



Association of the Serum Total Cholesterol to Triglyceride Ratio with Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes: A Community-Based Study

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ABSTRACT

Introduction: The relationship of total cholesterol (TC) or triglyceride (TG) to diabetic retinopathy (DR) has proven difficult to determine. In addition, there is no report of any study of the correlation between the TC/TG ratio and DR. This study was therefore undertaken to investigate the relationship between the TC/TG ratio and DR in Chinese adults with type 2 diabetes mellitus.

Methods: A community-based study was conducted from August to October 2014 in Fengyutan, Shenyang, China. DR was assessed based on the modified Airlie House classification of DR. Multivariable logistic regression models were used to evaluate the association

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between the TC/TG ratio and the presence of DR.

Results: Among the 420 diabetic participants in the study (157 men; mean (SD) age 61.7 (10.0) years), 76 (18.1%) presented with DR. When the TC/TG ratio was analyzed categorically, participants with T2DM in tertile 2 (i.e., TC/TG 2.91–4.00) were more likely (OR 2.01; 95% CI 1.01–3.99) to suffer from DR than patients in tertile 1 (i.e., TC/TG < 2.91) in multivariable models. Similarly, participants in tertile 3 (TC/TG > 4.00) were more likely (OR 2.59; 95% CI 1.11–3.14; $P = 0.011$) to suffer from DR than patients in tertile 1. This association persisted when the TC/TG ratio was analyzed continuously ($P = 0.014$).

Conclusion: We found a novel positive association between TC/TG ratio and presence of DR in Chinese individuals with T2DM. Although longitudinal data are needed, this finding contributes to the accumulating evidence that a high TC/TG ratio may be implicated in DR.

Keywords: Diabetic retinopathy; Total cholesterol; Triglycerides; Type 2 diabetes mellitus

INTRODUCTION

Diabetic retinopathy (DR) is not only a very common complication of diabetes mellitus (DM) but also an important cause of vision loss

and blindness in working-age adults [1, 2]. According to current scientific evidence, the pathogenesis of DR is still unclear, as it is complicated and related to many factors. Many previous studies have suggested that there is an association between abnormal lipid levels and the presence of DR [3–8]. In the Singapore Malay Eye study, a high total cholesterol (TC) level was found to protect against DR [9]. On the other hand, in another national survey performed in Korea by Yang et al., the serum TC level was not significantly associated with DR [10]. However, a cross-sectional study revealed that a higher triglyceride (TG) level was an independent risk factor for DR [11], although another cross-sectional study suggested that a lower TG level was associated with the presence of DR [12]. Hence, the relationship of TG or TC to DR is still unclear [13]. To date, no data on the correlation between the TC/TG ratio and DR have been reported.

In the study discussed in the present paper, we investigated the association of the TC/TG ratio with the presence of DR in a community-based sample of Chinese patients with type 2 DM.

METHODS

Study Population and Measurements

The Shenyang Diabetes Eye Study is a community-based cross-sectional study of clinical, behavioral, genetic, and environmental factors related to DR in Northeast China. The methodology of the Shenyang Diabetes Eye Study has been detailed in previous publications [14]. Briefly, a total of 595 Chinese Han adults with type 2 DM aged ≥ 18 years were recruited from Fengyutan Street, Shenyang from August to October 2014 according to their health files at Fengyutan Health Center. The present study utilized data collected from a subset of participants for whom TC/TG ratio data were available (both TC and TG levels; $n = 429$). Nine of those participants were subsequently excluded due to ungradable fundus images, leaving 420 participants available for analysis.

Each participant underwent a comprehensive assessment. Standardized interviews were done that covered the following information: age, gender, smoking, drinking, family history of DM, duration of DM, use of oral hypoglycemic agents, use of insulin, exercise, and history of high blood pressure (HBP). Height and weight were measured, and body mass index (BMI) was calculated using the following formula: $BMI = \text{weight (kg)}/\text{height (m}^2\text{)}$. Systolic blood pressure (SBP), diastolic blood pressure (DBP), waist, and hips were then measured. The waist-to-hip ratio (WHR) was determined as the circumference of the waist divided by that of the hips. Fasting (≥ 8 h) venous blood samples were obtained to measure fasting plasma glucose (FPG), hemoglobin A_{1c} (HbA_{1c}), triglyceride (TG), and total cholesterol (TC) levels. All laboratory examinations were performed at the Endocrinology Laboratory, China Medical University, using commercially available assays. The TC/TG ratio was evaluated as the TC level divided by that of the TG level.

