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High concentrations of triglycerides are associated with diabetic kidney disease in new-onset type 2 diabetes in China: Findings from the China Cardiometabolic Disease and Cancer Cohort (4C) Study

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Abstract

Aims: The aims of this study were to evaluate the associations of metabolic abnormalities with incident diabetic kidney disease (DKD) and to explore whether dyslipidaemia, particularly high fasting triglyceride (TG), was associated with the development of DKD.

Methods: In total, 11 142 patients with new-onset type 2 diabetes with baseline estimated glomerular filtration rates (eGFR) ≥60 mL/min/1.73 m^2 were followed up during 2011-2016. Incident DKD was defined as eGFR <60 mL/min/1.73 m^2 at follow-up. Multiple logistic regression analysis was conducted to explore the relationship of metabolic abnormalities at baseline and at follow-up with risks of DKD. High TG was defined by TG ≥1.70 mmol/L. Low high-density lipoprotein cholesterol (HDL-c) was defined by HDL-c <1.0 mmol/L for men or <1.3 mmol/L for women.

Results: Participants who developed DKD had higher levels of waist circumference and systolic blood pressure, and lower levels of HDL-c at both baseline and follow-up visits. The DKD group also had higher levels of post-load plasma glucose and TG at follow-up. Multivariate logistic regression analysis revealed that both high TG at baseline [odds ratio (OR) = 1.37, $p = .012$) and high TG at follow-up (OR = 1.71, $p < .001$) were significantly associated with increased risks of DKD. Patients with high TG levels at both baseline and follow-up had higher risk of DKD compared with constantly normal TG (OR = 1.65, $p < .001$) after adjustment for covariates.

Conclusions: In a large population of patients with new-onset type 2 diabetes, a high TG level was an independent risk factor for the development of DKD. Tight TG control might delay the occurrence of DKD.

KEYWORDS
diabetic kidney disease, new-onset type 2 diabetes, triglyceride

1 | INTRODUCTION

The prevalence of diabetes continues to increase significantly worldwide.[1,2] About 20%-40% of patients with diabetes are complicated with diabetic kidney disease (DKD), which is the leading cause of chronic kidney disease and end-stage renal disease.[3,4] It is important to note that DKD progresses even after strict control for risk factors such as blood glucose, blood pressure (BP) and body weight. Markers of diabetic kidney injury in patients with type 2 diabetes include uric acid, mean platelet volume/lymphocyte count ratio, neutrophil gelatinase-associated lipocalin and kidney injury molecule-1, etc.[5-8] Continued surveillance and effective control are needed to reduce the burden of DKD, which prompts investigations into the factors related to the onset and progression of DKD.[9,10]

Hypertriglyceridaemia is one of the most common clinical lipid abnormalities.[11] Severe hypertriglyceridaemia significantly increases the risk of pancreatitis, and a moderate level of triglycerides (TGs) increases the risk of cardiovascular disease.[12,13] In addition, we recently demonstrated that poor control of plasma TGs was associated with early decline of estimated glomerular filtration rates (eGFR) in new-onset type 2 diabetes.[10]

Accumulation of lipids in the kidney may lead to glomerular damage through induction of oxidative stress or release of proinflammatory cytokines that lead to glomerulosclerosis and interstitial fibrosis.[14,15] However, findings are controversial regarding the association between hypertriglyceridaemia and DKD. One study reported that lower high-density lipoprotein cholesterol (HDL-c) levels but not higher TG levels seem to be associated with the progression of DKD in men but not in women.[16] Another study in Asians showed that among serum lipids, only HDL-c was associated with the progression of albuminuria.[17] In contrast to these results, the UK Prospective Diabetes Study showed that TGs and low-density lipoprotein cholesterol (LDL-c) were reported to be independent risk factors for the progression of DKD.[18] Therefore, varied ethnicities, gender and other population characteristics might result in different findings, and the impact of hypertriglyceridaemia on the kidney in patients with diabetes needs further investigation. In addition, previous studies were mostly cross-sectional. Therefore, using data from a large, nationwide, multicentre, prospective cohort of Chinese adults, we examined the associations of metabolic abnormalities, particularly dyslipidaemia, at baseline and at follow-up with the development of DKD in patients with new-onset type 2 diabetes.

