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ORIGINAL ARTICLE

Triglyceride variability affects diabetic kidney disease in middle-aged and elderly people with type 2 diabetes mellitus in the Guangxi Zhuang population

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Abstract

Objective Dyslipidemia has been implicated in the development and progression of renal disease. To our knowledge, no reports have demonstrated an association between blood lipid level variability and diabetic kidney disease (DKD) in China. Our objective is to investigate the influence of variability in triglyceride levels on DKD incidence in a middle-aged to elderly Chinese Zhuang population with type 2 diabetes mellitus.

Methods In all, 276 participants with type 2 diabetes mellitus aged ≥ 45 years were followed up for 2 ~ 5 years and the results were analyzed. Variability in their triglycerides was evaluated using standard deviation, coefficient of variation, and variability independent of the mean, and the mean was calculated, and the outcome was DKD. We applied a Cox proportional hazard model to determine the relationship between variability TG levels and DKD.

Results During the mean 3-year follow-up, 74 participants developed DKD. In a multivariable cox regression model, triglyceride variability was a significant risk factor for DKD. The hazard ratios (HRs) (95% confidence intervals [CI]) for each increase in SD, CV, and VIM of triglycerides by 1 SD were 1.257 (1.038–1.522), 1.525 (1.059–2.195), and 1.007 (1.004–1.011), respectively. Compared to the lowest quartiles of SD of triglycerides, the HRs (95%CI) were 1.858 (1.359–2.542), 1.881 (1.354–2.612), and 1.858 (1.343–2.570) in Q2, Q3, and Q4. Consistency was seen when CV and VIM were used for calculating variability.

Conclusion High TG variability in middle-aged and elderly Chinese Zhuang patients with type 2 diabetes mellitus was associated with a significantly increased risk of developing DKD.

Keywords Triglyceride variability · Diabetic kidney disease · Type 2 diabetes · Zhuang population

Introduction

Diabetic kidney disease (DKD) is a severe irreversible complication of diabetes mellitus and is defined as a persistent rise in albuminuria excretion, a reduction in the estimated glomerular filtration rate (eGFR), or both [1, 2]. Data show that approximately 20–40% of diabetic patients have DKD in a Chinese population [3–5]. In China, DKD has become a major cause of ESRD in middle-aged and older age-groups [6]. Unfortunately, the awareness rate of DKD in our country is less than 20%, and the treatment rate is less than 50% [7]. In addition to low awareness of the disease, poor patient compliance and treatment inertia are the main reasons for inadequate DKD control [2, 8]. Despite improvements in diabetes risk factor control and management, only a small proportion of patients with type 2 diabetes achieve target levels of glucose, blood pressure, and lipids, especially if they are also affected by CKD [9–11]. Hypertriglyceridemia (HTG) is a common type of dyslipidemia, and the prevalence of HTG is particularly high in the Chinese population. Insulin resistance

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(IR) refers to the reduced ability of insulin target tissues to respond to physiological levels of insulin due to various reasons, and the body compensates by secreting too much insulin to maintain blood glucose stability [12]. Studies have shown that hypertriglyceridemia can cause insulin resistance and at the same time, insulin resistance, as a key causative factor in many metabolic diseases, can exacerbate hypertriglyceridemia [13]. Patients with type 2 diabetes mellitus (T2DM) frequently have concurrent lipid metabolism disorders, and abnormalities in lipid metabolism can be involved in kidney disease development [14–16]. In the World Health Organization's Multi-Country Follow-Up Study of Diabetic Vascular Disease, plasma triglycerides were found to be a significant predictor of renal failure in patients with type 2 diabetes [17]. Recent evidence has suggested that lipid variability can be used to predict renal insufficiency. Specifically, a Korean study involving 8 493 277 individuals reported an association between high total cholesterol (TC) variability and ESRD [18]. In the same year, a multicenter cohort study in Italy reported that low-density lipoprotein-C (LDL-C) and triglyceride (TG) variabilities led to reduced eGFRs in individuals with type 2 diabetes, and interestingly, lipid variability may have a greater impact on low-risk populations, such as young subjects without metabolic disease [19]. A recent Japanese study suggested that the standard deviation (SD), adjusted SD, and maximum minus minimum deviation of postprandial triglyceride (PTG) may increase the likelihood of patients with type 2 diabetes having reduced eGFR or microalbuminuria [20]. It is therefore unclear, based on the above evidence, what effect lipid variability has on renal insufficiency, which may be due to the differences in the populations, metabolic characteristics and ethnicities, and potential confounding factors in the studies. Moreover, few studies have focused on Chinese diabetic patients, and it is unclear whether previous findings can be translated to the high risk of DKD in middle-aged or elderly people from China with type 2 diabetes. Hence, we need additional consistent data that support the effect of lipid variability on DKD to draw more concrete conclusions. China is composed of 56 ethnic groups, with the Han nationality accounting for the main part and the remaining 55 ethnic minorities accounting for 9% of the national population. The ethnic minorities show distinct genetic backgrounds, socioeconomic status, disease burdens, languages, eating habits, and living environments [21, 22]. However, research into the risk factors of noncommunicable diseases in China often integrates ethnic minorities into a single ethnic category, ignoring ethnic differences, and the survey population is relatively limited. Therefore, we used a longitudinal cohort study to explore the link between TG variability and DKD development in middle-aged and elderly T2DM patients in a Chinese Zhuang population.

