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ORIGINAL RESEARCH

High Remnant Cholesterol is Associated with the Development of Diabetic Kidney Disease in Patients with Type 2 Diabetes

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Aim: The study aimed to explore the associations of the remnant cholesterol (RC) levels with the risk of diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM).

Methods: The study collected data from 23324 patients with T2DM from the UK Biobank (UKB) cohort and 3059 patients with T2DM from the Chongqing Diabetes Registry (CDR) cohort. UKB and CDR cohort were followed for incident DKD until October 2020 and March 2023, respectively. Cox proportional hazards regression was performed to explore the relationship between RC levels and incident DKD.

Results: Participants from the UKB and CDR were followed for a mean period of 13.72 years and 1.92 years, respectively. The incidences of DKD are 12.9% and 24.5%. Participants were divided into 4 groups: 0.41 mmol/L or less, 0.41 to 0.56 mmol/L, 0.56 to 0.73 mmol/L, and greater than 0.73 mmol/L according to RC levels. Lower RC levels (≤0.41 mmol/L) were used as a reference, multi-adjusted model showing that patients with higher RC levels (>0.73 mmol/L) in the UKB were associated with increased risk of incident DKD [hazard ratio [HR], 1.27; 95% CI, 1.10–1.46; P = 0.001]. These results were consistent in the CDR [HR (95% CI): 1.39 (1.03, 1.89); P = 0.034]. In the stratified analyses, we observed an increase in the risk of incident DKD with RC in the elderly patients, while not in the middle-aged patients in both UKB cohort [HR (95% CI): 1.33 (1.13, 1.57) vs 1.16 (0.89, 1.50), P for interaction = 0.043] and CDR cohort [HR (95% CI): 1.53 (1.02, 2.30) vs 1.23 (0.76, 2.00), P for interaction = 0.009].

Conclusion: High RC might be an independent risk factor for new-onset DKD in T2DM population after adjusting for traditional risk factors, especially in elderly T2DM patients.

Keywords: type 2 diabetes mellitus, remnant cholesterol, diabetic kidney disease, cohort study, ethnic differences

Introduction

Over the past few years, with the increased prevalence of diabetes and obesity, the incidence of diabetic kidney disease (DKD) has increased drastically in the global.[1–3] DKD contributes to the heavy burden of kidney-related diseases. In addition, DKD affects the kidney system but also other organ systems, such as the endocrine system, the nervous system, and the cardiovascular system.[2,4–7] Due to the prevalence of DKD and a multitude of serious health impacts of DKD, it is beneficial to reduce the heavy disease burden of DKD, if the susceptible population of DKD in type 2 diabetes mellitus (T2DM) is identified early by some noninvasive and simple indicators.

Dyslipidemia is a recognized pathogenic factor of DKD according to several epidemiological studies. Previous studies have confirmed the relationship of lipid components with renal dysfunction, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), and

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Apolipoprotein C-III.[8–11] Recently, it has been recognized that remnant cholesterol (RC) has a the negative influence of beyond the traditional blood lipid indicators. RC is composed of intermediate-density lipoproteins and very low-density lipoproteins in fasting state and of these 2 lipoproteins together with chylomicron remnants in the nonfasting state.[12] The causal relationship between atherosclerotic and RC cardiovascular disease is clarified.[13] Besides, high RC increases these risks of cardiovascular events, all-cause mortality in patients with long-term kidney transplant[14] as well as in overweight or obese patients.[15] In the middle age and older age population, higher RC is independently associated with an increased risk of prevalent chronic kidney disease (CKD).[16] However, the knowledge of RC is inadequate in the context of T2DM. A cross-sectional study showed that RC is an independent risk factor for diabetic retinopathy (DR).[17] Considering the strong association of involvement in RC and cardiovascular events, and the fact that DKD often coexists with DR, the question has been raised whether RC also contributes to the decline of renal function in individuals with diabetes mellitus. A recent study including 4237 Chinese patients with T2DM reported that for each standard deviation increase in RC, individuals with T2DM had a 22.1% increased risk of new-onset kidney disease.[18] However, the participants in this study were mainly from health management centers, and the patients were younger, had better glycemic control. In addition, the study excluded participants with DR which is closely associated with DKD.[19] However, DKD and DR have common risk factors such as blood glucose and blood pressure.[19] Some risk factors in the population were underestimated after excluding DR participants in the cohort. It will hide the real condition in population with T2DM and result in a lower incidence rate of DKD during the follow-up. Moreover, in this cohort, the proportion of new-onset diabetic nephropathy was low, only 5.9%, which was far lower than the incidence rate of diabetic nephropathy reported in previous literature. Finally, this study only recruited the Chinese participants. Thus, the impact of RC on the progression of diabetic nephropathy in other ethnic groups with T2DM remains uncertain.

