Association Between Triglyceride Level and Glycemic Control Among Insulin-Treated Patients With Type 2 Diabetes

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Context: Elevated blood triglyceride levels are known to increase the risks of diabetes and prediabetes. However, it is still unclear whether elevated triglyceride levels are associated with inadequate glycemic control in patients with type 2 diabetes mellitus.

Objective: To investigate the association between elevated triglyceride levels and inadequate glycemic control among insulin-treated patients with type 2 diabetes mellitus.

Design, Setting, and Patients: We recruited 20,108 patients with type 2 diabetes mellitus who were treated with a sufficient dose of insulin. These patients were from the 2013 China National HbA_{1c} Surveillance System study conducted in Mainland China. Multivariate logistic regressions were used to assess the association of triglyceride level with inadequate glycemic control.

Results: Overall, 56.0% of the subjects had elevated triglyceride levels (≥1.70 mmol/L); prevalence of HbA_{1c} ≥7.0% (53 mmol/mol) and ≥6.5% (48 mmol/mol) was 67.2% and 83.4%, respectively. The adjusted ORs (95% CIs) of HbA_{1c} ≥7.0% were 1.06 (0.98, 1.15), 1.35 (1.23, 1.48), and 3.12 (2.76, 3.53) for those with triglyceride levels in ranges of 1.70 to 2.29, 2.30 to 3.39, and ≥3.40 mmol/L, respectively, compared with those with triglyceride levels of <1.70 mmol/L. There was a similar association between triglyceride levels and HbA_{1c} ≥6.5%. This association was confirmed by subgroup analyses. There was also a strong nonlinear dose-response relationship between triglyceride level and inadequate glycemic control.

Conclusions: Elevated triglyceride levels were strongly associated with inadequate glycemic control; thus, suppressing triglyceride levels may attain more optimal glycemic control in patients with type 2 diabetes mellitus. (***J Clin Endocrinol Metab*** **104: 1211–1220, 2019)**

The number of people with type 2 diabetes mellitus is rapidly growing. In fact, China is experiencing the world's largest diabetes epidemic. The prevalence of type 2 diabetes mellitus in Mainland China has risen from a low of 0.67% in 1980 to an astounding 10.9% in 2013, which represents more than 100 million Chinese individuals (1). Several large population studies, such as the United Kingdom Prospective Diabetes Study and the Veterans Affairs Diabetes Trial, have shown the importance of adequate glycemic control in patients with type 2 diabetes mellitus (2, 3). In particular, these and other large studies showed that tight glycemic control in

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Abbreviations: BMI, body mass index; CNHSS, Mainland China National HbA_{1c} Surveillance System; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCD, noncommunicable disease; OAD, oral antidiabetic drug; SMBG, self-monitoring of blood glucose; TC, total cholesterol; TG, triglyceride.

patients with type 2 diabetes mellitus can prevent the development or slow the progression of macrovascular and microvascular complications (4–10). The International Diabetes Mellitus Practices Study, which comprised 17 less affluent countries in Eastern Europe, Asia, Latin America, and Africa, revealed that only 20% to 30% of patients with diabetes achieved the goal of HbA_{1c} <7.0% (11). In the Hong Kong Diabetes Registry study of 7549 Chinese patients with type 2 diabetes mellitus, 39.7% of patients undergoing therapy were able to attain the glycemic target of HbA_{1c} <7.0% (12).

It has been accepted that some patients with type 2 diabetes mellitus eventually require insulin therapy to achieve more satisfactory glycemic control. Nevertheless, some patients receiving insulin therapy still cannot attain adequate glycemic control. Results from a large-scale survey in Mainland China demonstrated that only 26% to 31% of patients receiving insulin therapy achieved the targeted HbA_{1c} level of <7.0% (13). A Johns Hopkins Hospital study of Americans showed that approximately half (51%) of patients with type 2 diabetes mellitus receiving insulin therapy, with a total daily dose >0.4 U/kg of body weight, remained hyperglycemic (14). This begs the question as to what accounts for the failure of insulin therapy. Several prospective studies have demonstrated that elevated blood triglyceride (TG) levels increased the risk of diabetes (15–21), impaired fasting glucose level (15, 22), and impaired glucose tolerance (21). However, the relationship between TG levels and glucose metabolism is more complex in the pathological status of diabetes and its complications and may be influenced by the actions of antidiabetic drugs, such as insulin and metformin, on glucose and lipid metabolism. Therefore, the simple inference that elevated TG levels in patients with diabetes necessarily account for the deterioration of glucose metabolism and resulting inadequate glycemic control is insufficient. Currently, the assessment of dyslipidemia in patients with diabetes has focused mainly on its "chronic" actions, which lead to cardiovascular complications (23, 24), whereas the association of TG level with glucose metabolism is more "acute" than its association with heart disease (25). To our knowledge, no study has assessed whether elevated blood TG levels are associated with unfavorable glycemic control in patients with type 2 diabetes mellitus.

Using the very large, multicenter, cross-sectional Mainland China National HbA_{1c} Surveillance System (CNHSS) study, we extracted a population of patients with type 2 diabetes mellitus without diabetes complications who were treated with sufficient insulin and assessed the association of elevated TG levels with inadequate glycemic control.