Material and methods

Study design

This was a single-center observational cohort study on middle-aged and elderly (age ≥ 45 years old) Chinese Zhuang individuals with T2DM. The participants were recruited from among ambulatory and hospitalized patients presenting at the Second Affiliated Hospital of Guilin Medical University in Guangxi Zhuang Minority Autonomous Region, China. We first confirmed that they had Guangxi household registration, that their nationality was shown as Zhuang on their ID cards, and they had lived there for more than five years. Patients with type 2 diabetes were identified, followed by baseline data collection, from January to December 2014. The follow-up for each patient ranged from 2 to 5 years (median 3.0 years). In 2014, there were 485 diabetic patients. Participants that had other conditions (congestive heart failure, infections of the urinary system, and primary kidney disease) or other forms of diabetes, complied with less than 2-year of follow-up, whose records were lacking blood lipid data, and eGFR of < 60 mL/min/1.73 m^2 were excluded. Data on 276 diabetic patients in the final cohort were used in data analysis. The research flow chart was shown in Fig. 1.

Measurement of anthropometric, clinical, and biochemical parameters

At each check-up, the participants were questioned regarding their medical history, focusing on metabolic diseases, such as hypertension, diabetes, and hyperlipidemia. We took readings of each person's height (cm) and weight (kg), with 0.1 cm or 0.1 kg accuracy, when they were barefoot and in light clothing. To calculate BMI, we divided the patient's weight (kg) by their squared height (m). Using an automatic electronic device (Model HEM-7117, OMRON Company, Dalian, China), three blood pressure readings were taken within 1 min after the individual had rested for 5 min, and the average of three measurements was calculated. Participants were categorized as having hypertension when their systolic BP (SBP) was ≥ 140 mmHg or diastolic BP (DBP) was ≥ 90 mmHg or they used antihypertensive agents. Fasting venous blood specimens were collected between 07:30 and 08:30 on the day of the test. Smoking, drinking, the consumption of high-sugar and high-fat food, and strenuous activities were prohibited during the blood sampling period. After overnight fasting for at least eight hours, blood was collected in the morning. Concentrations of plasma fasting

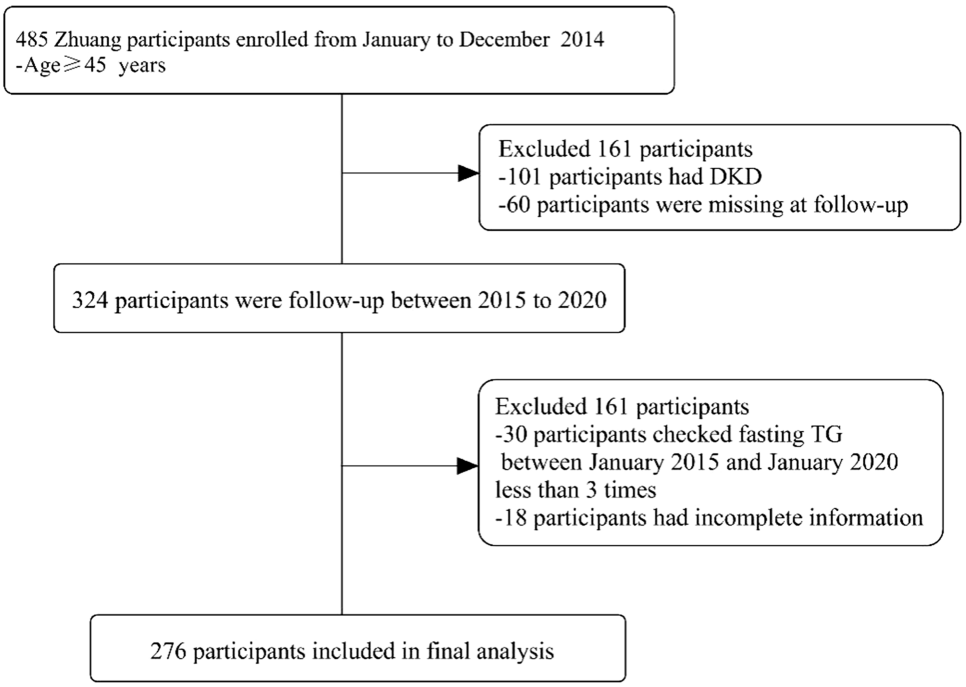

Fig. 1 Flowchart of included/excluded type 2 diabetic patients of Zhuang ethnicity. Abbreviations: DKD, diabetic kidney disease; TG, triglyceride

blood glucose (FBG), the two-hours postprandial blood glucose (2hPBG), TC, TG, LDL-C, and high-density lipoprotein-C (HDL-C) were measured with commercial colorimetric kits on an Architect c8000 analyzer (Abbott, IL, USA) using the manufacturer's protocol. HbA1c was determined by high-pressure liquid chromatography.

Outcomes and follow-up

DKD was the outcome of the present study, and diagnoses were formed using National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines. Patients were considered to have DKD when three standard criteria were applied to them: (1) a diagnosis of type 2 diabetes; (2) two consecutive urine tests within 6 months with urine albumin-to-creatinine ratio (UACR) $\geq$ 30 mg/g and/or eGFR $\leq$ 60 ml·min^{-1}·(1.73 m^2).$^{-1}$; (3) there was no clinical or laboratory evidence for other kidney diseases. The eGFR was evaluated based on revised Japanese Society of Nephrology Chronic Kidney Disease Initiative equations:$eGFR\ (ml/min/1.73m2) = 194 \times serum\ creatinine - 1.094 \times age - 0.287$ [if female, $\times$ 0.739] [23]

DKD status was reassessed annually during follow-up.

Parameters of lipid variability

We drew blood for fasting plasma lipids measurements the morning after the individual had fasted overnight ($\geq$ 8 h) during the annual physical examination. For each patient, TG parameter variability was evaluated using three indices: SD, coefficient of variation (CV), and variability independent of the mean (VIM). The CV was obtained as the SD-to-mean ratio. $VIM = 100 \times SD/mean\beta$, in which β represents the regression coefficient based on the natural log of SD divided by the natural log of the mean. Therefore, we included only those individuals with at least four lipid variable readings in the final analyses. The variabilities of the TG parameters were described in quartiles.