2 | METHODS

2.1 | Study population

The China Cardiometabolic Disease and Cancer Cohort (4C) Study is a multicentre, nationwide, population-based prospective cohort study exploring the associations of metabolic factors with incident diabetes, cardiovascular events, cancer and all-cause mortality in Chinese individuals aged ≥40 years. The details of the 4C Study design have been described previously.[19,20] During 2011-2012, participants underwent a comprehensive set of questionnaires, clinical measurements, oral glucose tolerance tests and laboratory examinations following a standard protocol at the baseline visit. During 2014-2016, participants were asked to come back and the examinations were repeated at the follow-up visit. At baseline, we defined 23 793 patients with new-onset type 2 diabetes based on the American Diabetes Association (ADA) diagnostic criteria.[21] In addition, we excluded: (a) participants with eGFR <60 mL/min/1.73 m^2 at baseline (n = 573); (b) participants with previously diagnosed hypertension including treated hypertension (n = 4126); (c) participants with previously diagnosed dyslipidaemia including treated dyslipidaemia (n = 152); (d) participants without eGFR levels at follow-up (n = 6724); and (e) participants with missing data on overweight/obesity, hypertension, glycaemic control and dyslipidaemia at baseline or at follow-up (n = 1076). Eventually, 11 142 participants were included for the current analysis and the median duration of follow-up was 3.1 years.

The study protocol and informed consent were approved by the Committee on Human Research at Ruijin Hospital affiliated to the Jiaotong University School of Medicine on 10 March 2011 (ethical approval number RUIJIN-2011-14). All participants provided written informed consent.

2.2 | Data collection and measurements

The methods of data collection and measurements have been described in detail in previous studies.[19,20] Generally, standard questionnaires were used to collect demographic characteristics, medical history and family history, and lifestyle such as smoking, drinking and physical activity. Height, weight, waist circumference and BP were measured according to a standard protocol, and body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. All participants underwent a 75-g oral glucose tolerance test after an overnight fast of at least 10 h. Fasting and 2 h post-load blood glucose (PBG) were measured locally with a glucose oxidase or hexokinase method. Fasting blood samples were centrifuged at study sites. Serum samples were aliquoted and frozen at −80°C within 2 h of collection and they were shipped in dry ice to the central laboratory in Shanghai accredited by the College of American Pathologists, where fasting serum TG, HDL-c, LDL-c and creatinine were measured by using an ARCHITECT ci16200 autoanalyser (Abbott Laboratories, Abbott Park, IL, USA). Finger capillary whole-blood samples were collected, frozen and then shipped to the central laboratory for the measurement of glycated haemoglobin (HbA1c) by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (BioRad Laboratories, Hercules, California). The eGFR was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22]

2.3 | Definition

Overweight was defined by BMI ≥25 kg/m^2. Obesity was defined by BMI ≥30 kg/m^2 Elevated BP was defined by systolic BP/diastolic BP ≥140/90 mmHg. Diabetes was defined by fasting blood glucose

≥7.0 mmol/L and/or PBG ≥11.1 mmol/L and/or HbA1c ≥6.5%, and poor glycaemic control was defined by HbA1c ≥6.5%. High TG was defined by TG ≥1.70 mmol/L. Low HDL-c was defined by HDL-c <1.0 mmol/L for men or <1.3 mmol/L for women. Out of target for LDL-c was defined by LDL-c ≥2.6 mmol/L. Incident DKD was defined by an eGFR<60 mL/min/1.73 m^2 at the follow-up visit.

2.4 | Statistical analysis

The continuous variables at baseline and follow-up visits are presented as means ± standard deviations (normal distribution) or medians (interquartile ranges) (skewed distribution). The categorical variables are presented as n (%). Skewed variables were logarithmically transformed before analysis. Differences between groups were analysed using the Student's t-test for continuous variables and the chi-squared test for categorical variables. In addition, we used the Cohen's d to estimate the standardized effect size for the comparisons of continuous variables between baseline and follow-up.[23] A value of Cohen's d between 0.20 and 0.49 is considered a small effect, 0.50-0.79 a medium effect, and ≥0.8 a large effect. Because the development of DKD was evaluated at the follow-up visit using eGFR levels, rather than collected during the entire follow-up period, and the proportional hazards assumption to Cox regression cannot be met, we used unadjusted and adjusted logistic regression models to examine the associations of metabolic abnormalities with DKD. Baseline eGFR was adjusted for the association between baseline metabolic abnormalities and DKD by including residual eGFR in the adjusted model to exclude the effect of multicollinearity. Based on Willett and Stampfer's residual approach,[24] we ran a single linear regression model in which the baseline eGFR was the dependent variable and all the other adjusted baseline variables were the independent variables. Ordinary least square residuals (i.e. 'residual eGFR') were then calculated by the actual eGFR minus predicted eGFR for each observation. The residual eGFR was the proportion of eGFR that was not related to the other adjusted variables in the model. The distributions of residual eGFR and actual eGFR are depicted in Supplementary Figure S1. We divided participants into four groups based on TG levels at baseline and follow-up: G1 (normal baseline TG and normal follow-up TG); G2 (high baseline TG and normal follow-up TG); G3 (normal baseline TG and high follow-up TG); and G4 (high baseline TG and high follow-up TG). The