Materials and Methods

Study subjects

The CNHSS study, which was launched by the Chinese Diabetes Society, was conducted between 2011 and 2013 in Mainland China. The CNHSS was established to monitor glycemic control among adult patients with type 2 diabetes mellitus. The survey was conducted from April to June in 2013, and recruited 238,639 outpatients with type 2 diabetes mellitus from 602 hospitals located in 90 cities in 29 provincial and administrative regions of Mainland China. The inclusion criteria were outpatients who had type 2 diabetes mellitus, were 18 years or older, and were treated with insulin, oral antidiabetic drugs (OADs), and other drugs (26, 27). The exclusion criteria included (i) diabetes secondary to other diseases; (ii) treatment with Chinese herbal medicines only; (iii) being pregnant or breastfeeding an infant; and (iv) unconsciousness or inability to communicate. During this survey period, on each workday the first seven consecutive outpatients who entered each hospital's endocrinology outpatient department and met the eligibility criteria were invited to participate in the survey until 400 patients were recruited from each participating hospital. In the present analysis, patients who had diabetes treated with insulin therapy alone or insulin therapy combined with OADs for more than 3 months were included. To avoid bias from insufficient insulin therapy, overtreatment, and diabetic complications, we excluded patients who were treated with a daily insulin dose <0.2 U/kg of body weight and those with severe hyperglycemia or severe hypoglycemia. To also reduce bias from the influence of other chronic noncommunicable diseases (NCDs) and their related treatments (*e.g.,* cholesterol-lowering statin and antihypertensive drugs), only patients without self-reported diagnoses of diabetic complications, hypertension, or dyslipidemia were included in this study. Furthermore, according to an insulin regimen for the management of type 2 diabetes mellitus with different glucose levels (28), patients treated with a daily insulin dose of <0.3, <0.4, or <0.5 U/kg of body weight who had a blood glucose level of 7.0 to 7.7, 7.8 to 11.1, or 11.1 to 22.2 mmol/L, respectively, were excluded in this study, as they were considered to be receiving insufficient insulin treatment.

Ultimately, 20,108 patients with type 2 diabetes mellitus (10,518 men and 9590 women) with complete information and blood sampling were included in this study. This study was approved by the Ethics Committee for Clinical Research of the Chinese PLA General Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. All participants gave their written informed consent before taking part in this survey.

Data collection

During the recruitment period, anthropometric and biochemical parameters were collected by trained professional workers (junior doctors, nurses, or postgraduate medical students) via a standardized questionnaire during face-to-face interviews. During the interviews, information was obtained regarding the patient's socioeconomic status and medical treatment, whether professional diabetes education was given by the doctors or nurses, and whether self-monitoring of blood glucose (SMBG) was recorded. Specific information on treatment was documented, including

the use of OADs and insulin. The date of diabetes diagnosis and medical history of NCDs and dates of their diagnosis were retrieved; these NCDs included hypertension, coronary heart disease, cerebrovascular disease, dyslipidemia, diabetic retinopathy, and diabetes-related foot ulcers. Standing height, body weight, and blood pressure levels were recorded during the interviews. Briefly, heights and weights were measured in light clothing with the use of standardized stadiometers and scales. Blood pressure level was measured on the right arm using a standard mercury sphygmomanometer or an electronic sphygmomanometer with the subjects resting for at least 5 minutes in a sitting position. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. All laboratory examinations, including total cholesterol (TC), TGs, low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose, and HbA_{1c}, were performed in the local hospitals where the interviews were conducted. The venous blood sample was taken on the next morning after at least 8 hours of overnight fasting. Blood glucose level was measured by the hexokinase/glucose oxidation method. HbA_{1c} was measured by HPLC. TGs and TC were determined by the oxidase method, and low density lipoprotein by the homogeneous method (29, 30). High-density lipoprotein cholesterol (HDL-C) was calculated using the Friedewald equation (31), where HDL-C = TC − LDL-C − TG/2.2, with all four quantities measured in mmol/L. One trained staff member entered all the data and uploaded the entered data into the central database.

Assessment of covariates

TG levels were categorized into four groups according to the guidelines on prevention and treatment of dyslipidemia (32) and quantiles of the sampling distribution. In addition, elevated TC and LDL-C profiles were classified in accordance with published criteria (32). BMI was assessed as either normal weight (BMI <24.0 kg/m^2) or overweight (BMI ≥ 24.0 kg/m^2). Elevated blood pressure level was considered to be a systolic blood pressure level ≥ 130 mm Hg and/or a diastolic blood pressure level ≥ 80 mm Hg.

Definition of inadequate glycemic control

The main outcome variable was inadequate glycemic control. On the basis of the HbA_{1c} target recommended in published guidelines (33, 34), two types of inadequate glycemic control were defined: $HbA_{1c} \geq 7.0\%$ (53 mmol/mol) and $HbA_{1c} \geq 6.5\%$ (48 mmol/mol).

Statistical analysis

Continuous data were expressed as mean plus SD. Frequencies and percentages were used to express categorical variables. Continuous variables in each of the groups were compared using the Kruskal-Wallis H test. Homoscedasticity of continuous variables among different TG groups were compared by performing the Bartlett test and Levene test. The χ^2 test was used to compare proportions for categorical variables. Logistic regressions were used to calculate ORs and 95% CIs for inadequate glycemic control. Subgroup analyses were conducted to further explore the association between TG levels and the risk of inadequate glycemic control by predefined stratifications of sex, age, BMI, blood pressure, and duration of diabetes. In addition, the presence of nonlinearity between continuous TG levels and ORs of individual glycemic control outcome was assessed by dose-response analyses using restricted cubic spline regression. For all analyses, a two-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed using *R* version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC).