Statistical analyses

Data were analyzed with SPSS 20 and other statistics formulae and tables. We represented continuous variables as means ± SD or median (interquartile range) and categorical variables as numbers (percentages). We used Student's t-test to compare normally distributed data between groups, the Wilcoxon test for non-normally distributed data, and the chi-square for categorical data. A Cox proportional hazards model was used to explore the relationships between different TG variabilities and the development of DKD; covariates included age, sex, disease duration, BMI, FBG, 2hPBG, HbA1c, TC, LDL-C,

and HDL-C, amongst others. The variabilities of the TG parameters were allocated to quartiles. Standardized Kaplan–Meier curves were employed for survival analysis, and log-rank tests were run to compare cumulative event rates differences according to TG variability quartiles. All tests were two-sided. p-values < 0.05 were deemed statistically significant.

Results

Baseline characteristics of participants

Table 1 shows an outline of the clinical characteristics of the study population categorized by DKD status. Patients were assigned to two groups according to their DKD status.

Table 1 Baseline and follow-up characteristics of the study participants

Characteristic	Overall ($n=276$)	Without DKD ($n=202$)	With DKD ($n=74$)	p-value
Baseline				
Age (y)	60.49 ± 11.05	61.63 ± 11.05	59.92 ± 11.03	0.740
Diabetes duration (y)	7.00 (2.00–12.00)	5.00 (1.00–9.00)	7.00 (2.50–14.00)	< 0.001
Female (*n*, %)	110 (39.86%)	77 (38.11%)	33 (44.59%)	0.330
Smoking (*n*, %)	97 (35.14%)	78 (38.61%)	19 (25.67%)	0.046
Alcohol-drinking (*n*, %)	79 (28.62%)	60 (29.70%)	19 (25.67%)	0.512
Education levels (*n*, %)				< 0.001
Primary school	51 (18.48%)	35 (17.32%)	16 (7.92%)	
High school	152 (55.07%)	100 (49.50%)	52 (70.27%)	
College or above	73 (26.45%)	67 (33.17%)	6 (8.10%)	
Rural residence (*n*,%)	86 (31.16%)	60 (29.70%)	26 (35.10%)	0.388
Diabetic retinopathy (*n*,%)	50 (18.12%)	31 (15.35%)	19 (25.67%)	0.048
Use of lipid-lowering agents (*n*,%)	84 (30.43%)	60 (29.70%)	24 (32.43%)	0.662
Insulin	148 (53.62%)	110 (54.46%)	38 (51.35%)	0.647
Antihypertensive drugs	118 (42.75%)	93 (46.03%)	25 (33.78%)	0.038
Hypoglycemic agents	196 (66.67%)	154 (77.72%)	48 (64.86%)	0.059
Family history of diabetes (*n*,%)	47 (17.03%)	35 (17.32%)	12 (16.21%)	0.828
BMI (kg/cm^2)	24.44 (22.19–26.75)	23.63 (21.91–26.35)	24.84 (22.50–26.74)	0.386
TC (mmol/L)	4.83 (4.07–5.65)	4.91 (4.12–5.65)	4.80 (4.01–5.67)	0.284
TG (mmol/L)	1.50 (1.00–2.36)	1.40 (1.00–2.31)	1.59 (1.00–2.35)	0.905
LDL cholesterol (mmol/L)	3.04 (2.40–3.56)	3.50 (3.06–4.04)	3.59 (3.09–4.04)	0.126
HDL cholesterol (mmol/L)	1.27 (1.08–1.43)	1.26 (1.03–1.45)	1.29 (1.11–1.42)	0.015
SBP(mmHg)	135.07 ± 21.75	137.75 ± 24.44	133.72 ± 20.21	0.017
DBP (mmHg)	78.83 ± 11.40	78.48 ± 12.68	79.00 ± 10.74	0.143
FBG (mmol/L)	7. 80 (6.29–9.87)	7.55 (6.40–9.60)	8.00 (6.31–9.90)	0.882
2hPBG(mmol/L)	12.50 (9.35–15.43)	13.62 (11.20–18.40)	12.00 (8.90–14.70)	0.001
HbA1c (%)	7.60 (6.50–9.20)	7.45 (6.50–8.80)	7.80 (6.60–9.40)	0.095
eGFR (mL/min/1.73m^2)	80.09 ± 8.19	86.40 ± 17.75	76.94 ± 16.51	< 0.001
UACR(mg/g)	3.92 (11.85–18.44)	7.29 (2.35–13.03)	14.59 (6.63–19.5)	< 0.001
Follow-up Variability				
Triglyceride_Mean	1.60 (1.14–2.40)	2.34 (1.42–3.17)	2.39 (1.70–3.84)	0.439
Triglyceride_SD	1.14 (0.74–1.48)	1.31 (0.76–1.79)	1.55 (1.26–1.96)	< 0.001
Triglyceride_CV	0.62 (0.22–0.84)	0.22 (0.14–0.66)	0.73 (0.56–0.89)	< 0.001
Triglyceride_VIM	100.93 (70.14–113.03)	79.20 (33.98–104.75)	107.21 (90.27–114.23)	< 0.001

Data represent percentages, means ± SD, or medians (25th–75th percentile), as appropriate. *DKD* diabetic kidney disease, *SD* standard deviation, *CV* coefficient of variation, *VIM* variability independent of the mean, *BMI* body mass index, *TC* total cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting plasma glucose, *2hPBG* two-hours postprandial blood glucose, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *UACR* urine Albumin-to-Creatinine Ratio

In comparison with those without DKD, patients with DKD had a greater likelihood of being female and having diabetes for longer, a lower literacy level, higher HDL-C, lower 2hPBG levels, and were more likely to have diabetic retinopathy (all $p < 0.05$). Fewer patients with DKD were on insulin or antihypertensive drugs; although there were lower proportions of lipid-lowering drugs in the DKD group, these differences were not significant. In addition, we found that DKD patients had higher TG variability compared to those without DKD ($p < 0.05$), but the mean TG values did not differ significantly between the two groups ($p > 0.05$).