TABLE 1 Characteristics of study participants at baseline and at follow-up

Characteristics	Baseline	Follow-up	*p* value	Cohen's d
Women (n, %)	6994 (62.8)	6994 (62.8)	—	—
Age (years)	58.2 ± 8.3	61.4 ± 8.3	<.001	0.39
Current smoker (n, %)	1655 (14.9)	1753 (15.7)	<.001	—
BMI (kg/m^2)	25.5 ± 3.5	25.2 ± 3.5	<.001	0.09
WC (cm)	86.9 ± 9.8	87.5 ± 10.0	<.001	0.06
SBP (mmHg)	137.0 ± 20.5	135.6 ± 19.3	<.001	0.07
DBP (mmHg)	80.4 ± 11.0	79.1 ± 11.2	<.001	0.11
FBG (mg/dL)	129.4 ± 38.7	125.8 ± 37.5	<.001	0.09
PBG (mg/dL)	223.2 ± 83.8	210.6 ± 84.1	<.001	0.15
HbA1c (%)	6.8 ± 1.3	6.5 ± 1.3	<.001	0.24
TG (mg/dL)	142.6 (99.2-209.0)	141.7 (100.1-203.7)	.021	0.01
LDL-c (mg/dL)	117.5 ± 35.6	123.3 ± 33.5	<.001	0.17
HDL-c (mg/dL)	50.2 ± 13.9	50.8 ± 11.9	<.001	0.05
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.2	<.001	0.43
eGFR (mL/min/1.73 m^2)	94.6 (85.8-100.9)	87.2 (78.3-94.7)	<.001	0.58
Overweight/obesity (n, %)	6082 (54.6)	5648 (50.7)	<.001	—
Elevated BP (n, %)	4880 (43.8)	4618 (41.4)	<.001	—
Poor glycaemic control (n, %)	6730 (60.4)	4090 (36.7)	<.001	—
High TG (n, %)	5126 (46.0)	5059 (45.4)	<.001	—
Low HDL-c (n, %)	4458 (40.0)	4117 (37.0)	<.001	—
Out of target for LDL-c (n, %)	7492 (67.2)	8361 (75.0)	<.001	—

Note: Overweight/obesity was defined by BMI ≥25 kg/m^2; elevated BP was defined by systolic BP/diastolic BP ≥140/90 mmHg; diabetes was defined by FBG ≥7.0 mmol/L and/or PBG ≥11.1 mmol/L and/or HbA1c ≥6.5%; poor glycaemic control was defined by HbA1c ≥6.5%; high TG was defined by TG ≥1.70 mmol/L; low HDL-c was defined by HDL-c <1.0 mmol/L for men or <1.3 mmol/L for women; out of target for LDL-c was defined by LDL-c ≥2.6 mmol/L. TG and eGFR were presented as medians (interquartile ranges). Date are n(%), mean ± SD and median (range).
Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; PBG, post-load blood glucose; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

association of different TG groups with the risk of DKD was estimated using univariate and multivariate logistic regression analysis. Factors associated with persistently high TG were examined using multivariate logistic regression analysis. $p < .05$ was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

TABLE 2 Characteristics of study participants by incident diabetic kidney disease (DKD) status