Results

Among the 20,108 patients included in the study, the mean age was 56.6 ± 11.6 years. The characteristics of the study population categorized along the different blood TG levels are summarized in Table 1. Results of the homoscedasticity test for continuous variables among the different TG groups are provided in Table 2. Overall, 56% of insulin-treated patients with diabetes had elevated TG levels (≥1.70 mmol/L). The prevalence of HbA_{1c} values ≥7.0% and ≥6.5% was 67.2% and 83.4%, respectively. Individuals with higher TG levels less frequently self-monitored their blood glucose level and generally had higher blood pressure levels and TC and LDL-C values. These individuals with higher TG levels also had a higher prevalence of inadequate glycemic control. There were statistically significant increasing trends in the proportion of patients with $HbA_{1c} \geq 7.0\%$ and $HbA_{1c} \geq 6.5\%$ with respect to the different categories of TG levels.

After step-forward adjustments for sex, age (model 1), BMI (model 2), blood pressure, TC, LDL-C, and HDL-C (model 3), duration of diabetes, diabetes education, and the frequency of SMBG (model 4) in the multivariable-adjusted models, graded positive ORs of inadequate glycemic control for those with step-elevated TG levels were similar across the different models. In the analyses of the final model adjusted simultaneously for all potential confounding factors, the ORs (95% CI) of $HbA_{1c} \geq 7.0\%$ for those with TG levels in the ranges of 1.70 to 2.29, 2.30 to 3.39, and ≥3.40 mmol/L were 1.06 (0.98, 1.15), 1.35 (1.23, 1.48), and 3.12 (2.76, 3.53), respectively, compared with patients with TG levels <1.70 mmol/L (Table 3). There were statistically significant trends with increased odds of inadequate glycemic control in the four categories of TG levels ($P < 0.001$ for trend for all comparisons). For inadequate glycemic control of $HbA_{1c} \geq 6.5\%$, the results were similar to those of $HbA_{1c} \geq 7.0\%$ (Table 3). When all patients with TG levels ≥1.70 mmol/L were combined as one group, this group was associated with 35% (OR: 1.35; 95% CI: 1.26, 1.44) and 36% (OR: 1.36; 95% CI: 1.25, 1.48) increased odds of having $HbA_{1c} \geq 7.0\%$ and $HbA_{1c} \geq 6.5\%$, respectively, compared with the group

Table 1. Characteristics of Study Patients According to TG Level

Characteristic	Subclass of TG Level (mmol/L)				P
	<1.70 (n = 8853)	1.70–2.29 (n = 4392)	2.30–3.39 (n = 3367)	≥3.40 (n = 3496)	
Male sex, n (%)[a]	4631 (52.3)	2352 (53.6)	1833 (54.4)	1702 (48.7)	<0.001
Age, y	56.0 (11.3)	56.0 (11.1)	56.6 (10.7)	59.3 (13.1)	<0.001
BMI, kg/m^2	23.4 (2.7)	23.9 (2.7)	24.2 (2.8)	24.3 (2.6)	<0.001
SBP, mm Hg	126.2 (13.0)	129.1 (11.2)	130.7 (11.2)	130.9 (11.6)	<0.001
DBP, mm Hg	79.1 (8.8)	80.7 (8.4)	82.0 (8.9)	88.0 (10.4)	<0.001
Times of SMBG per wk, n (%)					<0.001
0	4777 (54.0)	2497 (56.8)	2026 (60.2)	2780 (79.5)	
1–2	2109 (23.8)	1070 (24.4)	756 (22.4)	413 (11.8)	
≥3	1967 (22.2)	825 (18.8)	585 (17.4)	303 (8.7)	
Diabetes education, n (%)	4814 (54.4)	2423 (55.2)	1667 (49.5)	1097 (31.4)	<0.001
Duration, y	5.5 (4.8)	5.1 (4.7)	5.0 (4.5)	5.0 (3.7)	<0.001
TC, mmol/L	4.3 (1.3)	4.6 (1.2)	5.2 (2.3)	5.6 (2.8)	<0.001
LDL-C, mmol/L	2.3 (0.8)	2.6 (0.8)	2.8 (0.9)	3.5 (1.6)	<0.001
HDL-C (<1 mmol/L), n (%)	3258 (36.8)	1976 (45.0)	1718 (51.0)	3059 (87.5)	<0.001
TG/HDL-C, n (%)					<0.001
<1.70	6632 (74.9)	1995 (45.4)	942 (28.0)	99 (2.8)	
1.70–2.29	631 (7.1)	717 (16.3)	497 (14.7)	87 (2.5)	
≥2.30	1590 (18.0)	1680 (38.3)	1928 (57.3)	3310 (94.7)	
FPG, mmol/L	7.4 (1.9)	7.6 (1.8)	8.0 (2.0)	8.1 (1.7)	<0.001
HbA_{1c}, %, n (%)					<0.001
<6.50	1845 (20.8)	746 (17.0)	509 (15.1)	231 (6.6)	
6.50–6.99	1719 (19.4)	860 (19.6)	469 (13.9)	217 (6.2)	
≥7.00	5289 (59.8)	2786 (63.4)	2389 (71.0)	3048 (87.2)	

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure.