The present research aims to discover the relationship between RC and emerging diabetic nephropathy in the white population and to be validated in the diabetic cohort of Chongqing, China.

Methods

This cohort study was approved by the North West Multicenter Research ethics committee in the UK, and the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University in China. All individuals from both databases signed written informed consent. The data have been analyzed from a subset of patients with T2DM in the Chongqing Diabetes Registry (CDR) and patients in the UK Biobank (UKB) with T2DM at enrollment. Relevant risk factors and demographics have been collected at enrollment and follow up, including age, sex, HDL-C, LDL-C, TC, TG, body mass index (BMI), blood pressure, urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). Biospecimens were collected and assayed in affiliated laboratories from both cohorts. The RC level was calculated as TC - (HDL - C) - (LDL - C).[20] UKB and CDR cohort were followed for incident of DKD until October 2020 and March 2023, respectively. Participants from UKB and CDR were followed prospectively for an average of 13.72 years and 1.92 years, respectively.

UK Biobank

More than 500,000 participants aged 40–72 years were recruited from the UK general community population into the UK Biobank (UKB) cohort between 2006 and 2010, details of the study design have been reported previously.[21] Patients with T2DM were enrolled in our study. Then, these patients with incomplete lipid data and negative values of RC were excluded. Finally, 23324 T2DM patients entered into the cross-sectional study, and we analyzed the correlation of RC with baseline DKD. Subsequently, 20892 T2DM patients without DKD were included in the longitudinal analysis to investigate the predictive value of RC for incident DKD (Figure 1).

We identified DKD using renal replacement therapy from ICD-10 codes (Z49, Z99.2, Z94.0), diabetes mellitus with renal complications from ICD-10 codes (E102, E112, E122, E132, E142), renal failure from ICD-10 codes (N18–19), which is widely used in similar studies.[22–24]

CDR

The CDR cohort is an ongoing, prospective and multistage population study in the First Affiliated Hospital of Chongqing Medical University, it randomly enrolled T2DM patients from March 2018 to January 2022. A total of 3278 patients

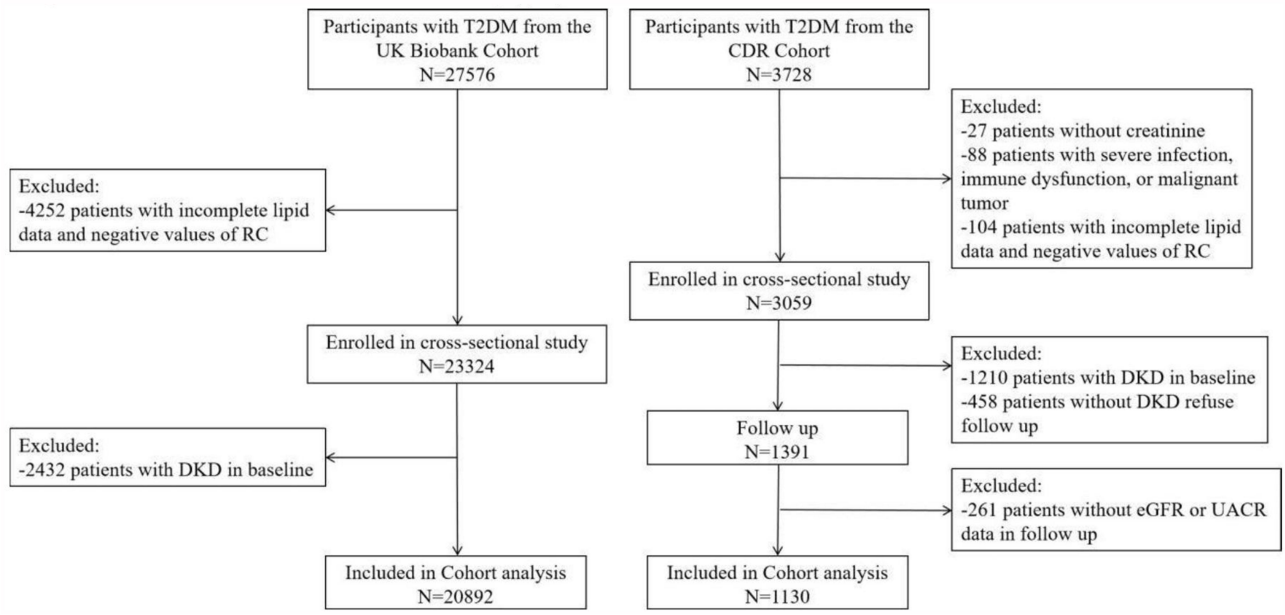

Figure 1 Flow chart of the study population.
Abbreviations: CDR, Chongqing Diabetes Registry; T2DM, type 2 diabetes mellitus; RC, remnant cholesterol; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