Characteristics		Without incident DKD (N = 10 789)	With incident DKD (N = 353)	*p* value
Women (n, %)	Baseline	6794 (63.0)	200 (56.7)	.016
Age (years)	Baseline	57.9 ± 8.1	66.7 ± 8.3	<.001
Current smoker (n, %)	Baseline	1610 (14.9)	45 (12.8)	.379
	Follow-up	1705 (15.8)	48 (13.6)	.478
BMI (kg/m^2)	Baseline	25.5 ± 3.5	25.5 ± 3.4	.877
	Follow-up	25.2 ± 3.5	25.3 ± 3.4	.791
WC (cm)	Baseline	86.8 ± 9.8	88.9 ± 9.2	<.001
	Follow-up	87.4 ± 10.0	89.3 ± 9.4	<.001
SBP (mmHg)	Baseline	136.7 ± 20.5	144.1 ± 21.4	<.001
	Follow-up	135.4 ± 19.2	140.7 ± 21.0	<.001
DBP (mmHg)	Baseline	80.3 ± 10.9	81.1 ± 12.4	.194
	Follow-up	79.1 ± 11.1	78.8 ± 12.2	.591
FBG (mg/dL)	Baseline	129.5 ± 38.7	128.0 ± 38.8	.489
	Follow-up	125.7 ± 37.4	128.4 ± 41.7	.187
PBG (mg/dL)	Baseline	223.2 ± 83.7	223.2 ± 85.6	.990
	Follow-up	210.2 ± 83.6	225.1 ± 97.4	.001
HbA1c (%)	Baseline	6.8 ± 1.3	6.8 ± 1.4	.819
	Follow-up	6.5 ± 1.2	6.6 ± 1.3	.062
TG (mg/dL)	Baseline	141.7 (99.2-209.9)	148.8 (108.9-204.6)	.328
	Follow-up	141.7 (100.1-202.8)	155.0 (116.9-220.5)	<.001
LDL-C (mg/dL)	Baseline	117.5 ± 35.5	117.6 ± 39.4	.942
	Follow-up	123.2 ± 33.3	124.7 ± 39.5	.408
HDL-C (mg/dL)	Baseline	50.2 ± 13.9	48.3 ± 14.1	.011
	Follow-up	50.9 ± 11.9	48.2 ± 11.0	<.001
Creatinine (mg/dL)	Baseline	0.8 ± 0.1	0.9 ± 0.2	<.001
	Follow-up	0.8 ± 0.1	1.2 ± 0.4	<.001
eGFR (mL/min/1.73 m^2)	Baseline	94.9 (86.6-101.1)	73.1 (65.6-83.2)	<.001
	Follow-up	87.7 (79.3-94.9)	54.6 (50.1-57.8)	<.001
Overweight/obesity (n, %)	Baseline	5891 (54.6)	191 (54.1)	.854
	Follow-up	5469 (50.7)	179 (50.7)	.995
Elevated BP (n, %)	Baseline	4684 (43.4)	196 (55.5)	<.001
	Follow-up	4441 (41.2)	177 (50.1)	<.001
Poor glycaemic control (n, %)	Baseline	6515 (60.4)	215 (60.9)	.844
	Follow-up	3948 (36.6)	142 (40.2)	.163
High TG (n, %)	Baseline	4950 (45.9)	176 (49.9)	.140
	Follow-up	4871 (45.1)	188 (53.3)	.003
Low HDL-c (n, %)	Baseline	4301 (39.9)	157 (44.5)	0.082
	Follow-up	3979 (36.9)	138 (39.1)	.397
Out of target for LDL-c (n, %)	Baseline	7256 (67.3)	236 (66.9)	.875
	Follow-up	8104 (75.1)	257 (72.8)	.324

Note: Date are n(%), mean ± SD and median (range). Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; PBG, post-load blood glucose; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

3 | RESULTS

3.1 | Baseline and follow-up characteristics of study participants

The demographics and laboratory results of study participants are shown in Table 1. All characteristics were compared between baseline and follow-up visits. Although characteristics at the follow-up visit showed lower levels of BMI, BP, blood glucose and TG, and higher levels of HDL-c, the proportions of various metabolic abnormalities were also very high. Besides, waist circumference and LDL-c levels increased during follow-up and eGFR decreased on average from 94.6 to 87.2 mL/min/1.73 m^2. However, the Cohen's d revealed that most changes between baseline and follow-up were small.

3.2 | Characteristics of study participants by diabetic kidney disease status

To explore the possible related factors of DKD occurrence in new-onset type 2 diabetes, we divided study participants into two groups based on the DKD status at follow-up. As shown in Table 2, participants with incident DKD were probably not female and were older in age, had higher levels of waist circumference and systolic BP, and lower levels of HDL-c at both baseline and follow-up. In addition, although the baseline levels of PBG and TG were not significantly different between groups, participants with incident DKD presented higher levels of PBG and TG at follow-up.