[a] *P* values for sex differences in TG levels are 0.485, 0.276, 0.857, and 0.016 among four groups with TG levels <1.70, 1.70–2.29, 2.30–3.39, and ≥3.40 mmol, respectively.

with TG level <1.70 mmol/L (Table 3). When all patients with TG levels ≥2.30 mmol/L were combined as one group, this group was associated with 77% (OR: 1.77; 95% CI: 1.64, 1.91) and 53% (OR: 1.53; 95% CI: 1.39, 1.69) increased odds of having HbA_{1c} ≥7.0% and HbA_{1c} ≥6.5%, respectively, compared with the group with TG level <2.30 mmol/L (Table 3).

Table 2. Homoscedasticity Test of Continuous Variables Among Four TG Groups

Characteristic	Bartlett Test		Levene Test	
	χ^2 Statistic	P	*F* Statistic	P
Age, y	183.6	<0.001	65.1	<0.001
BMI, kg/m^2	27.1	<0.001	10.9	<0.001
SBP, mm Hg	200.5	<0.001	74.8	<0.001
DBP, mm Hg	211.9	<0.001	49.2	<0.001
TC, mmol/L	4875.7	<0.001	86.1	<0.001
LDL-C, mmol/L	2914.3	<0.001	550.8	<0.001
HDL-C, mmol/L	5443.0	<0.001	128.9	<0.001
Duration, y	329.7	<0.001	31.7	<0.001
FPG, mmol/L	77.6	<0.001	17.8	<0.001
HbA_{1c}, %	313.7	<0.001	48.2	<0.001

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasmas glucose; SBP, systolic blood pressure.

Using multivariate logistic regression, we also analyzed other factors associated with inadequate glycemic control. We found that elevated blood pressure level, high TC level, and high LDL-C level were each positively associated with inadequate glycemic control, which is either HbA_{1c} ≥7.0% or HbA_{1c} ≥6.5%, whereas diabetes education and frequency of SMBG were negatively associated with inadequate glycemic control. Notably, elevated TG level is the strongest of these associated factors (Table 4). Furthermore, the independent association between TG/HDL-C ratio and glycemic control was also assessed. The adjusted ORs and 95% CIs for HbA_{lc} ≥7.0% comparing TG/HDL-C ratios in the range of 1.70 to 2.29, 2.30 to 3.39, and ≥3.40 with the lowest group were 1.45 (1.31, 1.62), 1.43 (1.27, 1.61), and 1.66 (1.54, 1.80), respectively (Table 5). Our analysis also showed a similar positive association between TG/HDL-C ratios and HbA_{lc} ≥6.5% (Table 5).

To examine the consistency of the association between elevated TG levels and inadequate glycemic control, we performed subgroup analyses among the different subpopulations defined by the multiple characteristics of these patients. The positive association of TG levels and inadequate glycemic control were generally similar across

Table 3. ORs (95% CI) for Inadequate HbA_{1c} Control by TG Groups Among 20,108 Patients With Type 2 Diabetes Mellitus Treated With Insulin

	Subclass of TG Level (mmol/L)				Combined Category (mmol/L)	
Model	**<1.70**	**1.70–2.29**	**2.30–3.39**	**≥3.40**	**≥1.70[a]**	**≥2.30[b]**
HbA_{1c} value ≥7.0%						
Model 1	1.00	1.17 (1.09–1.26)	1.65 (1.51–1.80)	4.48 (4.02–4.99)	1.81 (1.71–1.92)	2.40 (2.25–2.58)
Model 2	1.00	1.18 (1.09–1.27)	1.67 (1.53–1.82)	4.55 (4.08–5.07)	1.82 (1.72–1.94)	2.43 (2.27–2.60)
Model 3	1.00	1.06 (0.98–1.14)	1.38 (1.26–1.51)	3.47 (3.07–3.92)	1.38 (1.30–1.48)	1.89 (1.75–2.04)
Model 4	1.00	1.06 (0.98–1.15)	1.35 (1.23–1.48)	3.12 (2.76–3.53)	1.35 (1.26–1.44)	1.77 (1.64–1.92)
HbA_{1c} value ≥6.5%						
Model 1	1.00	1.29 (1.18–1.42)	1.48 (1.33–1.65)	3.66 (3.18–4.24)	1.72 (1.60–1.86)	1.99 (1.82–2.18)
Model 2	1.00	1.30 (1.18–1.43)	1.51 (1.35–1.68)	3.73 (3.23–4.32)	1.74 (1.61–1.88)	2.02 (1.85–2.20)
Model 3	1.00	1.17 (1.06–1.29)	1.26 (1.12–1.41)	3.13 (2.67–3.68)	1.39 (1.28–1.51)	1.63 (1.48–1.80)
Model 4	1.00	1.18 (1.07–1.30)	1.23 (1.09–1.38)	2.81 (2.40–3.31)	1.36 (1.25–1.48)	1.53 (1.39–1.69)

Model 1: adjusted for sex and age. Model 2: adjusted for the same variables as in model 1 plus BMI. Model 3: adjusted for the same variables as in model 2 plus blood pressure, TC, LDL-C, and HDL-C. Model 4: adjusted for the same variables as in model 3 plus duration of diabetes, diabetes education, and frequency of SMBG.

[a]Reference group was TG levels <1.70 mmol/L.