Risk factors for DKD in follow-up

To investigate how different TG variability influenced the emergence of DKD, Cox regression was used to conduct a multivariate factor analysis among related factors. After further adjustments for confounders, the results (Table 2) were relatively consistent. Overall, TG variability was a DKD risk factor of significance. After further adjustments for age, sex, diabetes duration, BMI, SBP, DBP, FBG, HbA1c, TC, HDL, and LDL, the hazard ratios (HRs) and 95% confidence intervals (CIs) of an increase by 1 SD of SD, CV, and VIM of TG were 1.235 (1.017–1.499), 1.481 (1.028–2.133), and 1.008 (1.004–1.011), respectively ($p < 0.05$).

TG variability and diabetic kidney disease

When the lowest quartile of TG variability was included as a reference (Table 3) across the models, we found a significant rise in the risk of DKD in the upper quartiles (Q2-Q4) compared with the lowest (Q1). In the unadjusted Model 1, the HRs and 95%CIs for the highest quartiles of SD, CV, and VIM of TG variability were 1.826 (95%CI: 1.429, 2.333), 1.485 (95%CI: 1.174, 1.879), and 1.572 (95%CI: 1.317, 1.875). In Model 3 (after adjusting for age, sex, BMI, SBP, DBP, FBG, 2hPBG, HbA1c, TC, LDL-C, and HDL-C levels, etc.), the HRs and 95%CIs for the highest quartiles of SD,

Table 2 Multivariate Cox proportional hazards regression model to study the relationship between TG variability and DKD

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	*p*-value
TG-SD	1.106 (1.005–1.217)	0.039	1.204 (1.026–1.412)	0.023	1.235 (1.017–1.499)	0.033
TG-CV	1.365 (1.056–1.763)	0.017	1.417 (1.055–1.903)	0.021	1.481 (1.028–2.133)	0.035
TG-VIM	1.007 (1.004–1.010)	0.000	1.007 (1.004–1.010)	0.000	1.008 (1.004–1.011)	0.000

Data presented as HR and 95%CI. *HR* hazard ratio, *CI* confidence interval, *DKD* diabetic kidney disease, *SD* standard deviation, *CV* coefficient of variation, *CV* coefficient of variation, *VIM* variability independent of the mean

Table 3 Relationships between TG variability and diabetic kidney disease

Variable			Model 1		Model 2		Model 3	
			HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
TG-SD	Q1	ref						
	Q2		1.601 (1.251–2.047)	< 0.001	1.484 (1.156–1.906)	0.002	1.668 (1.226–2.269)	< 0.001
	Q3		1.800 (1.412–2.295)	< 0.001	1.649 (1.279–2.125)	< 0.001	1.750 (1.282–2.389)	< 0.001
	Q4		1.826 (1.429–2.333)	< 0.001	1.785 (1.313–2.428)	< 0.001	2.051 (1.428–2.945)	< 0.001
TG-CV	Q1	ref						
	Q2		1.729 (1.367–2.188)	< 0.001	1.592 (1.251–2.027)	< 0.001	1.651 (1.251–2.180)	< 0.001
	Q3		1.684 (1.322–2.128)	< 0.001	1.592 (1.245–2.035)	< 0.001	1.655 (1.225–2.237)	0.001
	Q4		1.485 (1.174–1.879)	0.001	1.491 (1.155–1.925)	0.002	1.574 (1.153–2.150)	0.004
TG-VIM	Q1	ref						
	Q2		1.233 (0.944–1.612)	0.124	1.303 (0.990–1.715)	0.059	1.612 (1.168–2.224)	0.004
	Q3		1.256 (1.007–1.566)	0.043	1.32 (1.060–1.661)	0.013	1.456 (1.116–1.901)	0.006
	Q4		1.572 (1.317–1.875)	< 0.001	1.563 (1.300–1.879)	< 0.001	1.733 (1.389–2.164)	< 0.001

Data presented as HR and 95%CI. Model 1: non-adjusted. Model 2:adjusted for adjusted for age, sex, BMI, diabetes duration, mean TG. Model 3: adjusted for age, sex, BMI, diabetes duration, mean TG, smoking, drinking, family history of diabetes, SBP, DBP, FBG, 2hPBG, HbA1c, TC, HDL, and LDL. **Abbreviations:** *HR* hazard ratio, *CI* confidence interval, *DKD* diabetic kidney disease, *SD* standard deviation, *CV* coefficient of variation, *VIM* variability independent of the mean, *BMI* body mass index, *TC* total cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate

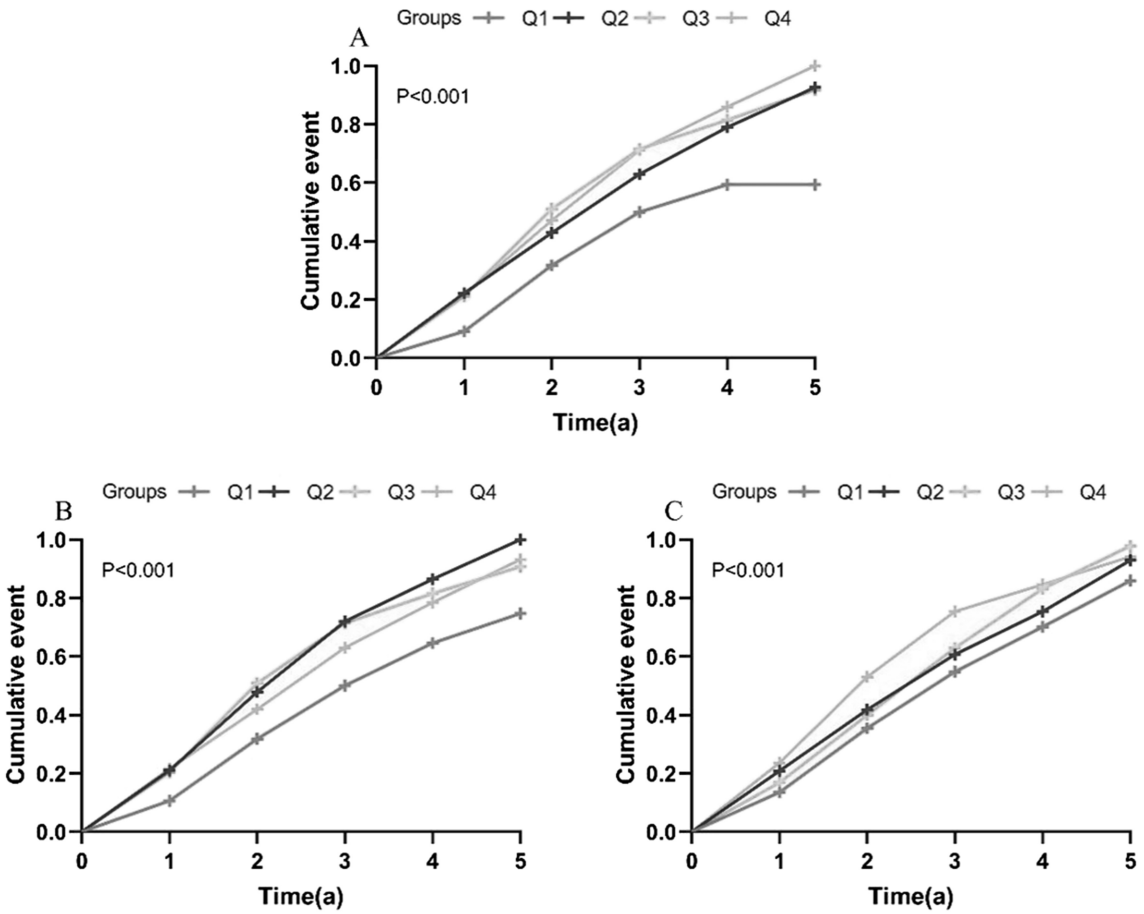

Fig. 2 Kaplan–Meier curves of cumulative events of diabetic kidney disease by quartile variability of lipid parameters (A: TG variability by SD; B: TG variability by CV; C: TG variability by CV)

CV, and VIM of TG variability were 2.051 (95%CI: 1.428, 2.945), 1.574 (95%CI: 1.153, 2.150), and 1.733 (95%CI: 1.389, 2.164). In addition, when the variability of TG was calculated using CV, the risk of DKD occurrence was still increased in the Q4 group, but it was lower than those in the Q2 and Q3 groups. Figure 2 shows the survival curves of cumulative incidence of DKD grouped by quartiles of TG variability, and higher TG variability (Q2-Q4) had an increased probability of association with an increased cumulative incidence of DKD.

Discussion

In our investigation, we found a link between higher TG variability and an increased prevalence of DKD, with the retention of significance after adjustment for demographic and clinical features. This concurs with the outcomes of a previous Italian study, although we used a different index for calculating variability[24]. However, there are known biological differences in lipid responses [25, 26]. Thus, it is important to explore the specific characteristics of particular populations, and in our study, we focused on middle-aged and elderly residents of Guangxi Zhuang, China, for whom both dietary habits and customs differ substantially from those of the Han Chinese. A Japanese report [20] claimed that PTG variability was a new risk factor for decreased eGFR and microalbuminuria incidence in type 2 diabetic individuals, but the study did not perform simultaneous blood collection and lacked a standardized diet for quality control, which may have directly affected the lipid variability measurements. TG concentrations are susceptible to dietary patterns, for example, short-term very-low-calorie factors can induce myocardial triglyceride accumulation. Lai et al. used the Environment-Wide Association Study (EWAS) approach to characterize dietary factors associated with triglycerides and found that alcohol consumption, cigarette smoking, and carbohydrate intake were the main influences on triglycerides [27], and that changes in TG concentrations were also affected by mealtimes, exercise, heredity, and free fatty acids (FFA) in the body [28]. It has been reported that inter-day variations in TG concentrations are closely