3.3 | Associations of baseline and follow-up metabolic abnormalities with diabetic kidney disease

The associations of baseline and follow-up metabolic abnormalities with risks of incident DKD are shown in Table 3. At baseline, high TG [odds ratio (OR) = 1.37, 95% confidence interval (CI) = 1.07-1.74] was significantly associated with an increased risk of DKD after adjustment for covariates (age, gender, education, physical activity, current drinking status, current smoking status, overweight/obesity, elevated BP, poor glycaemic control, high TG, low HDL-c, out of target for LDL-c and residual eGFR at baseline). The association between baseline low HDL-c and DKD was borderline significant (OR = 1.30,

TABLE 3 Associations of baseline and follow-up metabolic abnormalities with risks of incident diabetic kidney disease

Variables	Unadjusted		Model 1	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Baseline analysis				
Age (per year)	**1.14 (1.12-1.16)**	**<.001**	**1.17 (1.16-1.19)**	**<.001**
Sex (women vs. men)	**0.77 (0.62-0.95)**	**.016**	0.96 (0.73-1.28)	.796
Current smoking	0.82 (0.60-1.13)	.635	1.15 (0.78-1.71)	.467
Overweight/obesity	0.98 (0.79-1.21)	.854	0.99 (0.78-1.26)	.952
Elevated BP	**1.63 (1.31-2.01)**	**<.001**	1.19 (0.93-1.51)	.164
Poor glycaemic control	1.02 (0.82-1.27)	.844	0.99 (0.78-1.26)	.949
High TG	1.17 (0.95-1.45)	.140	**1.37 (1.07-1.74)**	**.012**
Low HDL-c	1.21 (0.98-1.50)	.082	1.30 (0.99-1.70)	.057
Out of target for LDL-c	0.98 (0.78-1.23)	.875	1.12 (0.86-1.46)	.412
Follow-up analysis				
Age (per year)	**1.14 (1.12-1.16)**	**<.001**	**1.14 (1.13-1.16)**	**<.001**
Sex (women vs. men)	**0.77 (0.62-0.95)**	**.016**	0.80 (0.63-1.02)	.074
Current smoking	0.85 (0.62-1.16)	.226	1.11 (0.77-1.60)	.754
Overweight/obesity	1.00 (0.81-1.24)	.995	1.01 (0.81-1.27)	.922
Elevated BP	**1.44 (1.16-1.78)**	**<.001**	1.05 (0.84-1.30)	.693
Poor glycaemic control	1.17 (0.94-1.45)	.164	1.16 (0.93-1.46)	.193
High TG	**1.38 (1.12-1.71)**	**.003**	**1.71 (1.35-2.16)**	**<.001**
Low HDL-c	1.10 (0.88-1.37)	.397	1.10 (0.85-1.41)	.480
Out of target for LDL-c	0.89 (0.70-1.13)	.324	0.94 (0.73-1.21)	.625

Note: For the baseline analysis, model 1 was adjusted for education, physical activity at baseline, current drinking status at baseline, residual estimated glomerular filtration rate at baseline, and all other baseline variables in the table. For follow-up analysis, model 1 was adjusted for education, physical activity at follow-up, current drinking status at follow-up and all other follow-up variables in the table. Significant *P* values (<0.05) are indicated in bold.

Abbreviations: BP, blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride.

TABLE 4 Associations of high triglyceride at baseline or at follow-up with risks of incident diabetic kidney disease

Variables	No. of cases/no. of participants (%)	Unadjusted		Model 1		Model 2	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
High TG							
G1	122/4565 (2.67)	1.00	–	1.00	–	1.00	–
G2	43/1518 (2.83)	1.06 (0.75-1.51)	.740	1.21 (0.84-1.74)	.300	1.13 (0.77-1.68)	.533
G3	55/1451 (3.79)	**1.43 (1.04-1.98)**	**.029**	**1.81 (1.29-2.53)**	**<.001**	**1.77 (1.23-2.55)**	**.002**
G4	133/3608 (3.69)	**1.39 (1.09-1.79)**	**.009**	**1.90 (1.46-2.47)**	**<.001**	**1.65 (1.23-2.22)**	**<.001**

Note: G1, normal baseline TG and normal follow-up TG; G2, high baseline TG and normal follow-up TG; G3, normal baseline TG and high follow-up TG; G4, high baseline TG and high follow-up TG. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, education, physical activity, current smoking status, current drinking status, body mass index, systolic blood pressure, diastolic blood pressure, glycated haemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and residual estimated glomerular filtration rate. All the adjusted variables were from the baseline visit. Significant *P* values (<0.05) are indicated in bold.