[b]Reference group was TG levels <2.30 mmol/L.

these subgroups stratified by sex, age, BMI, blood pressure, and duration of diabetes (Figs. 1 and 2). Nonlinear positive association between elevated TG level and inadequate glycemic control was observed by performing a restricted cubic spline logistic regression. Restricted cubic spline curves showed a J-shaped association between continuous TG level and inadequate HbA_{1c} control (Fig. 3). ORs and 95% CIs were calculated for continuous TG levels with respect to the reference value of 1.70 mmol/L after simultaneous adjustment for all potential confounding factors (Fig. 3). Based on the TG-outcome association trajectory, we found significant nonlinear dose-response relationships between glycemic control outcomes and change in continuous TG levels (all P values <0.001 for linearity of TG level in the logistic regression analysis). The odds of HbA_{1c} ≥7.0% and

Table 4. Multivariate Logistic Regression Analysis of Inadequate Glycemic Control in Relation to Clinical and Laboratory Measurements

	HbA_{1c} ≥7.0%		HbA_{1c} ≥6.5%	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**
Sex (ref. female)	0.88	0.82–0.93	0.86	0.79–0.92
Age, y (ref. <50)				
50–59	1.03	0.95–1.12	1.05	0.95–1.16
60–69	0.99	0.91–1.08	1.11	1.00–1.23
≥70	1.25	1.11–1.41	1.09	0.95–1.26
BMI, kg/m^2 (ref. <24)	0.88	0.82–0.93	0.85	0.79–0.92
Blood pressure, mm Hg (ref. SBP/DBP <130/80)	1.39	1.29–1.50	1.50	1.37–1.64
TG level, mmol/L (ref. <1.70)				
1.70–2.29	1.06	0.98–1.15	1.18	1.07–1.30
2.30–3.39	1.35	1.23–1.48	1.23	1.09–1.38
≥ 3.40	3.12	2.76–3.53	2.81	2.40–3.31
TC, mmol/L (ref. <5.20)	1.15	1.06–1.26	1.14	1.02–1.28
LDL-C, mmol/L (ref. <2.60)				
2.60–3.39	1.40	1.30–1.50	1.48	1.35–1.62
≥3.40	1.39	1.25–1.56	1.16	1.01–1.33
HDL-C, mmol/L (ref. ≥1.00)	1.06	0.99–1.14	0.96	0.88–1.05
Duration, y	1.00	0.99–1.00	1.01	1.00–1.02
Diabetes education (ref. No)	0.68	0.63–0.72	0.73	0.68–0.80
Frequency of SMBG, times per wk	0.96	0.95–0.97	0.94	0.93–0.95

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 5. Multivariate Logistic Regression Analysis of Inadequate Glycemic Controls With Ratios of TG/HDL and Other Variables

	HbA_{1c} ≥7.0%		HbA_{1c} ≥6.5%	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**
Sex (ref. female)	0.86	0.81–0.92	0.84	0.78–0.91
Age, y (ref. <50)				
50–59	1.00	0.92–1.08	1.02	0.92–1.12
60–69	0.98	0.90–1.06	1.09	0.98–1.20
≥70	1.29	1.15–1.44	1.11	0.97–1.28
BMI, kg/m^2 (ref. <24)	0.90	0.84–0.96	0.87	0.80–0.94
Blood pressure, mm Hg (ref. SBP/DBP <130/80)	1.46	1.36–1.58	1.58	1.44–1.72
TG/HDL-C ratio (ref. <1.70)				
1.70–2.29	1.45	1.31–1.62	1.47	1.28–1.70
2.30–3.39	1.43	1.27–1.61	1.39	1.20–1.62
≥3.40	1.66	1.54–1.80	1.40	1.28–1.55
TC, mmol/L (ref. <5.20)	1.44	1.33–1.57	1.41	1.27–1.56
LDL-C, mmol/L (ref. <2.60)				
2.60–3.39	1.32	1.23–1.42	1.41	1.29–1.54
≥3.40	1.43	1.28–1.60	1.19	1.04–1.37
Duration, y	1.00	0.99–1.00	1.01	1.00–1.02
Diabetes education (ref. No)	0.64	0.60–0.68	0.70	0.64–0.76
Frequency of SMBG, times per wk	0.96	0.95–0.97	0.94	0.93–0.95

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

HbA_{1c} ≥6.5% were significantly higher in those with higher TG levels compared with reference levels of 1.70 mmol/L and 2.30 mmol/L, respectively.

Discussion

Inadequate glycemic control remains a major problem despite the many diabetes treatments. HbA_{1c} is the recommended indicator of glycemic control in patients with type 2 diabetes mellitus (33). The criteria for optimal glycemic control in these patients is HbA_{1c} <7.0%, whereas for patients without complication, the criteria is stricter at HbA_{1c} <6.5% (33, 34). In this large population-based multicenter study, we found that 67.2% and 83.4% of patients without diabetic complications who were treated with a sufficient dose of insulin did not reach the HbA_{1c} <7.0% and HbA_{1c} <6.5% targets, respectively. We showed in this patient population that elevated TG levels were strongly associated with inadequate glycemic control, defined by the criteria of HbA_{1c} ≥7.0% and HbA_{1c} ≥6.5%. This association was further confirmed by consistency in subgroup analyses across subgroups categorized by sex, age, BMI, blood pressure, and duration of diabetes. Notably, the strength of the association between TG level and glycemic control was the strongest among all factors associated with inadequate glycemic control. To the best of our knowledge, this is the only large population–based study that has examined the association between elevated TG levels and inadequate glycemic control in patients with type 2 diabetes mellitus who were receiving sufficient insulin treatment.