were enrolled until March 1, 2022. Patients with missing data, immune dysfunction, malignant tumor, or severe infection were excluded. Ultimately, 3059 T2DM patients entered into the cross-sectional study to analyse the correlation of RC with baseline DKD. Next, 1130 T2DM patients without DKD completed annual medical examinations with full follow-up data, and the predicted value of the RC for incident DKD has been shown (Figure 1).

DKD was defined as eGFR <60 mL/min/ 1.73 m^2 over 3 months or two of three specimens should have a UACR of ≥30 mg/g in three tests within a 3 to 6 month period in T2DM patients, and patients did not have other kidney diseases. It is based on ADA Standards of Medical Care in Diabetes.[25]

Statistical Analysis

Participants with T2DM were sorted into 4 groups based on the RC levels: 0.41 mmol/L or less, 0.41 to 0.56 mmol/L, 0.56 to 0.73 mmol/L, and greater than 0.73 mmol/L. Continuous data was shown as means and standard deviations (SDs) and compared by an one-way analysis of variance, while categorical variables were represented as numbers and percentages and compared by the $\chi 2$ test.

The study obtained odds ratios (ORs) and 95% confidence intervals (CIs) by logistic regression analyses to assess the association of different RC levels with baseline DKD and continuous RC with baseline DKD, according to the following models: model 1 controlled for age, sex; model 2 additionally controlled for diastolic blood pressure (DBP), BMI, fasting plasma glucose (FPG), LDL-C and hypolipidemic therapy. These covariates were chosen according to the risk factors of DKD.[26–28] The longitudinal study implemented two proportional hazards models (Cox regression) to evaluate the independent association of the RC with incident DKD after adjusting for potential confounders. Longitudinal study results were shown as forest plots. The predictive accuracy assessed by Harrell's concordance index (C-statistic). We further performed subgroups analyses and presented the result to determine whether the association of very high RC levels with incidence of incident DKD differed by gender (male/female) or not, age (≥60years/<60years), overweight/obesity (yes/no), fasting glucose levels (≥7mmol/L/<7mmol/L), and LDL-C levels (≥3.4 mmol/L/<3.4 mmol/L) adjusting for aforementioned covariates. Multiplicative interaction terms between RC levels and subgroup were included in separate models to assess whether the effect of subgroup differed for patients in diffrernt RC levels.

All of the analyses were performed by R open-source software (version 4.2.1). A two-sided $P < 0.05$ was regarded as statistically significant.

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Results

UKB

The 23324 T2DM participants of UKB (average age, 59.56 years; 14285 men [61.25]; 2432 baseline DKD [10.43]), there were 2702 new-onset DKD (12.9%) during a mean follow up of 13.72 years. The number of participants without data of BMI, TC, FPG, TG, HDL-C and LDL-C were 231, 28, 15, 0, 0 and 0, respectively (Table 1).

It was shown that increased RC was correlated with higher rates of baseline DKD after adjusting mentioned confounders in patients with T2DM (Table 2). In model 1, compared to participants in quartile 1 (≤0.41mmol/L), those participants in quartile 4 (>0.73mmol/L) had a higher risk of prevalent DKD after adjustment for sex and age (OR = 1.17, 95% CI = 1.04–1.32, P = 0.008). It was shown a similar result when we treat RC as a continuous variable (OR =

Table 1 Baseline Characteristics by RC Categories of Participants From UK Biobank Cohort and CDR Cohort