Diabetes mellitus (DM) was defined as FPG ≥ 7.0 mmol/L, HbA_{1c} $\geq 6.5\%$, self-reported use of antidiabetic medication, or physician-diagnosed diabetes [15]. Hypertension was defined as a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or any use of an antihypertensive medication. Smokers were defined as current smokers, regardless of the number of cigarettes they smoked per day. Drinkers were defined as those who reported that they drank at least five (for males) or four (for females) drinks at least once a week for one year.

After pupil dilation, the presence of DR was graded based on two-field (one centered on the optic disk; the other centered on the fovea) fundus photographs (CR6-45NM; Canon, Inc., Tokyo, Japan) according to the Early Treatment for Diabetic Retinopathy Study (ETDRS) standards [16]. This analysis of the fundus photographs was carried out in a blinded manner. DR was considered to be present if any characteristic lesion was present: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous bleeding, or new vessels. Data from the worst eye were used in the analyses. This study was carried out in compliance with the Helsinki

Declaration and approved by the ethics committee of the First Affiliated Hospital of China Medical University. All participants signed an informed consent form. The present study was a population-based investigation rather than clinical trial, so it was not registered.

Statistical Analysis

The Statistical Program for Social Sciences (SPSS, version 20.0, IBM) for Windows was used for statistical analysis. The mean \pm standard deviation (SD) was used to describe normally distributed data, while the median (interquartile range, IQR) was used if the data were non-normally distributed. The chi-square test was used for categorical outcomes. The Wilcoxon–Mann–Whitney test or *t* test was employed to compare the characteristics of the participants with and without DR according to the continuous data distribution. Subjects were classified into three groups according to TC, TG, and TC/TG ratio using specific threshold values (TC/TG: tertile 1, < 2.91 ; tertile 2, 2.91 – 4.00 ; and tertile 3, > 4.00 ; TC: tertile 1, < 4.74 ; tertile 2, 4.74 – 5.74 ; and tertile 3, > 5.74 ; TG: tertile 1, < 1.69 ; tertile 2, 1.69 – 2.20 ; and tertile 3, > 2.20), respectively. Logistic regression models (model 1: adjusted for age and gender; model 2: adjusted for age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels) were used to assess the associations of TC, TG, and the TC/TG ratio with DR. For all tests, a *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Among the 420 participants with type 2 DM included in this study, 76 (18.1%) had DR. The characteristics of all the study participants are shown in Table 1. Compared with the participants who did not have DR, the patients with DR were more likely to be males with a longer diabetes duration, to more frequently use oral hypoglycemic agents and insulin, and to have higher diastolic BP, HbA_{1c}, and TC/TG ratio values but smaller waist and WHR values.

The TC/TG ratio was assessed continuously (per SD change). In model 1 (after adjusting for age and gender), a higher TC/TG ratio was associated with the presence of DR (odds ratio, OR 1.51; 95% confidence interval CI 1.19–1.91; *P* = 0.001); see Table 2. In model 2 (after adjusting for potential confounders such as age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels), a higher TC/TG ratio was still associated with an increased risk for DR (OR 1.39; 95% CI 1.07–1.82; *P* = 0.014). When the TC/TG ratio was assessed categorically after adjusting for age and gender, the participants in tertile 3 (TC/TG > 4.00) were found to be more likely (OR 1.92; 95% CI 1.05–3.49; *P* = 0.034) to suffer from DR than the patients in tertile 1 (TC/TG < 2.91). After adjusting for potential confounders (age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels), participants in tertile 2 (TC/TG 2.91 – 4.00) were more likely (OR 2.01; 95% CI 1.01–3.99; *P* = 0.048) to suffer from DR than patients in tertile 1 (TC/TG < 2.91). Similarly, participants in tertile 3 (TC/TG > 4.00) were more likely (OR 2.59; 95% CI 1.11–3.14; *P* = 0.011) to suffer from DR than patients in tertile 1 (TC/TG < 2.91).

In the present study, we also conducted additional analyses to confirm the associations of TC and TG with DR, respectively. In Tables 3 and 4, after adjusting for age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels, the logistic regression analysis showed that TC (OR 0.86; 95% CI 0.65–1.13; *P* = 0.275) and TG (OR 0.84; 95% CI 0.59–1.18; *P* = 0.329) were nonsignificant risk factors for DR. These associations persisted when the TC and TG levels were analyzed categorically.

