers are defined as the patients who are currently smoking. Hypertension is defined as systolic/diastolic blood pressure higher than 140/90 mmHg or active use of antihypertensive drugs based on 2018 Chinese guidelines for the management of hypertension.¹² T2DM is defined as fasting glucose level higher than 126 mg/dL or active use of antidiabetic drugs. Fasting blood samples were taken on the first morning of in-hospital day when no lipid-lowering drugs were used yet. Samples were transported to Department of Clinical Laboratory of our hospital for measurement of biochemical parameters. Triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid, glucose, and homocysteine were measured by using enzymatic method. Apolipoprotein B, apolipoprotein AI, lipoprotein (a), hypersensitive C-reactive protein (hs-CRP), and cystatin C were measured by using immunoturbidimetric assay. Total glycated hemoglobin (GHb) and glycated hemoglobin A1c (HbA1c) were measured by high-performance liquid affinity chromatography. All the measurements were carried out using an automatic clinical chemistry analyzer (Beckman Coulter AU5800, USA).

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation. Log transformation was done for the variables

Table 1. Clinical characteristics of the patients enrolled in the study.

Variables	CAD patients without T2DM (N=205)	CAD patients with T2DM (N=205)	p value
Weight (kg)	60.88 ± 15.89	63.84 ± 13.51	0.06
BMI (kg/m ²)	24.21 ± 3.09	24.77 ± 2.98	0.09
Hypertension, n (%)	115 (56.1%)	123 (60%)	0.24
Glucose (mmol/L)	5.23 ± 1.30	8.76 ± 4.33	<0.001
Total GHb (%)	7.63 ± 2.42	9.98 ± 2.71	<0.001
HbA1c (%)	6.19 ± 1.43	7.57 ± 1.59	<0.001
Total cholesterol (mmol/L)	4.18 ± 1.12	4.18 ± 1.20	0.95
LDL-C (mmol/L)	2.49 ± 0.83	2.39 ± 0.86	0.20
HDL-C (mmol/L)	1.00 ± 0.30	0.97 ± 0.30	0.33
VLDL-C (mmol/L)	0.71 ± 0.46	0.92 ± 0.76	<0.001
Triglyceride (mmol/L)	1.53 ± 0.83	2.10 ± 1.88	<0.001
Apolipoprotein AI (g/L)	1.05 ± 0.20	1.03 ± 0.21	0.41
Apolipoprotein B (g/L)	0.76 ± 0.23	0.79 ± 0.26	0.23
Lipoprotein (a) (mg/L)	312.42 ± 342.60	297.02 ± 356.81	0.66
hs-CRP (mg/L)	7.74 ± 18.28	11.74 ± 25.05	0.07
Homocysteine (μmol/L)	13.29 ± 6.30	12.08 ± 4.84	0.03
Uric acid (μmol/L)	343.32 ± 97.75	339.69 ± 107.85	0.72
Cystatin C (mg/L)	0.86 ± 0.32	0.92 ± 0.63	0.23
Gensini score	29.82 ± 28.34	38.11 ± 32.37	<0.01
≥2 diseased vessels, n (%)	112 (54.6%)	150 (73.2%)	<0.001
>90% stenosis, n (%)	61 (29.8%)	80 (39.0%)	0.05

CAD: coronary artery disease; T2DM: type 2 diabetes mellitus; BMI: body mass index; GHb: glycated hemoglobin; HbA1c: glycated hemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; VLDL-C: very low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; ANOVA: analysis of variance.

Differences between CAD patients with and without T2DM were analyzed by chi-square test for categorical variables and one-way ANOVA for continuous variables.

which were not normally distributed. Differences between CAD patients with and without T2DM were analyzed by chi-square test for categorical variables and one-way analysis of variance (ANOVA) analysis for continuous variables. Correlations of VLDL-C and triglycerides with severity of CAD were analyzed by Pearson's test, Spearman's test, and partial correlation test. Associations of VLDL-C and triglycerides with Gensini scores were analyzed by univariate and stepwise multivariate linear regression analyses, and the results were presented as beta coefficient as well as 95% confidence interval (CI). Associations of VLDL-C and triglycerides with the number of diseased coronary arteries and the extent of coronary stenosis were analyzed by univariate and multivariate ordinal logistic regression analyses, and the results were presented as odds ratio (OR) as well as 95% CI. PASS 14 software was employed to calculate the necessary sample size to ensure adequate statistical power for hypothesis tests and the results showed that the sample size of 410 subjects could provide ≥80% power to detect a significant association between the cardiovascular risk factors and the severity of CAD ($\alpha=0.05$) in univariate and multivariate logistic regression analyses. All *p* values were two-tailed and differences were considered significant if $p \leq 0.05$. All statistical analyses were carried out by using SPSS software (SPSS version 13.0, Chicago, USA).