	UK Biobank	CDR Cohort
n	23324	3059
Male, n (%)	14,285 (61.25)	1818 (59.43)
Age (years)	59.56 (7.20)	58.12 (11.23)
SBP (mmHg)	143.20 (18.64)	134.48 (19.35)
DBP (mmHg)	81.45 (10.40)	78.81 (12.02)
BMI (kg/m^2)	31.27 (5.89)	24.76 (5.92)
FPG (mmol/L)	7.47 (3.39)	8.90 (3.30)
HbA1c (%)	6.93 (1.28)	9.12 (2.90)
Cr (μmol/L)	75.96 (30.98)	78.1 (102.75)
TC (mmol/L)	4.40 [3.80, 5.13]	4.27 [3.58,5.07]
TG (mmol/L)	1.82 [1.26, 2.59]	1.51 [1.04,2.38]
HDL-C (mmol/L)	1.15 [0.98, 1.38]	1.08 [0.89,1.34]
LDL-C (mmol/L)	2.61 [2.18, 3.15]	2.51 [1.87,3.19]
eGFR (mL/min/1.73m^2)	88.65 (16.73)	91.61 (24.05)
UACR (mg/g)	14.21 [7.71, 33.93]	15.9 [6.2,66.4]
RC (mmol/L)	0.56 [0.41, 0.73]	0.44 [0.25,0.74]
DKD, n (%)	2432 (10.43)	1210 (39.56)
Hypolipidemic therapy, n (%)	237 (1.02)	1593 (52.08)

Notes: Data are expressed as mean (SD), percentages, or as medians [IQR]. Quartile limits were measured in mmol/L.

Abbreviations: RC, remnant cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, Fasting plasma glucose; HbA1c, glycated hemoglobin; Cr, creatinine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; DKD, diabetic kidney disease.

Table 2 Association Between RC Quartiles and Risk of Prevalent DKD

Cohort	Model	RC Level		RC Quartiles							
		All (per mmol/L Increase)		Quartile 1 (≤0.41mmol/L)	Quartile 2 (0.41–0.56mmol/L)		Quartile 3 (0.56–0.73mmol/L)		Quartile 4 (>0.73mmol/L)	
		OR (95% CI)	*p*-value	Reference	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
UKB	Model 1	1.32 (1.15, 1.52)	<0.001	1.00	0.95 (0.84, 1.07)	0.383	0.97 (0.86, 1.09)	0.570	1.17 (1.04, 1.32)	0.008
	Model 2	1.74 (1.45, 2.09)	<0.001	1.00	0.97 (0.85, 1.10)	0.619	1.04 (0.90, 1.19)	0.599	1.40 (1.20, 1.65)	<0.001
CDR	Model 1	1.27 (1.17, 1.38)	<0.001	1.00	1.36 (1.10, 1.70)	0.006	2.16 (1.71, 2.72)	<0.001	2.05 (1.71, 2.47)	<0.001
	Model 2	1.21 (1.11, 1.32)	<0.001	1.00	1.32 (1.05, 1.64)	0.016	2.03 (1.60, 2.58)	<0.001	1.82 (1.51, 2.20)	<0.001

Notes: Data are Expressed as OR (95% CI) + p-value, Unless Stated Otherwise. Model 1 was Adjusted for Age, Sex. Model 2 was Adjusted for BMI, DBP, FPG, LDL-C, Hypolipidemic Therapy in Addition to the Variables in Model 1.

Abbreviations: RC, Remnant Cholesterol; DKD, Diabetic Kidney Disease; UKB, UK Biobank Cohort; CDR, Chongqing Diabetes Registry Cohort.