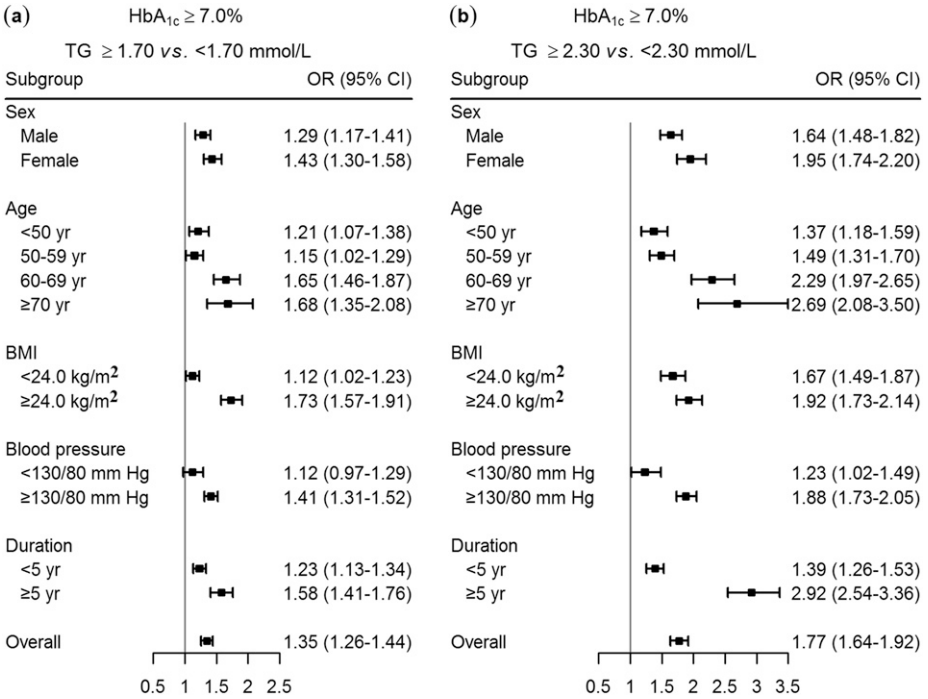

Figure 1. Subgroup analysis of the association between TG level and inadequate glycemic control, HbA_{1c} value ≥7.0%. The horizontal lines represent 95% CIs. ORs and 95% CIs are for comparisons of a combined group of hypertriglyceridemia (TG levels ≥1.70 mmol/L or ≥2.30 mmol/L) with patients with normal TG levels (<1.70 mmol/L or <2.30 mmol/L). The multivariable model was adjusted for sex, age, BMI, blood pressure, TC, LDL-C, HDL-C, duration of diabetes, diabetes education, and frequency of SMBG. (a) TG levels ≥1.70 mmol/L vs <1.70 mmol/L. (b) TG levels ≥2.30 mmol/L vs <2.30 mmol/L.

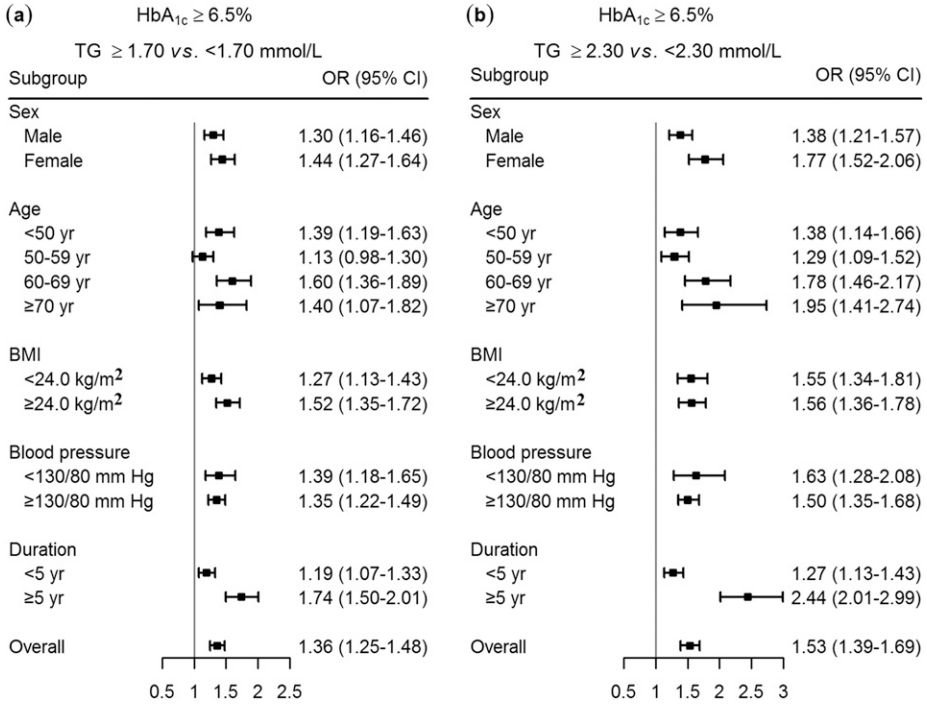

Figure 2. Subgroup analysis of the association between TG level and inadequate glycemic control, HbA_{1c} ≥6.5%. Horizontal lines represent 95% CIs. ORs and 95% CIs are for comparisons of a combined group of hypertriglyceridemia (TG levels ≥1.70 mmol/L or ≥2.30 mmol/L) with patients with normal TG levels (<1.70 mmol/L or <2.30 mmol/L). The multivariable model was adjusted for sex, age, BMI, blood pressure, TC, LDL-C, HDL-C, duration of diabetes, diabetes education, and frequency of SMBG. (a) TG levels ≥1.70 mmol/L vs <1.70 mmol/L. (b) TG levels ≥2.30 mmol/L vs <2.30 mmol/L.