related to diet composition and time of measurement, that similar food compositions can lead to different results in PTG responses [29, 30], and that peak TG often occurs at different time points [31, 32]. Currently, the oral fat tolerance testing (OFTT) protocol is most commonly utilized for the assessment of PTG and recommends the use of a dietary meal standard containing 75 g of fat to assess PTG [33–35]. According to the Greek consensus, a PTG level of > 220 mg/dL after the consumption of high-fat food is considered high [36]. Recently, researchers in China showed this threshold to be effective for assessing dyslipidemia in those with a fasting triglyceride (FTG) level of 1.0–1.7 mmol/L [37]. In contrast, a Mexican study showed that a cut-off value of 280 mg/dL PTG at any timepoint after a meal following the OFTT test was effective for differentiating patients with fasting hypertriglyceridemia (> 150 mg/dL) [38]; however, their calculated PTG threshold is inconsistent with the consensus and, despite the inclusion of only 50 g of fat in the meal, a similar FTG response was seen in the Chinese study following the consumption of75 g of high-fat food, suggesting the existence of population variability in the definition of PTG thresholds. Furthermore, this recently discovered threshold cannot be directly correlated with cardiovascular or mortality events. Consistent with previous studies, this study found that TG variability in women was more strongly associated with the risk of diabetic nephropathy, which may be related to both estrogen and gene expression [39]. However, in previous studies, some important sex differences were observed in the management of risk factors. Compared with men with T2 DM, women with T2 DM had worse cardiovascular risk factor management, especially when they had cardiovascular disease [39]. These results suggest that stabilization of lipid levels is important in diabetic patients, especially women. Currently, patients' fasting lipids are still normative measurements in China [40]. Although some recent guidelines and consensus statements suggest that PTG is more reliable than FTG for predicting cardiovascular disease risk [35, 41, 42], the PTG does not have wide clinical application and is disadvantaged by an absence of standard clinical guidelines for the detection of postprandial lipid levels and population-based normal reference values. There have been many studies demonstrating the correlation between TG and DKD [43, 44], but no causal factors linking TG and DKD have been demonstrated. It has recently been reported that altered TG only, without other concomitant metabolic abnormalities, does not seem to have any causal association with kidney disease development [45, 46]. However, a Mendelian randomization (MR) analysis from China showed that higher TG levels were linked to a higher likelihood of developing chronic kidney disease [47]; it is possible that this lack of consensus may be the result of discrepancies in sample sizes, ethnicities, and outcome classification of the studies. Diabetic dyslipidemia and different stages of nephropathy differ in their outcomes, indicating that the complexity of the pathogenesis and the likelihood of several biologically plausible mechanisms to explain the development of DKD. When adipose tissue becomes insulin resistant, it releases large amounts of free fatty acids (FFA), and increased FFA levels cause the liver to synthesize very low-density lipoproteins (VLDL) and increase the relative amount of low-density lipoproteins (LDL); in addition, the clearance of total triglycerides (TG) by lipoprotein lipase (LPL) is prolonged, resulting in the main manifestations of lipid metabolism disorders in DKD patients being hypertriglyceridemia and steatohepatitis [48]. TG levels exceeding the upper limit of its storage in adipose tissue aggravate lipid deposition in the glomerulus, and ectopic deposition of lipids leads to endothelial cell injury, which, in turn, penetrates into adjacent endothelial tissues, such as mesangial cells, pedunculated cells, and renal tubular epithelial cells (RTECs), further exacerbating glomerular injury and sclerosis [49]. In addition, the accumulation of lipid can further aggravate glomerular damage and sclerosis. Lipid accumulation can also lead to podocyte damage [50], increased extracellular matrix deposition [51], and macrophage infiltration [52], which is associated with pathways involving inflammatory responses [53], oxidative stress [54], endoplasmic reticulum stress [55], and mitochondrial damage [56].

Therefore, whether higher TG variability is a pathogenic factor of or a compensatory response to DKD, our current understanding of this regulatory network is incomplete and further studies are still needed to elucidate its features.

Study limitations

This was a study to assess the relationship between TG variability and DKD among Chinese minorities at follow-up, but a number of limitations warrant consideration. First, our sample size was relatively small, some of the data were lost during follow-up, and the cohort study was based in a tertiary care hospital, thus lacking broad representation and having the potential of a certain degree of sampling bias. Second, although patient medication information was collected at baseline, we did not monitor patient glycemic variability, elevated blood uric acid, inflammation, effects of nephrotoxic drugs and dietary habits during follow-up, which are known to lead to faster progression of renal damage. Moreover, because diet has strong regional and ethnic variations, this may have affected our actual results. Third, we conducted a short-term follow-up period of a maximum of only 5 years, and it is necessary to continue to conduct cohort studies with larger samples for longer periods of time to more clearly define the link between TG variability and DKD in the short and late stages. Despite these limitations, our study also has some advantages in that less attention was paid to ethnic minorities at home

and abroad. Furthermore, it was based on a natural cohort of ethnic minorities in Guangxi, where the Zhuang population lives in clusters, is less mobile, and the areas of residence are relatively concentrated, and thus have a better representation. Our study has practical reference value for the development of prevention and control strategies and measures for diabetic nephropathy in the Zhuang population.

Conclusion

In conclusion, after adjusting for confounders, three different high TG variants were risk-associated with DKD development in middle-aged and elderly type 2 diabetic patients in Guangxi Zhuang. This suggests that achieving lipid stabilization, especially TG, may help to reduce the propensity for renal dysfunction. Future studies should focus on whether interventional tools have beneficial effects on TG variability.

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Declarations

Ethical clearance The study was given approval by the Ethics Committee of Second Affiliated Hospital of Guilin Medical University and First Affiliated Hospital of Guangxi Medical University and followed the Declaration of Helsinki. All participants submitted their written informed consent.

Conflict of interest The authors declare no conflict of interest.