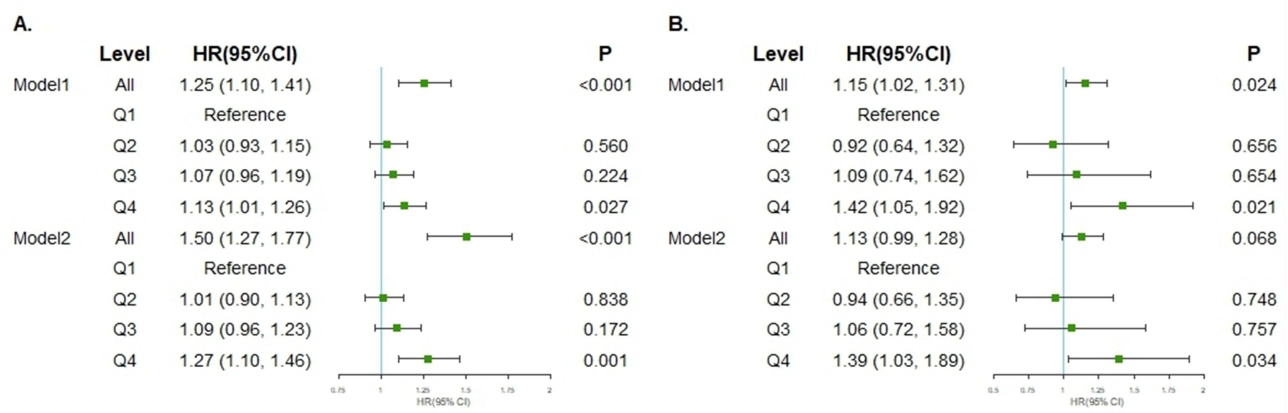

Figure 2 Cox regression for DKD according to the quartiles of the RC in longitudinal data. (**A**) UK Biobank Cohort, new-onset DKD. (**B**) CDR Cohort, new-onset DKD. Model 1 was adjusted for age, sex. Model 2 was adjusted for BMI, DBP, FPG, LDL-C, eGFR, hypolipidemic therapy in addition to the variables in model 1.
Abbreviations: DKD, diabetic kidney disease; RC, remnant cholesterol; Q1, remnant cholesterol in the first quartile; Q2, remnant cholesterol in the second quartile; Q3, remnant cholesterol in the third quartile; Q4, remnant cholesterol in the fourth quartile.

1.32, 95% CI = 1.15–1.52, P < 0.001). After extra adjustment for BMI, DBP, FPG, LDL-C and hypolipidemic therapy (model 2), this tendency was still retained.

In order to further demonstrate that RC is effective in predicting incidence of DKD, 20892 T2DM patients who exclude DKD at baseline were included into the longitudinal study. We obtained values of new-onset DKD predicted by RC through cox regression analysis in three models. In model 1, with the RC's quartile 1 (≤0.41mmol/L) as the reference, those with RC located in quartile 4 (>0.73mmol/L) had higher risk of new-onset DKD (HR = 1.13, 95% CI = 1.01–1.26, P = 0.027), even by further adjustment for DBP, BMI, FPG, LDL-C, hypolipidemic therapy, and baseline eGFR (HR = 1.27, 95% CI = 1.10–1.46, P = 0.001) (Figure 2A). The results showed that RC predicted new-onset DKD with a C-statistic (95% CI) of 0.707 (0.697–0.718).

CDR

The baseline characteristics about the participants from the CDR cohort who divided by RC quartiles are presented in Table 1. Three thousand fifty-nine T2DM participants were included in the cross-sectional analysis, 1210 participants (39.56%) had baseline DKD. The number of participants without data of FPG, BMI, TG, TC, HDL-C and LDL-C were 20, 6, 1, 0, 0 and 0, respectively. The average ages of participants were 58.12 years. 59.43% participants were men. During a mean follow up of 1.92 years, there were a total of 277 new-onset DKD (24.5%) (Table 1).

We used binary logistic regression analysis of cross-sectional data to evaluate the correlation of the RC with baseline DKD (Table 2). After adjusting for age, sex, DBP, BMI, FPG, LDL-C, hypolipidemic therapy, a significant increase in the ORs for baseline DKD in the fourth RC quartile participants (>0.73mmol/L) was observed (P < 0.001), compared with participants in the first quartile (≤0.41mmol/L), and the OR (95% CI) in participants in the fourth quartile of RC was 1.82 (1.51–2.20) for baseline DKD compared to the first quartile. It was shown a similar result when we treat RC as a continuous variable (OR = 1.21, 95% CI = 1.11–1.32, P < 0.001).

Results from Cox regression analyses are shown in Figure 2B. As compared with individuals with RC in quartile 1 (≤0.41mmol/L), those in the highest group (>0.73mmol/L) showed a significantly greater risk of new-onset DKD in model 1 (HR = 1.42, 95% CI = 1.05–1,92; P = 0.021). In fully adjusted models (model 2), the group with the highest RC levels had a higher risk of new-onset DKD (HR = 1.39, 95% CI = 1.03–1.89, P = 0.034). The results showed that RC predicted new-onset DKD with a C-statistic (95% CI) of 0.607 (0.570–0.644).