Several studies have examined the determinants for inadequate glycemic control in patients with type 2 diabetes mellitus and demonstrated a positive association between long disease duration and complications with inadequate glycemic control (*i.e.*, HbA_{1c} ≥7.0%) (11–13). However, only one study has examined whether elevated TG levels were associated with inadequate glycemic control in patients with type 2 diabetes mellitus. Findings from this study showed only that elevated TG levels were associated with increased odds of inadequate glycemic control, defined as HbA_{1c} ≥6.5% in Chinese patients with diabetes treated with OADs (35). That study was relatively small, including only 455 patients with type 2 diabetes mellitus treated with OADs, and did not consider the possible confounding role of diabetic complications and their related treatment, which could

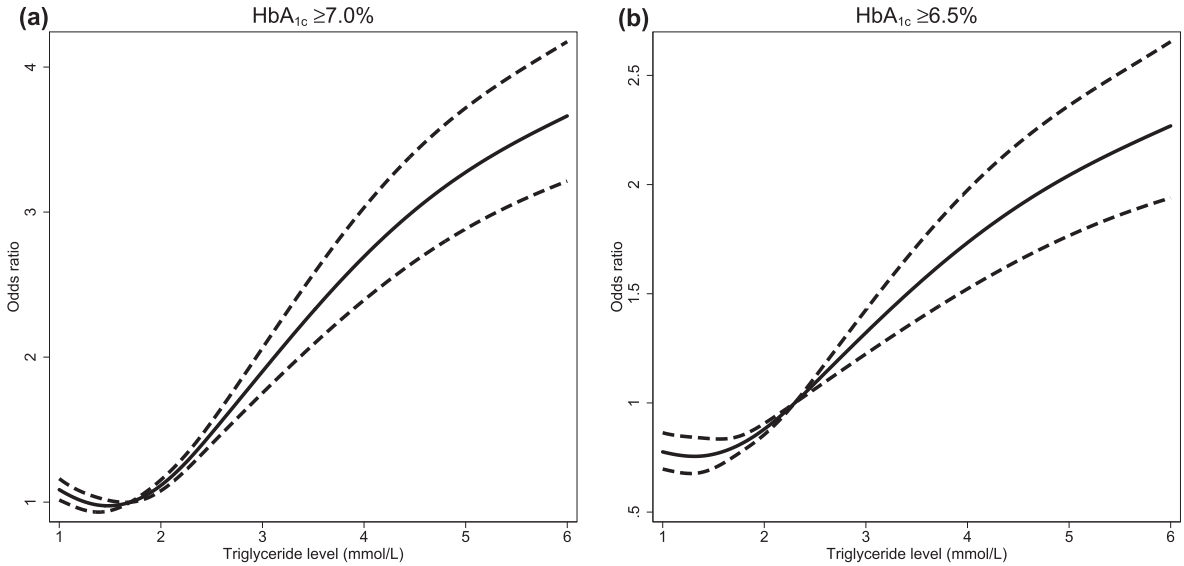

Figure 3. Adjusted dose-response relationship between TG levels and inadequate glycemic control. The dose-response relationship is presented using a restricted cubic spline curve. 95% CIs for ORs with the reference level 1.70 mmol/L are shown. (a) HbA_{1c} ≥7.0%. (b) HbA_{1c} ≥6.5%.

have contributed to glycemic control; thus, that study may have biased the strength of the association between TG levels and glycemic control (35).

We attempted to reduce these deficiencies of the previous study, as our study subjects were from a well-defined patient population treated with sufficient insulin and without other NCDs. In this population, less than half of patients attained the glycemic target, which enabled us to identify the determinant factors for inadequate glycemic control and assess whether elevated TG levels were associated with risk of inadequate glycemic control. In this study, hypertriglyceridemia was stratified into three groups of borderline elevation (1.70 to 2.29 mmol/L), elevation (2.30 to 3.39 mmol/L), and high elevation (≥3.40 mmol/L) levels, which showed respective increases of 35% (95% CI: 25%, 48%) and 212% (95% CI: 176%, 253%) in the odds of having HbA_{1c} ≥7.0% for the elevated and high elevation levels of TG; all three levels of hypertriglyceridemia were associated with the lower HbA_{1c} ≥6.5%. When all groups (≥1.70 mmol/L or ≥2.30 mmol/L) with hypertriglyceridemia were combined, this group was associated with 35% (77%) and 36% (53%) increased risks of HbA_{1c} ≥7.0% and ≥6.5%, respectively, compared with TG levels <1.70 mmol/L (or <2.30 mmol/L). This positive association was confirmed by its consistency in the different subgroups, including patients with different sex, age, BMI, blood pressure level, and duration of diabetes (Figs. 1 and 2). These results indicated that the association of TG with glycemic metabolism in insulin-treated patients with type 2 diabetes mellitus was similar to that in nondiabetic patients with developing type 2 diabetes mellitus (15–21), impaired fasting glucose level (15, 22), and impaired glucose tolerance (21).