DISCUSSION

The relationship of TG or TC to DR has been difficult to determine [13]. Hence, we conducted this population-based cross-sectional study to reveal the association between the TC/TG ratio and the risk of DR. The present study suggests that TC and TG levels are not

Table 1 Basic characteristics of the study participants

Variables	Overall (<i>n</i> = 420)	DR (<i>n</i> = 76)	NDR (<i>n</i> = 344)	<i>P</i> value
Age (years)	61.7 ± 10.0	60.1 ± 9.6	62.0 ± 10.0	0.138
Gender (male, %)	157 (37.4)	36 (47.4)	121 (35.2)	0.051
Current smoker (yes, %)	87 (20.7)	14 (18.4)	73 (21.2)	0.642
Current drinker (yes, %)	38 (9.0)	6 (7.9)	32 (9.3)	0.827
Family history of DM (yes, %)	111 (26.4)	25 (32.9)	86 (25.0)	0.195
Duration of DM (years)	4.0 (0.1–9.0)	14.8 (10.0–20.0)	7.0 (3.0–13.0)	< 0.001
HBP (yes, %)	202 (48.1)	43 (56.6)	159 (46.2)	0.128
Use of oral hypoglycemic agents (yes, %)	202 (48.1)	46 (60.5)	156 (45.3)	0.022
Use of insulin (yes, %)	77 (18.3)	28 (36.8)	49 (14.2)	< 0.001
Exercise (yes, %)	31 (7.4)	3 (3.9)	28 (8.1)	0.33
Height (cm)	163.0 (160.0–170.0)	163.5 (159.3–172.0)	162.5 (160.0–170.0)	0.705
Weight (kg)	68.0 (60.0–72.0)	68.0 (60.0–72.8)	68.0 (60.3–72.0)	0.976
BMI (kg/m ²)	24.4 (23.1–26.1)	24.0 (22.6–26.0)	24.5 (23.2–26.3)	0.526
SBP (mmHg)	135.0 (130.0–145.0)	140.0 (130.0–145.0)	135.0 (130.0–145.0)	0.497
DBP (mmHg)	80.0 (76.3–90.0)	85.0 (80.0–90.0)	80.0 (75.3–87.8)	0.024
Waist (cm)	86.0 (82.0–90.0)	83.0 (80.0–86.0)	87.0 (82.0–90.0)	< 0.001
Hip (cm)	98.0 (90.3–105.0)	98.0 (92.0–105.0)	98.0 (90.0–106.0)	0.972
WHR	0.9 (0.80–0.9)	0.8 (0.7–0.9)	0.9 (0.8–1.0)	0.008
FPG (mmol/L)	6.8 (5.8–8.6)	7.3 (6.2–9.2)	6.7 (5.8–8.3)	0.171
TG (mmol/L)	1.7 (1.3–2.2)	1.4 (1.0–2.0)	1.7 (1.3–2.2)	0.054
TC (mmol/L)	4.7 (4.4–5.7)	4.5 (4.4–5.4)	4.9 (4.4–5.6)	0.057
HbA _{1c} (%)	6.8 (6.2–8.0)	7.8 (6.2–9.2)	6.7 (6.1–7.7)	0.004
TC/TG ratio	2.9 (2.1–4.0)	3.3 (2.2–4.6)	2.8 (2.1–4.0)	0.016

HBP high blood pressure, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WHR* waist-to-hip ratio, *FPG* fasting plasma glucose, *NDR* patients without diabetic retinopathy, *DR* patients with diabetic retinopathy, *DM* diabetes mellitus, *HbA_{1c}* hemoglobin A_{1c}, *TG* triglyceride, *TC* total cholesterol

associated with DR, respectively, while the TC/TG ratio is significantly associated with a high risk of DR.

The association between the TC/TG ratio and any measure of DR is yet to be reported in the literature. However, the TC/TG ratio was found to be increased in patients with metabolic disease [17–19]. The risk factors for metabolic disease, such as diabetes, hypertension, and

dyslipidemia, all contribute to DR [20] and may partly explain this association.

No clear association between dyslipidemia and DR has been established, as studies have reported inconsistent findings regarding this association. TC was associated with DR prevalence in the Singapore Epidemiology of Eye Diseases Study (which included Malay, Indian, and Chinese patients) [21]. In other population-

Table 2 Associations of the TC/TG ratio with diabetic retinopathy (DR)

	<i>n</i>	DR (<i>n</i> , %)	Model 1 ^a		Model 2 ^b	
			OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
TC/TG						
Tertile 1, TC/TG < 2.91	212	29 (13.7)	1	–	1	–
Tertile 2, TC/TG 2.91–4.00	104	22 (21.2)	1.68 (0.91–3.12)	0.098	2.01 (1.01–3.99)	0.048
Tertile 3, TC/TG > 4.00	104	25 (24.0)	1.92 (1.05–3.49)	0.034	2.59 (1.11–3.14)	0.011
				<i>P</i> for trend = 0.027		<i>P</i> for trend = 0.123
Per SD increase in TC/TG	420	76 (18.1)	1.51 (1.19–1.91)	0.001	1.39 (1.07–1.82)	0.014