Results

Clinical characteristics of the study population

Table 1 gives the clinical characteristics of CAD patients with or without T2DM. CAD patients with T2DM had higher Gensini scores ($p < 0.01$) than CAD patients without T2DM. The prevalence of patients with two or more diseased coronary arteries ($p < 0.001$) or of patients with over 90% stenosis ($p = 0.05$) was higher in patients with T2DM than in patients without T2DM. CAD patients with T2DM had higher levels of glucose ($p < 0.001$), total GHb ($p < 0.001$), HbA1c ($p < 0.001$), VLDL-C ($p < 0.001$), triglycerides ($p < 0.001$), and lower levels of homocysteine ($p = 0.03$) than CAD patients without T2DM. Body weight ($p = 0.06$), BMI ($p = 0.09$), and hs-CRP level ($p = 0.07$) in CAD patients with T2DM were marginally insignificantly higher in patients with T2DM than in patients without T2DM. There were no significant differences in total cholesterol, LDL-C, HDL-C, apolipoprotein AI, apolipoprotein B, lipoprotein (a), uric acid, cystatin C, and prevalence of hypertension between the two groups.

Correlations of VLDL-C and triglycerides with severity of CAD in patients with T2DM

The results of the correlation analyses of VLDL-C and triglycerides with severity of CAD in patients with T2DM are

Table 2. Correlations of VLDL-C and triglycerides with the severity of CAD in patients with T2DM.

Analysis methods	Gensini scores		Number of diseased coronary arteries		Extent of coronary stenosis	
	r	p value	r	p value	r	p value
VLDL-C						
Pearson	0.21	<0.01	0.16	0.03	0.19	<0.01
Spearman	0.27	<0.001	0.19	<0.01	0.23	<0.01
Partial correlation	0.15	0.03	0.15	0.04	0.14	0.05
Triglyceride						
Pearson	0.14	0.04	0.12	0.08	0.12	0.07
Spearman	0.26	<0.001	0.14	0.05	0.21	<0.01
Partial correlation	0.11	0.13	0.07	0.33	0.06	0.42

CAD: coronary artery disease; T2DM: type 2 diabetes mellitus; VLDL-C: very low-density lipoprotein cholesterol.

Partial correlation analysis was adjusted for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, lipoprotein (a), and triglyceride in the analysis for VLDL-C, and for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, lipoprotein (a), and VLDL-C in the analysis for triglyceride.

shown in Table 2. VLDL-C was positively correlated with Gensini scores (Pearson: $r=0.21$, $p<0.01$; Spearman: $r=0.27$, $p<0.001$), the number of diseased coronary arteries (Pearson: $r=0.16$, $p=0.03$; Spearman: $r=0.19$, $p<0.01$), and the extent of coronary stenosis (Pearson: $r=0.19$, $p<0.01$; Spearman: $r=0.23$, $p<0.01$) when analyzed by Pearson's test and Spearman's test. The correlations between VLDL-C and Gensini scores ($r=0.15$, $p=0.03$), the number of diseased coronary arteries ($r=0.15$, $p=0.04$), or the extent of coronary stenosis ($r=0.14$, $p=0.05$) remained significant in partial correlation analysis even when other lipid parameters such as total cholesterol, LDL-C, HDL-C, apolipoprotein AI, apolipoprotein B, lipoprotein (a), and triglycerides were adjusted.

Triglycerides were positively correlated with Gensini scores ($r=0.26$, $p<0.001$), the number of diseased coronary arteries ($r=0.14$, $p=0.05$), and the extent of coronary stenosis ($r=0.21$, $p<0.01$) by Spearman's test and was positively correlated with Gensini scores ($r=0.14$, $p=0.04$) by Pearson's test. However, they became insignificant in partial correlation analysis when adjusted for other lipid parameters.