References

1. Pereira PR, Carrageta DF, Oliveira PF, et al. Metabolomics as a tool for the early diagnosis and prognosis of diabetic kidney disease [J]. Med Res Rev. 2022;42:1518–44.
2. Gembillo G, Ingrasciotta Y, Crisafulli S, et al. Kidney disease in diabetic patients: from pathophysiology to pharmacological aspects with a focus on therapeutic inertia [J]. Int J Mol Sci. 2021;22(9).
3. Zhang L, Long J, Jiang W, et al. Trends in Chronic Kidney Disease in China [J]. N Engl J Med. 2016;375(9):905–6.
4. American Diabetes A. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020 [J]. Diabetes Care. 2020;43(Suppl 1):S135–51.
5. Hu J, Yang S, Zhang A, et al. Abdominal Obesity Is More Closely Associated With Diabetic Kidney Disease Than General Obesity [J]. Diabetes Care. 2016;39(10):e179-180.
6. Hou JH, Zhu HX, Zhou ML, et al. Changes in the Spectrum of Kidney Diseases: An Analysis of 40,759 Biopsy-Proven Cases from 2003 to 2014 in China [J]. Kidney Dis (Basel). 2018;4(1):10–9.
7. Luk AO, Li X, Zhang Y, et al. Quality of care in patients with diabetic kidney disease in Asia: The Joint Asia Diabetes Evaluation (JADE) Registry [J]. Diabet Med. 2016;33(9):1230–9.
8. Chan FL, Li YC, Chen XRC. Therapeutic inertia in proteinuria management among type 2 diabetes (T2DM) patients in primary care settings: prevalence and associated risk factors [J]. BMC Fam Pract. 2021;22(1):118.
9. Amatruda M, Gembillo G, Giuffrida AE, et al. The aggressive diabetic kidney disease in youth-onset type 2 diabetes: pathogenetic mechanisms and potential therapies [J]. Medicina (Kaunas), 2021, 57(9).
10. De Cosmo S, Viazzi F, Pacilli A, et al. Achievement of therapeutic targets in patients with diabetes and chronic kidney disease: insights from the Associazione Medici Diabetologi Annals initiative [J]. Nephrol Dial Transplant. 2015;30(9):1526–33.
11. Bayram F, Sonmez A, Haymana C, et al. Utilization of statins and LDL-cholesterol target attainment in Turkish patients with type 2 diabetes - a nationwide cross-sectional study (TEMD dyslipidemia study) [J]. Lipids Health Dis. 2020;19(1):237.
12. Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus [J]. World J Diabetes. 2015;6(3):456–80.
13. Parhofer KG, Laufs U. The Diagnosis and Treatment of Hypertriglyceridemia [J]. Dtsch Arztebl Int. 2019;116(49):825–32.
14. Peng J, Zhao F, Yang X, et al. Association between dyslipidemia and risk of type 2 diabetes mellitus in middle-aged and older Chinese adults: a secondary analysis of a nationwide cohort [J]. BMJ Open. 2021;11(5):e042821.
15 Hirano T, Satoh N, Kodera R, et al. Dyslipidemia in diabetic kidney disease classified by proteinuria and renal dysfunction: A cross-sectional study from a regional diabetes cohort [J]. J Diabetes Investig. 2021;13(4):657–67.
16. Sas KM, Lin J, Wang CH, et al. Renin-angiotensin system inhibition reverses the altered triacylglycerol metabolic network in diabetic kidney disease [J]. Metabolomics. 2021;17(7):65.
17. Chi ZS, Lee ET, Lu M, et al. Vascular disease prevalence in diabetic patients in China: standardised comparison with the 14 centres in the WHO Multinational Study of Vascular Disease in Diabetes [J]. Diabetologia. 2001;44(Suppl 2):S82-86.
18. Kim MK, Han K, Koh ES, et al. Variability in Total Cholesterol Is Associated With the Risk of End-Stage Renal Disease: A Nationwide Population-Based Study [J]. Arterioscler Thromb Vasc Biol. 2017;37(10):1963–70.
19. Ceriello A, De Cosmo S, Rossi MC, et al. Variability in HbA1c, blood pressure, lipid parameters and serum uric acid, and risk of development of chronic kidney disease in type 2 diabetes [J]. Diabetes Obes Metab. 2017;19(11):1570–8.
20. Matsuoka-Uchiyama N, Uchida HA, Okamoto S, et al. The Association of Postprandial Triglyceride Variability with Renal Dysfunction and Microalbuminuria in Patients with Type 2 Diabetic Mellitus: A Retrospective and Observational Study [J]. J Diabetes Res. 2022;2022:3157841.
21. Zhao X, Hong F, Yin J, et al. Cohort Profile: the China Multi-Ethnic Cohort (CMEC) study [J]. Int J Epidemiol. 2021;50(3):721–721l.
22. Hui-Fang L, Cai L, Wang XM, et al. Ethnic disparities in prevalence and clustering of cardiovascular disease risk factors in rural Southwest China [J]. BMC Cardiovasc Disord. 2019;19(1):200.
23. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan [J]. Am J Kidney Dis. 2009;53(6):982–92.
24. Bardini G, Innocenti M, Rotella CM, et al. Variability of triglyceride levels and incidence of microalbuminuria in type 2 diabetes [J]. J Clin Lipidol. 2016;10(1):109–15.
25. Dias CB, Moughan PJ, Wood LG, et al. Postprandial lipemia: factoring in lipemic response for ranking foods for their healthiness [J]. Lipids Health Dis. 2017;16(1):178.
26. Vors C, Pineau G, Gabert L, et al. Modulating absorption and postprandial handling of dietary fatty acids by structuring fat in the meal: a randomized crossover clinical trial [J]. Am J Clin Nutr. 2013;97(1):23–36.