Association of RC with new-onset DKD in stratified Analysis

The correlations between RC and new-onset DKD in subgroups based on gender, age, overweight/obesity, blood glucose, LDL-C, and DKD events were investigated to further confirm whether the results are stable or not. As shown in Figure 3, compared

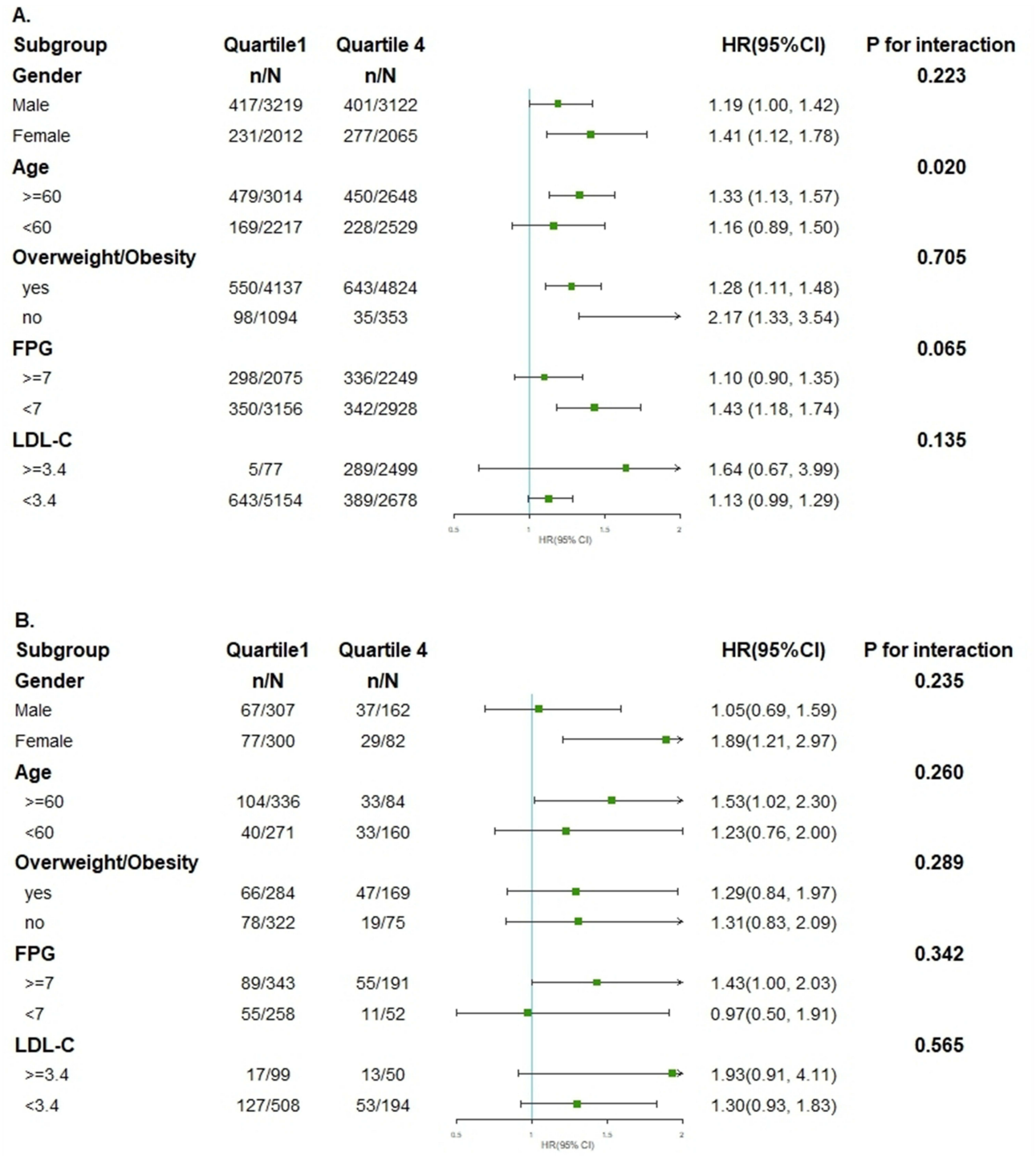

Figure 3 Hazard ratios for cox regression in model 2 of the association between highest RC and DKD in different subgroups. Cox regression analysis of RC in the fourth quartile and new-onset DKD in different subgroups of the UK Biobank Cohort (**A**) and CDR Cohort (**B**) after adjusting for variables in model 2. Model 2 was adjusted for age, sex, eGFR, BMI, DBP, FPG, LDL-C, hypolipidemic therapy.