Associations of VLDL-C and triglycerides with severity of CAD in patients with T2DM

As shown in Table 3, VLDL-C is significantly associated with Gensini scores, the number of diseased coronary arteries, and the extent of coronary stenosis in CAD patients with T2DM by univariate regression analysis in Model 1. Subsequent multivariate regression analysis revealed that VLDL-C is independently and significantly associated with Gensini scores and the number of diseased coronary arteries after adjusting for age, sex, weight, BMI, smoking, hypertension, triglycerides, total cholesterol, HDL-C, LDL-C, apolipoprotein AI, apolipoprotein B, hs-CRP, homocysteine,

Table 3. Association between VLDL-C and the severity of CAD in patients with T2DM.

Models	Adjusted beta or OR	95% CI	p value
Gensini score			
Model 1	0.21 (beta)	0.07–0.29	<0.01
Model 2	0.19 (beta)	0.03–0.30	0.02
Model 3	0.19 (beta)	0.03–0.30	0.02
Model 4	0.18 (beta)	0.03–0.33	0.02
Number of diseased coronary arteries			
Model 1	1.50 (OR)	1.08–2.10	0.02
Model 2	1.91 (OR)	1.26–2.92	<0.01
Model 3	2.17 (OR)	1.12–1.55	0.02
Model 4	2.09 (OR)	1.01–4.34	0.05
Extent of coronary stenosis			
Model 1	1.55 (OR)	1.11–2.16	0.01
Model 2	1.50 (OR)	1.00–2.26	0.05
Model 3	1.40 (OR)	0.75–2.62	0.30
Model 4	1.83 (OR)	0.91–3.69	0.09

CAD: coronary artery disease; OR: odds ratio; CI: confidence interval; VLDL-C: very low-density lipoprotein cholesterol; T2DM: type 2 diabetes mellitus; Model 1: analyzed by univariate analysis without adjustment; Model 2: adjusted for age, sex, weight, body mass index, smoking, and hypertension; Model 3: adjusted for the variables in Model 2 plus triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein (a); Model 4: adjusted for the variables in Model 3 plus hypersensitive C-reactive protein, homocysteine, uric acid, and cystatin C.

uric acid, and cystatin C in Models 2–4. The association between VLDL-C and the extent of coronary stenosis was significant after adjustment for age, sex, weight, BMI, smoking, and hypertension in Model 2, but it became insignificant when triglycerides, total cholesterol, HDL-C, LDL-C, apolipoprotein AI, and apolipoprotein B were added in Model 3.

Regarding the association between triglycerides and severity of CAD in patients with T2DM, the results of univariate regression analysis showed that triglycerides

Table 4. Association between triglycerides and the severity of CAD in patients with T2DM.

Models	Adjusted beta or OR	95% CI	p value
Gensini score			
Model 1	0.14	0.004 to 0.28	0.04
Model 2	0.18	0.03 to 0.32	0.02
Model 3	0.18	−0.03 to 0.36	0.08
Model 4	0.09	−0.21 to 0.39	0.55
Number of diseased coronary arteries			
Model 1	1.13	0.99 to 1.33	0.07
Model 2	1.23	1.06 to 1.45	0.01
Model 3	1.19	0.99 to 1.43	0.07
Model 4	1.19	0.97 to 1.46	0.09
Extent of coronary stenosis			
Model 1	1.11	0.98 to 1.27	0.11
Model 2	1.18	1.01 to 1.38	0.04
Model 3	1.25	0.95 to 1.67	1.12
Model 4	1.17	0.32 to 1.59	0.31

CAD: coronary artery disease; OR: odds ratio; CI: confidence interval; T2DM: type 2 diabetes mellitus; Model 1: analyzed by univariate analysis without adjustment; Model 2: adjusted for age, sex, weight, body mass index, smoking, and hypertension; Model 3: adjusted for the variables in Model 2 plus triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein (a); Model 4: adjusted for the variables in Model 3 plus hypersensitive C-reactive protein, homocysteine, uric acid, and cystatin C.

are significantly associated with Gensini score, but not the number of diseased coronary arteries and the extent of coronary stenosis in Model 1 (Table 4). The association between triglycerides and Gensini scores remained significant after adjusting for age, sex, weight, BMI, smoking, and hypertension in Model 2, but it became insignificant when triglycerides, total cholesterol, HDL-C, LDL-C, apolipoprotein AI, and apolipoprotein B were added in Model 3.