In addition, we found that high TG levels had the strongest association with inadequate glycemic control among those factors (Table 4). This led us to conclude that elevated TG levels were strongly and positively associated with inadequate glycemic control in patients with type 2 diabetes mellitus treated with sufficient doses of insulin. Because TG is usually concomitantly increased with the glucose level in individuals with obesity, we tried to reduce the confounding interference of obesity on the association by adjustment of BMI, which only slightly affected the association (OR: 1.81; 95% CI: 1.71, 1.92 and OR: 1.82; 95% CI: 1.72, 1.94 before and after adjustment of BMI for HbA_{1c} ≥7.0%, respectively) (Table 3). In fact, we found that elevated TG levels were also significantly associated with inadequate glycemic control even in patients with diabetes and normal BMI (OR: 1.67; 95% CI: 1.49, 1.87 for HbA_{1c} ≥7.0%) [Fig. 1(b)]. We also demonstrated that the association is specific, as evidenced by the dose-response relationship between elevated TG levels and inadequate glycemic control and the much weaker association of inadequate glycemic control with total cholesterol (OR: 1.15; 95% CI: 1.06, 1.26 for HbA_{1c} ≥7.0%) (Table 4). These results all indicate that the association is not simply a consequence of a more generalized metabolic disorder frequently observed in type 2 diabetes mellitus, but is more specific. The positive association between TG/HDL-C ratios and inadequate glycemic control was also shown in this study.

Further investigation of the association between TG/HDL-C ratios and glycemic control based on the measurement of HDL-C levels will be pursued in our future work. Some previous reports provide some clues for understanding the mechanisms underlying this association of high TG levels and inadequate glycemic control. From these reports, we speculate the following possible mechanisms. First, high plasma TG level can increase insulin resistance in peripheral tissues. The intrinsic insulin resistance of patients with type 2 diabetes mellitus can attenuate the effect of insulin in suppressing TG lipolysis to glycerol and fatty acids; thus, high levels of TGs lead to release of more free fatty acids (36). The latter can contribute to further deterioration in insulin sensitivity, a vicious cycle between elevated TG levels and insulin resistance (37), causing further reduction in glucose uptake and utilization by the peripheral tissues (38). This speculation is supported by results from a double-blind study that demonstrated that treatment of hypertriglyceridemia may be able to break this vicious and potentially atherogenic cycle of hypertriglyceridemia and hyperinsulinemia (39). Second, the products of TG lipolysis, glycerol, and fatty acids can enhance gluconeogenesis in the liver. Glycerol is a direct substrate for gluconeogenesis in the liver, whereas free fatty acids are oxidized in the liver into acetyl coenzyme A, which is a potent activator of pyruvate carboxylase, a critical rate-limiting enzyme in gluconeogenesis (40, 41). Third, the converse hypothesis is that a high blood glucose level may be a contributing "cause" of hypertriglyceridemia. The latter is suggested by a population-based study of 372 consecutive patients with diabetes from the PreCIS database, which demonstrated that HbA_{1c} reduction seemed to have some limited effects on TG reduction, whereby each unit (a large-scale level) of HbA_{1c} changes was associated with a <10% change in plasma TG concentration (42). In that study, >55.8% of the patients were taking lipid-lowering drugs (42), and the analysis did not adjust for the lipid-lowering effects of these drugs, which may have overestimated the effect of blood glucose on blood lipid metabolism. We therefore do not favor the third possibility.

This study has several major strengths. It was a multicenter study with a large sample size. The targeted study population was patients with type 2 diabetes mellitus treated with sufficient doses of insulin, which greatly reduced statistical uncertainty and diminished the

bias that an insufficient dose of insulin was a confounding cause of inadequate glycemic control (which would influence the strength of the association with elevated TG levels). Excluding patients with diabetic complications further reduced bias from the influence of these complications and their treatments (*i.e.*, lipid-lowering drugs) on metabolism. Furthermore, this study benefited from detailed information in the clinical medical records of each research center, allowing us to adjust for potential confounding factors. Lastly, it is noteworthy that the results are largely robust because of the rigorous analyses we used.

This study also has some limitations. First, the cross-sectional study design is not warranted for inferring causal relationships between TG levels and inadequate glycemic control. Second, it may have biased the association between TG levels and risk of inadequate glycemic control because the biochemistry parameters, including HbA_{1c} and TG, were measured in different laboratories and at only one time point. Third, because some of the included patients were treated with various drugs in addition to insulin, the effect of these treatments on glycemic control cannot be ignored. Fourth, our analyses were restricted to the Mainland Chinese population treated with sufficient insulin and may not be generalized to patients with diabetes treated only with OADs; in addition, they may not translate to a similar association in non-Chinese populations.

In conclusion, we showed a graded positive association between elevated TG levels and inadequate glycemic control for patients with insulin-treated type 2 diabetes mellitus in China. The results from this study imply that in these patients treated with a sufficient dose of insulin, elevated TG levels may be an independent and strong factor contributing to inadequate glycemic control. This emphasized that a parallel therapeutic strategy of suppressing TG levels might benefit not only from attenuating its "chronic" actions on inflicting cardiovascular complications but also from the "acute" actions of TG on the dysregulation of glucose metabolism; thus, attenuating the latter could promote more optimal glycemic control in patients with type 2 diabetes mellitus who are receiving sufficient insulin therapy.

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