27. Lai CQ, Parnell LD, Lee YC, et al. The impact of alcoholic drinks and dietary factors on epigenetic markers associated with triglyceride levels [J]. Front Genet. 2023;14:1117778.
28. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease [J]. Lancet. 2014;384(9943):626–35.
29. Yang D, Cai Q, Qi X, et al. Postprandial Lipid Concentrations and Daytime Biological Variation of Lipids in a Healthy Chinese Population [J]. Ann Lab Med. 2018;38(5):431–9.
30. Keirns BH, Sciarrillo CM, Hart SM, et al. Comparison of a Standardized High-Fat Meal versus a High-Fat Meal Scaled to Body Mass for Measuring Postprandial Triglycerides: A Randomized Crossover Study [J]. Metabolites. 2022;12(1):81.
31. Tan SY, Wan-Yi Peh E, Marangoni AG, et al. Effects of liquid oil vs. oleogel co-ingested with a carbohydrate-rich meal on human blood triglycerides, glucose, insulin and appetite [J]. Food Funct. 2017;8(1):241–9.
32. Tan SY, Peh E, Siow PC, et al. Effects of the physical-form and the degree-of-saturation of oil on postprandial plasma triglycerides, glycemia and appetite of healthy Chinese adults [J]. Food Funct. 2017;8(12):4433–40.
33. Kolovou GD, Watts GF, Mikhailidis DP, et al. Postprandial Hypertriglyceridaemia Revisited in the Era of Non-Fasting Lipid Profile Testing: A 2019 Expert Panel Statement, Main Text [J]. Curr Vasc Pharmacol. 2019;17(5):498–514.
34. Hou X, Guan Y, Tang Y, et al. A correlation study of the relationships between nonalcoholic fatty liver disease and serum triglyceride concentration after an oral fat tolerance test [J]. Lipids Health Dis. 2021;20(1):54.
35. Kolovou GD, Watts GF, Mikhailidis DP, et al. Postprandial Hypertriglyceridaemia Revisited in the Era of Non-Fasting Lipid Profile Testing: A 2019 Expert Panel Statement, Narrative Review [J]. Curr Vasc Pharmacol. 2019;17(5):515–37.
36. Tian F, Xiang QY, Zhang MY, et al. Changes in non-fasting concentrations of blood lipids after a daily Chinese breakfast in overweight subjects without fasting hypertriglyceridemia [J]. Clin Chim Acta. 2019;490:147–53.
37. Hou X, Song A, Guan Y, et al. Identification of the Chinese Population That Can Benefit Most From Postprandial Lipid Testing: Validation of the Use of Oral Fat Tolerance Testing in Clinical Practice [J]. Front Endocrinol (Lausanne). 2022;13: 831435.
38. Sevilla-Gonzalez MDR, Aguilar-Salinas CA, Munoz-Hernandez L, et al. Identification of a threshold to discriminate fasting hypertriglyceridemia with postprandial values [J]. Lipids Health Dis. 2018;17(1):156.
39. Gembillo G, Cernaro V, Giuffrida AE, et al. Gender differences in new hypoglycemic drug effects on renal outcomes: a systematic review [J]. Expert Rev Clin Pharmacol. 2022;15(3):323–39.
40. Tabrizi R, Ostadmohammadi V, Lankarani KB, et al. The effects of probiotic and synbiotic supplementation on inflammatory markers among patients with diabetes: A systematic review and meta-analysis of randomized controlled trials [J]. Eur J Pharmacol. 2019;852:254–64.
41. Higgins V, Adeli K. Postprandial Dyslipidemia: Pathophysiology and Cardiovascular Disease Risk Assessment [J]. EJIFCC. 2017;28(3):168–84.
42. Kolovou GD, Mikhailidis DP, Kovar J, et al. Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement [J]. Curr Vasc Pharmacol. 2011;9(3):258–70.
43. Russo GT, De Cosmo S, Viazzi F, et al. Plasma Triglycerides and HDL-C Levels Predict the Development of Diabetic Kidney Disease in Subjects With Type 2 Diabetes: The AMD Annals Initiative [J]. Diabetes Care. 2016;39(12):2278–87.
44. Jia X, Zang L, Pang P, et al. A study on the status of normoalbuminuric renal insufficiency among type 2 diabetes mellitus patients: A multicenter study based on a Chinese population [J]. J Diabetes. 2022;14(1):15–25.
45. Lanktree MB, Theriault S, Walsh M, et al. HDL Cholesterol, LDL Cholesterol, and Triglycerides as Risk Factors for CKD: A Mendelian Randomization Study [J]. Am J Kidney Dis. 2018;71(2):166–72.
46. Liu HM, Hu Q, Zhang Q, et al. Causal Effects of Genetically Predicted Cardiovascular Risk Factors on Chronic Kidney Disease: A Two-Sample Mendelian Randomization Study [J]. Front Genet. 2019;10:415.
47. Zhang YB, Sheng LT, Wei W, et al. Association of blood lipid profile with incident chronic kidney disease: A Mendelian randomization study [J]. Atherosclerosis. 2020;300:19–25.
48. Nofer JR. Hyperlipidemia and cardiovascular disease: triglycerides - a revival of cardiovascular risk factor? [J]. Curr Opin Lipidol. 2011;22(4):319–21.
49. Bozzetto L, Della Pepa G, Vetrani C, et al. Dietary Impact on Postprandial Lipemia [J]. Front Endocrinol (Lausanne). 2020;11:337.
50. Wang Q, Zhao B, Zhang J, et al. Faster lipid beta-oxidation rate by acetyl-CoA carboxylase 2 inhibition alleviates high-glucose-induced insulin resistance via SIRT1/PGC-1alpha in human podocytes [J]. J Biochem Mol Toxicol. 2021;35(7):e22797.
51. Guebre-Egziabher F, Alix PM, Koppe L, et al. Ectopic lipid accumulation: A potential cause for metabolic disturbances and a contributor to the alteration of kidney function [J]. Biochimie. 2013;95(11):1971–9.
52. Ducasa GM, Mitrofanova A, Fornoni A. Crosstalk Between Lipids and Mitochondria in Diabetic Kidney Disease [J]. Curr Diab Rep. 2019;19(12):144.
53. Yu R, Bo H, Villani V, et al. The Inhibitory Effect of Rapamycin on Toll Like Receptor 4 and Interleukin 17 in the Early Stage of Rat Diabetic Nephropathy [J]. Kidney Blood Press Res. 2016;41(1):55–69.
54. Vasconcelos EM, Degasperi GR, de Oliveira HC, et al. Reactive oxygen species generation in peripheral blood monocytes and oxidized LDL are increased in hyperlipidemic patients [J]. Clin Biochem. 2009;42(12):1222–7.
55. Cansby E, Caputo M, Gao L, et al. Depletion of protein kinase STK25 ameliorates renal lipotoxicity and protects against diabetic kidney disease [J]. JCI Insight. 2020;5(24):e140483.
56. Qi H, Casalena G, Shi S, et al. Glomerular Endothelial Mitochondrial Dysfunction Is Essential and Characteristic of Diabetic Kidney Disease Susceptibility [J]. Diabetes. 2017;66(3):763–78.