Discussion

In this study, CAD patients with T2DM had higher Gensini scores, more numbers of diseased coronary arteries ($p < 0.001$), and higher degrees of coronary stenosis than those without T2DM. Plasma levels of VLDL-C and triglycerides were also higher in CAD patients with T2DM than in CAD patients without T2DM. Therefore, we hypothesized that VLDL-C and/or triglycerides are associated with the severity of CAD in patients with T2DM. In line with our hypothesis, VLDL-C was found to be independently and significantly associated with the extent and severity of CAD in patients with T2DM, but not in those without T2DM by correlation and regression analyses.

The underlying mechanisms whereby VLDL-C is associated with the severity of CAD in patients with T2DM have not been clarified yet. One possible explanation is that VLDL-C is considered as a marker of atherogenic lipoprotein remnants.¹³ VLDL particles are a type of triglyceride-rich

lipoproteins produced in the liver. They become to VLDL remnants when most of the triglycerides are hydrolyzed by lipoprotein lipase in the circulation. Almost all cholesterol molecules in VLDL particles are directly transferred to VLDL remnants, so VLDL-C represents the amounts of VLDL remnants in the circulation. Yoshida et al.¹⁴ demonstrated that serum concentrations of VLDL-C are closely correlated with lipoprotein remnants in T2DM patients. The remnant particles have reduced contents of triglycerides, but increased contents of cholesterol and become smaller and denser than the parent particles. There is growing evidence that lipoprotein remnants are strongly atherogenic.^{15–21} The Framingham Heart Study found that an elevation in lipoprotein remnant levels is an independent risk factor for CAD in women.¹⁵ In another study from Japan,¹⁶ the investigators demonstrated that CAD patients with the highest tertile of remnant levels have a significantly higher probability of developing coronary events than those with the lowest tertile of remnant levels, and that higher levels of lipoprotein remnants in fasting serum predict future coronary events in patients with CAD independently of other risk factors. In a large Danish population of 73,513 subjects, the researchers observed a 2.8-fold higher causal odds of ischemic heart disease for each 1 mmol/L increase in remnant cholesterol.¹⁷

As shown by higher Gensini scores, more numbers of diseased coronary arteries, and higher degrees of coronary stenosis in CAD patients with T2DM than in CAD patients without T2DM, CAD patients with T2DM were much more severe than those without T2DM in this study. The elevation of lipoprotein remnants in T2DM patients may be one of the reasons why CAD patients with T2DM are more severe than the patients without T2DM. Lipoprotein remnant particles, including chylomicron remnants and VLDL remnants, were elevated up to four times in T2DM subjects compared with non-diabetic subjects.²² Chen et al.²³ demonstrated that T2DM in mice induces the overexpression of hepatic sulfatase 2, which suppresses the uptake of remnant lipoproteins by liver and leads to an increase in serum remnant lipoproteins. In the present study, we found that CAD patients with T2DM had higher levels of triglycerides, but not total cholesterol, LDL-C, and HDL-C than patients without T2DM. Similarly, Watanabe et al.²² and Schaefer et al.²⁴ also demonstrated a significant difference in triglyceride levels, but not in total cholesterol or LDL-C levels between T2DM patients and non-diabetic controls. However, Wang et al.²⁵ reported that patients with T2DM had not only higher levels of triglycerides but also higher levels of LDL-C and lower levels of HDL-C than those without T2DM. These discrepancies may partly be explained by differences in characteristics of patients, experimental design, and measurement methods. In addition, the different medical treatments among studies may also account for these inconsistent results.

Although a variety of methods have been developed to measure lipoprotein remnants, most are not applicable to clinical practice due to high demands on instruments and

expensive costs. The most readily available measure for lipoprotein remnants is to determine VLDL-C, which can be calculated out by subtracting LDL-C and HDL-C from total cholesterol. Our findings should be considered in the context of several potential limitations. First, lipoprotein remnants were not determined for the participants, so direct association between VLDL-C and lipoprotein remnants was unable to be analyzed. Second, the patients included in this study are exclusively Chinese Han people, and therefore the findings may not apply to other ethnic groups.

Conclusion

VLDL-C may be a useful predictor for assessing the severity of CAD and be a target for treatment in CAD patients with T2DM, but further investigations with large sample size and multi-ethnicities are required to validate these findings.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the ethics committee of North Sichuan Medical College (2017008).

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Informed consent

All patients provided written informed consent prior to their participation in the study.

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