^a Adjusted for age and gender

^b Adjusted for age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels

Table 3 Associations of TC with diabetic retinopathy (DR)

	<i>n</i>	DR (<i>n</i> , %)	Model 1 ^a		Model 2 ^b	
			OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
TC						
Tertile 1, TC < 4.74	211	46 (21.8)	1	–	1	–
Tertile 2, TC 4.74–5.74	104	14 (13.5)	0.54 (0.28–1.05)	0.070	0.53 (0.26–1.09)	0.084
Tertile 3, TC > 5.74	105	16 (15.2)	0.67 (0.34–1.25)	0.206	0.57 (0.28–1.17)	0.126
				<i>P</i> for trend = 0.119		<i>P</i> for trend = 0.078
Per SD increase in TC	420	76 (18.1)	0.91 (0.71–1.17)	0.471	0.86 (0.65–1.13)	0.275

^a Adjusted for age and gender

^b Adjusted for age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels

based studies (the Beijing Eye Study and the 2008–2009 Korea National Health and Nutrition Examination Survey), dyslipidemia (both TC and TG levels) was not significantly associated with DR prevalence [10, 22]. Our group previously reported that there was no association between TC and DR prevalence [23]. Similarly, in the current study, there was no

significant association between hyperlipidemia (TC and TG) and risk of DR (Tables 3, 4). Even with inconsistent findings regarding the association of dyslipidemia (TC and TG levels and the TC/TG ratio) with DR, it is still important for clinicians to encourage patients to optimize their lipid profiles due to their associations with the risk of other complications of diabetes as

Table 4 Associations of TG with diabetic retinopathy (DR)

	<i>n</i>	DR (<i>n</i> , %)	Model 1 ^a		Model 2 ^b	
			OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
TG						
Tertile 1, TG < 1.69	215	47 (21.9)	1	–	1	–
Tertile 2, TG 1.69–2.20	102	15 (14.7)	0.60 (0.32–1.15)	0.123	0.61 (0.29–1.23)	0.165
Tertile 3, TG > 2.20	103	14 (13.6)	0.57 (0.29–1.11)	0.097	0.57 (0.27–1.18)	0.128
				<i>P</i> for trend = 0.061		<i>P</i> for trend = 0.087
Per SD increase in TG	420	76 (18.1)	0.82 (0.59–1.12)	0.211	0.84 (0.59–1.18)	0.329

^a Adjusted for age and gender

^b Adjusted for age, gender, duration of DM, use of insulin, use of oral hypoglycemic agents, DBP, WHR, and HbA_{1c} levels

well as DR. The strengths of our study include the following: the association between the TC/TG ratio and DR was adjusted for major potential confounders including age, gender, HbA_{1c}, DBP, WHR, duration of DM, antidiabetic medication (such as oral hypoglycemic agents and insulin); it was the first investigation of an association between the TC/TG ratio and DR; and it used a population-based study design. However, potential limitations of our study should be mentioned. First, nearly 90.8% of the participants with diabetes had nonproliferative diabetic retinopathy (NPDR); subjects with proliferative changes were less common. This could have led to the underestimation of the association between the TC/TG ratio and the risk of PDR. Second, the association between the TC/TG ratio and DR was not adjusted for the effects of other potential confounders such as socioeconomic status and education, as the information required to adjust for these potential confounders was not collected. Third, two-field retinal photographs were used to evaluate and monitor for the presence of DR. This may have led to underestimation of the true prevalence of DR. Additionally, our study was a cross-sectional investigation which primarily did not allow statements about longitudinal

relationships. Hence, a longitudinal population-based study is needed to investigate the association between TC/TG ratio and risk of DR.

CONCLUSION

In summary, after adjusting for potential confounders, the TC/TG ratio in Chinese individuals with diabetes was found to be associated with DR events. This significant association may help us to better understand the risk of DR and may lead to new targeted therapy aimed at preventing DR.

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Authorship Contributions. Lei Liu designed the study and reviewed the manuscript. Yifan Zhong, Song Yue, and Jingyang Wu collected data. Peng Guan, Guisen Zhang, Lei Liu, and Lei Chen analyzed the data and drafted the manuscript.

Disclosures. Yifan Zhong, Song Yue, Jingyang Wu, Peng Guan, Guisen Zhang, Lei Liu, and Lei Chen have nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the institutional review board of The First Affiliated Hospital of the China Medical University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individuals included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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