95% CI = 0.99-1.70). However, at follow-up, only high TG was found to be significantly correlated with increased risks of DKD (OR = 1.71, 95% CI = 1.35-2.16). The associations of baseline and changes of lipids during follow-up with annual reductions in eGFR are shown in the Supplementary Table S1.

3.4 | Associations of different triglyceride control status with diabetic kidney disease

The associations of the four TG groups with risks of incident DKD are presented in Table 4. For patients with high TG levels at baseline, the risk of DKD did not increase by tight control of TG (OR = 1.13, 95% CI = 0.77-1.68). Patients with high TG levels at follow-up or at both baseline and follow-up had significantly increased risks of DKD compared with constantly normal TG (OR = 1.77, 95% CI = 1.23-2.55 for elevated TG at follow-up; OR = 1.65, 95% CI = 1.23-2.22 for persistently elevated TG) after adjustment for covariates (age, sex, education, physical activity, current smoking status, current drinking status, BMI, systolic BP, diastolic BP, HbA1c, HDL-c, LDL-c and residual eGFR at baseline). Men and women were not significantly different in the association between TG groups and DKD (Supplementary Table S2). Examination of factors associated with persistently high TG revealed that age, gender, overweight/obesity, elevated BP, low HDL and high LDL were all significantly associated (Supplementary Table S3).

4 | DISCUSSION

Using data from a large, nationwide, multicentre, prospective cohort study of Chinese adults ≥40 years, we found that among many metabolic abnormalities such as overweight/obesity, elevated BP, poor glycaemic control and dyslipidaemia, high TG was significantly associated with the development of DKD in patients with new-onset diabetes. In addition, participants with good control of high TG during follow-up might have a reduced risk of DKD compared with those without. Therefore, long-term TG control may be very important for the prevention of DKD in diabetic patients in China, which remains to be tested in more randomized trials.

DKD is a major microvascular complication of type 2 diabetes, which is the leading cause of end-stage renal disease, accounting for nearly half of all patients receiving renal replacement therapy and is associated with cardiovascular disease and high public health care costs.[25,26] Studies of both patients with type 1 diabetes and patients with type 2 diabetes indicate that intensive glycaemic control can reduce the incidence and progression of DKD. Overall, results of interventional studies have suggested that glucose plays only a partial role in the development of renal damage, and that a range of factors, including hypertension and dyslipidaemia, may play important roles in the development and progression of DKD.[27-29] Elevated BP was significantly associated with DKD in univariate analysis in the current study. However, adjustment for age attenuated the association towards null. Many patients with diabetes meet the recommended targets for blood glucose and BP control, but the residual risk of DKD remains high. Therefore, in addition to hyperglycaemia and hypertension, the identification of other modifiable risk factors is needed. A recent systematic review and meta-analysis showed that age, smoking and TG were the most powerful baseline risk factors for detecting DKD.[30]

In our study, both high TG and low HDL-c at baseline were significantly or borderline significantly associated with increased risk of DKD. Previous studies have shown that high TG and low HDL-c levels play a crucial role in the development and progression of DKD.[9,31] However, at follow-up, only high TG was significantly correlated with the occurrence of DKD. A cross-sectional analysis of the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study also found significant associations of high TG with chronic kidney disease in subjects with type 2 diabetes.[32] However, there are also studies that have suggested that only HDL-c levels but not TG levels are associated with the progression of DKD.[16] There are conflicting study results in the literature about TG levels in DKD in type 2 diabetes. While elevated TG levels have been reported in patients with diabetes with kidney disease,[6] other reports found no difference in TG levels between diabetic subjects with and without diabetic kidney injury.[5] These differences may be related to race, gender and genetic

background of study participants. Interventional studies reducing TG levels have provided additional evidence. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study is a multinational randomized controlled trial involving 9795 patients with type 2 diabetes.[33] After 4 months of treatment, the fenofibrate group significantly reduced the rate of proteinuria progression compared with the placebo group. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[34] incidence of both microalbuminuria and macroalbuminuria was lower in the fenofibrate group than in the placebo group.