Abbreviations: DKD, diabetic kidney disease; RC, remnant cholesterol; FPG, fast plasma glucose; LDL-C, low-density lipoprotein cholesterol.

with subjects with age lower 60 years, higher risk of new-onset DKD was detected in subjects with age over 60 years in UKB cohort [HR (95% CI): 1.16 (0.89, 1.50) vs 1.33 (1.13, 1.57), P for interaction = 0.043] and CDR cohort [HR (95% CI): 1.23 (0.76, 2.00) vs 1.53 (1.02, 2.30), P for interaction = 0.009]. When the age was treated as a continuous variable, the difference is significant in UKB cohort [P for interaction = 0.020] rather than CDR cohort [P for interaction = 0.260]. However, gender

(P for interaction = 0.223 and 0.235, respectively), overweight/obesity (P for interaction = 0.705 and 0.289, respectively), blood glucose (P for interaction = 0.065 and 0.342, respectively), and LDL-C (P for interaction = 0.135 and 0.565, respectively) did not affect the relationship between RC quartiles and new-onset DKD in both cohorts. The results of quartile 2 and quartile 3 have been showed in Supplementary Figure 1.

Discussion

Our study results suggest that with T2DM patients, compared to low RC levels (≤0.41 mmol/L) patients, high RC levels (>0.73 mmol/L) patients have a higher risk of new-onset DKD, and the risk is independent of hypolipidemic use and traditional renal risk factors. The result was confirmed in two cohorts. The study indicates that the results are stable in white and Asian populations. The results need to be verified in other racial. Meanwhile, we observed the different prevalence of DKD between the CDR and UKB cohorts. It might be attributable to the difference of UKB and CDR cohort participants. Most participants in the CDR cohort were recruited from hospitalized patients who usually had a severe state of illness and a worse control of blood glucose. However, participants in the UKB cohort were recruited from the UK general community population.

It is well known that abnormal lipid metabolism plays an indispensable role in DKD and remains a significant risk factor for DKD. Previous studies have demonstrated the association of lipid abnormalities including high TG, high TC, high LDL-C, and low HDL-C with DKD.[10,29–33] However, the above-mentioned traditional indicators are relatively single, which cannot comprehensively reflect the blood lipid disorder. RC, as a novel blood lipid index, more comprehensively reflects the levels of cholesterol in all the triglyceride-rich lipoproteins in the body compared with the conventional blood lipid indicators. Recently, other novel lipid markers have got attention. The triglyceride-glucose (TyG) index and the triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio are surrogate markers of insulin resistance.[32] They have been extensively studied in multiple diseases.[33–35] TyG index has been proven to be associated with DKD.[32,36,37] And the TG/HDL-C ratio is a risk factor for CKD.[38] However, the calculation of TyG index need the value of fasting glucose, which is fluctuating due to factors such as time and physical activity. Therefore, stability might be an advantage of RC. Furthermore, TyG primarily reflects the effects of triglycerides and glucose on DKD. On the other hand, RC reflects the levels of triglycerides and cholesterol. It will provide a more comprehensive assessment of the effects of lipid on DKD.

An increasing number of reports suggested that elevated RC levels are strongly and independently associated with high risks of atherosclerosis and negative cardiovascular outcomes.[39–41] Unfortunately, there is a lack of studies focusing on the relationship between RC and CKD, particularly in T2DM patients. In a cross-sectional study based on the Chinese community adults, including 35848 participants, high RC levels were found to be highly correlated with increased UACR.[42] Another cross-sectional study involved 7356 Chinese participants aged ≥ 40 years and reported that Higher level of RC was independently connected to the increased risk of prevalent CKD, and RC may be a novel risk biomarker for CKD, especially in women.[16] More recently, a cohort study based on Chinese patients with T2DM who had better glycemic control showed a significant association between increased RC and elevated risk of emerging nephropathy in people with T2DM.[18] Our results also confirmed that a high level of RC was significantly associated with incidence of DKD in Chinese T2DM patients, independent of BMI, blood glucose, blood pressure, and blood lipids. In addition, that this relationship is also present in the white population. Furthermore, both the UKB cohort and the CDR cohort found a higher risk of new-onset DKD in patients of age over 60 years, compared with patients less than 60 years.

The underlying mechanism of the association between RC and DKD remains uncertain and complex. Therefore, we assume that possible mechanisms are as follows: (1) Lipotoxicity: RC is composed of very-low-density lipoproteins, intermediate-density lipoproteins and chylomicron remnants, it is the cholesterol content of TG-rich lipoproteins.[43] Hypertriglyceridemia is closely related to lipotoxicity, and lipotoxicity leads to a result of overload of free fatty acid levels in pancreatic islets and renal parenchyma, which in turn leads to insulin resistance[44] and renal dysfunction.[45] (2) Inflammation: RC was reported to have a close relationship with systemic low-grade inflammation. It has been demonstrated that RC is responsible for a higher increase of C-reactive protein level, promoting the occurrence of inflammation.[46] The possible mechanism is that remnant lipoprotein particles induce

the production of TNF-α and IL-1β via activated LOX-1.[47] The hypothesis need further research to provide direct evidence.