The underlying mechanism of renal dysfunction caused by dyslipidaemia remains unclear. Lipids may accumulate in renal tissue due to an imbalance of synthesis, uptake or outflow.[35,36] Lipid deposition may lead to damage of mesangial cells, endothelial cells and podocytes by inducing inflammatory response, increasing oxidative stress and promoting the release of growth factors, leading to glomerulosclerosis and tubular damage.[37,38] The kidney is negatively affected by dyslipidaemia and lipid accumulation that bring about alterations in renal lipid metabolism.[39] Besides, hyperglycaemia[40] in diabetes promotes lipid toxicity and is necessary for the development of DKD. AMP-activated protein kinase, sterol regulatory element binding protein-1 and some metabolic hormone receptors, including liver X receptors, farnesoid X receptors and peroxisome proliferator-activated receptors regulate the crosstalk of hyperglycaemia and dyslipidaemia in DKD.[41] Hyperglycaemia can cause dysregulation of polyol and hexosamine fluxes, advanced glycation end-products and activation of protein kinase C isoforms.[40] High-fat diet has been shown to aggravate proteinuria and glomerulopathy in diabetic mice, suggesting a synergistic effect of lipid and glucose on renal damage.[42,43]

In our study, overweight/obesity, elevated BP, poor glycaemic control were not significantly associated with the risks of DKD development, which was also found in previous studies.[44-46] This might be due to the selection of study participants who were patients with new-onset type 2 diabetes but without a history of hypertension and dyslipidaemia. The early effect of obesity, hypertension and hyperglycaemia was associated with glomerular hyperfiltration rather than a decline of eGFR.

Our study has several strengths and limitations. The strengths of this study include the large number of patients recruited from 20 study sites across mainland China, standardized collection of data and centralized measurements of laboratory parameters. There are several limitations. First, DKD was defined by an eGFR<60 mL/min/1.73 m^2. The KDIGO guidelines base their definition of kidney disease not only on the existence of low eGFR values but also on the existence or absence of albuminuria.[47] Data on albuminuria were not available in our study population. Second, glucose and lipid concentrations were measured only once and misclassification cannot be avoided. Third, we used data from the follow-up visit, potentially to show the control of metabolic factors during follow-up. However, control of metabolic abnormalities at follow-up and incident DKD were examined at the same time, thus the association at follow-up was essentially a cross-sectional analysis. A second follow-up is desirable to examine the development of DKD after evaluation of metabolic control. Fourth, LDL-c target should be individualized as recommended by the guidelines.[48] However, unfortunately some of the risk factors to categorize participants into very-high, high, moderate and low risk were not available in the current study. Participants had newly detected diabetes without previously diagnosed hypertension or previously diagnosed dyslipidaemia, thus we used the LDL-c target of <2.6 mmol/L for people with diabetes according to the 2020 Chinese Guideline[49] for the Prevention and Treatment of Type 2 Diabetes Mellitus. Finally, causality cannot be inferred due to the observational nature of the current study.

In conclusion, we found that high TG is an independent risk factor for DKD development, providing new evidence for lipid control in patients with diabetes. Large, long-term interventional studies might be needed to examine whether lipid-lowering drugs that reduce TG levels can effectively reduce the DKD risk in patients with type 2 diabetes.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Li Chen and Xinguo Hou designed the study. Guang Ning, Weiqing Wang, Gang Chen, Qin Wan, Guijun Qin, Li Yan, Guixia Wang, Yingfen Qin, Zuojie Luo, Xulei Tang, Yanan Huo, Ruying Hu, Zhen Ye, Lixin Shi, Zhengnan Gao, Qing Su, Yiming Mu, Jiajun Zhao, Lulu Chen, Tianshu Zeng, Xuefeng Yu, Qiang Li, Feixia Shen, Li Chen, Yinfei Zhang, Youmin Wang, Huacong Deng, Chao Liu, Shengli Wu, Tao Yang, Yufang Bi, Jieli Lu, Mian Li, Yu Xu, Min Xu, Tiange Wang, Zhiyun Zhao, Lei Gong and Chuan Wang collected the epidemiological and clinical data. Lei Gong and Chuan Wang analysed data. Lei Gong and Chuan Wang drafted the manuscript. Li Chen and Xinguo Hou revised the final manuscript. All authors approved the final version.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The dataset generated during the current study is available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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