Considering the possible mechanisms of RC, currently available drugs that can reduce the RC levels may include statins, ezetimibe, PCSK9 inhibitors, fibrates, etc. A result showed that all statins can significantly reduce RC by inhibiting HMG-CoA reductase and minimizing cholesterol production in the PREVAIL US trial.[48] Previous study reported that the combination of ezetimibe and simvastatin make RC decreased by 65%.[49] Two real world studies about PCSK9 inhibitors reported a reduced RC.[50,51] In addition, Tsunoda et al demonstrated that RC of T2DM can be reduced by fibrates.[52] In particular, Ishibashi and Pradhan et al revealed that selective peroxisome proliferator-activated receptors (PPARs) α modulator (SPPARM α)–pemafibrate enables RC to reduce by 25.6% to 50.1% which surpasses fenofibrate.[53,54] More importantly, pemafibrate is metabolized in liver. Therefore, it is available for T2DM patients with renal dysfunction.[55] Based on the results of our study, we think that the use of lipid-lowering drugs might be beneficial for preventing new-onset DKD in patients with T2DM and high RC level. However, the point needs intervention trials to be clarified.

There were following strengths in our study: This is the first large-scale study of T2DM patients who came from different ethnic populations in two countries on different mainlands and had a long-term follow-up for new-onset DKD events in UKB cohort. Besides, our study further showed that high levels of RC were related to an increased risk of new-onset DKD in patients with T2DM, especially in older and in female people. However, the main limitations need to be noticed. At first, we obtained the data of RC levels through formula calculation rather than direct measurement. Nevertheless, the formula has been widely used in multiple diseases and show unique clinical values and the reliability of method.[15,56,57] Even though it is practicable to measure RC directly. Because it is hard to be popularized in clinical practice. And then, as a general blood lipid index, RC contains many lipoprotein subclasses, but we did not measure the specific lipoprotein subclasses in the study. Therefore, more research will be needed to reveal the association between DKD and lipoprotein subclasses. In addition, even though known confounding factors have been adjusted in the cox regression analysis, we cannot exclude potential residual confounding factors because other medications which might influence the association was not investigated, although we adjusted for hypolipidemic drugs in our analysis. And then, the definition of DKD in the UKB cohort based on ICD codes which may introduce diagnostic bias, even if the method has been widely used in similar studies to supporting its feasibility in DKD research.[21–24]. Finally, follow-up time in CDR cohort is short in cox regression. A longer-term follow-up cohorts may be required to evaluate the stability of the relationship between RC and new-onset DKD in Asian populations.

In summary, our study firstly demonstrated a value of RC in predicting the development of DKD in T2DM patients through two large population-based cohorts. The relationship between RC and adverse cardiovascular events has been proved, and it has an unneglectable impact on the formation of atherosclerotic plaque, and development of DKD. Our study demonstrated a significant value of high RC in identifying high risk individuals of DKD development. These individuals are usually ignored on account of the targeted blood lipid levels. To summarize, early screening of RC level is essential in clinical practice, especially among T2DM populations. More significantly, RC might be both a new predictor and observation index to manage DKD populations with diabetes. Due to confounding factors, Cohort studies provide weaker evidence for causality than RCTs. It remains uncertain Whether RC is a potential target in manage DKD populations with diabetes. However, the indicator is promising and needs randomized controlled trials to support intervention effects.

Conclusions

In this cohort study, results suggested that a high RC level (>0.73 mmol/L) in baseline is associated with the new-onset of DKD in T2DM patients. Our finding highlights that RC may be an independently predictive indicator in new-onset DKD with T2DM patients, especially concerning about the risks of RC in elderly T2DM patients. In addition, lipid-lowering treatment may be beneficial in patients with T2DM and high RC level for non-DKD. Our study provides a data support for future randomized controlled trials to explore the benefit of decreasing the RC level to reduce the incidence of DKD.

Data Sharing Statement

The study data supporting the results are available from the corresponding author based on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. [NCT03692884] CDR cohort is an ongoing, prospective and multistage population study. Informed consents were collected from all individuals who were included in this study.

Consent for Publication

Informed consents were collected from all individuals in this study. All authors and individual participants gave their consent for publication.

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Disclosure

All authors declare that they didn't have appeared to influence the work reported in this paper due to known potential conflict of financial interests or personal relationships.

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