Comparisons of the Relationships Between Multiple Lipid Indices and Diabetic Kidney Disease in Patients With Type 2 Diabetes: A Cross-Sectional Study

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Background: Dyslipidemia is a well-recognized risk factor for diabetic kidney disease (DKD) in patients with type 2 diabetes (T2D). Growing evidences have shown that compared with the traditional lipid parameters, some lipid ratios may provide additional information of lipid metabolism. Thus, the present study aimed to investigate which lipid index was most related to DKD.

Methods: This study was a cross-sectional study that enrolled patients with T2D from January 2021 to October 2021. Each participant was screened for DKD, and the diagnostic criterion for DKD is estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² or urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g for 3 months. Fasting blood was collected to determine lipid profiles by an automatic biochemical analyzer, and lipid ratios were calculated based on corresponding lipid parameters. Spearman’s correlation analyses were conducted to assess the correlations between lipid indices and kidney injury indices, and binary logistic regression analyses were conducted to explore the relationship between lipid indices and the risk of DKD.

Results: A total of 936 patients with T2D were enrolled in the study, 144 (15.38%) of whom had DKD. The LDL-C/Apo B ratios were positively correlated with eGFR (r = 0.146, p < 0.05) and inversely correlated to cystatin C and UACR (r = -0.237 and -0.120, both p < 0.001). Multiple logistic regression demonstrated that even after adjusting for other clinical covariates, the LDL-C/Apo B ratios were negatively related to DKD, and the odds ratio (95% confidence interval) was 0.481 (0.275–0.843). Furthermore, subgroup analyses revealed that compared with patients with normal lipid profiles and a high LDL-C/Apo B ratio, the odds ratio of DKD in patients with normal lipid metabolism and a low LDL-C/Apo B ratio was 2.205 (1.136–4.280) after adjusting for other clinical covariates.
INTRODUCTION

As one of the major microvascular complications of type 2 diabetes (T2D), diabetic kidney disease (DKD) affects about 20% of patients with T2D (1). The presence of DKD not only is susceptible to progress to end-stage renal disease requiring dialysis (2), but also significantly increases the risk of cardiovascular disease (CVD) (3), thus creating a great impact on patients with T2D. An integrated approach should be taken for the prevention and control of DKD for the fact that DKD is a multifactorial disease. Among them, lipid metabolism disorder exerts key roles on the pathogenesis of DKD and functions as an important target for DKD prevention and treatment. Dyslipidemia in patients with T2D is typically characterized with high levels of triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C), and low level of high-density lipoprotein cholesterol (HDL-C) (4). Statins, the mainstay of current lipid-lowering drugs, reduce plasma levels of LDL-C and TG through inhibiting cholesterol synthase (5). However, although statins are recommended by all available guidelines and can reduce proteinuria and all-cause mortality, they fail to delay the progression of end-stage renal disease (6). Therefore, it is plausible that it is not fully to reflect the risk of DKD based on the traditional lipid indices, and it is desirable to search for new lipid-lowering therapeutic targets.

In recent years, growing evidences have shown that compared with the traditional lipid indices, apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B) and lipid ratios may provide additional information of lipid metabolism. Apo A1 and Apo B are structural components of HDL-C and atherosclerotic lipoprotein respectively (7), thus the Apo B/Apo A1 ratio is a surrogate maker of the cholesterol balance between atherogenic and antiatherogenic lipoprotein particles. Multiple studies have demonstrated that the Apo B/Apo A1 ratio is closely associated with cardiac vulnerable plaques (8), and in-stent restenosis (9). Zhao et al. also revealed that a high level of Apo B/Apo A1 ratio can predict the progression of DKD (10). Moreover, the TG/HDL-C ratio, HDL-C/Apo A1 ratio and LDL-C/Apo B ratio have drawn extensive attention. TG/HDL-C ratio is identified as an atherosclerosis index, and a longitudinal follow-up study showed that the TG/HDL-C ratio was a predictor of microvascular complications in patients with T2D (11). Other research has shown that the HDL-C/Apo A1 ratio and LDL-C/Apo B ratio are closely related to the deterioration of glycemia and the onset of T2D (12). In a word, these lipid indices may be more conducive to DKD risk stratification in patients with T2D, but few studies have focused on comparing the relationships between these parameters and DKD in patients with T2D. Therefore, the present study was designed to explore which lipid index is optimal-related to DKD in patients with T2D.

**Conclusion:** In patients with T2D, the LDL-c/Apo B ratio was most closely associated with DKD among various lipid indices, and a lower LDL-C/Apo B ratio was associated with increased risks of DKD among patients with T2D.

**Keywords:** type 2 diabetes, diabetic kidney disease, lipid indices, low-density lipoprotein cholesterol/apolipoprotein B ratio, small dense low-density lipoprotein cholesterol

METHODS

**Study Design and Participants**

In this observational cross-sectional study, patients diagnosed with T2D according to the statement of the American Diabetes Association and screened for DKD were enrolled from the inpatient department of the Second Affiliated Hospital of Nantong University from January 2021 to October 2021 (13). The following cases were excluded: type 1 diabetes, secondary diabetes, previous and current malignant tumors, chronic hepatitis and heart failure, acute diabetic complications and other kidney diseases and urinary tract infection. Finally, 936 patients with T2D were included in the present study. After full understanding of the present study protocol, each subject signed written informed consent. The study was in accordance with the Declaration of Helsinki and approved by the medical research ethics committee of the Second Affiliated Hospital of Nantong University.

**Basic Data Collection**

At enrollment, all subjects completed a questionnaire with the assistance of experienced physicians to collect the demographic data, lifestyle, medication history and diagnosis history of diseases. Body mass index (BMI) was calculated as the weight/height squared. Blood pressure was measured by a standard mercury sphygmomanometer, and the average of three recordings was recorded.

**Laboratory Examination and Calculation**

After enrollment, fasting blood samples and fresh first-void morning urine samples were taken for measurement of laboratory parameters, urinary albumin and urinary creatinine, respectively. Lipid profiles and urinary creatinine were measured by an automated biochemical analyzer (Model 7600, Hitachi), and lipid ratios were calculated based on corresponding lipid parameters. Urinary albumin level was evaluated by the immunoturbidimetry method (Immage 800, Beckman Coulter). The algorithm of urinary albumin creatinine ratio (UACR) was the ratio of urinary albumin to urinary creatinine. Estimated glomerular filtration rate (eGFR) was calculated based on the CKD-EPI creatinine-cystatin C equation (2012) (14). If a patient with T2D has an eGFR < 60 ml/min/1.73 m² or a UACR ≥ 30
mg/g lasted for more than 3 months, a DKD diagnosis can be made (15).

**Grouping Criteria**
To explore the relationship between low LDL-C/Apo B ratio and the risk of DKD in T2D patients with normal lipid profiles, the total population was divided into A, B, C and D four groups according to lipid profiles and LDL-C/Apo B ratio. In our laboratory, the reference ranges of lipid metabolism parameters TG, TC, HDL-C and LDL-C were respectively 0.2 - 2.0 mmol/L, 2.9 – 6.0 mmol/L, 1.1 – 1.7 mmol/L and 1.55 – 3.35 mmol/L. Therefore, dyslipidemia was defined as any lipid parameter above the normal ranges described above. Then, a low or a high LDL-C/Apo B ratio was defined according to the median of LDL-C/Apo B ratio (2.8804). Ultimately, group A, B, C and D respectively represented normal lipid profile with a high LDL-C/Apo B ratio, normal lipid profile with a low LDL-C/Apo B ratio, abnormal lipid profile with a high LDL-C/Apo B ratio and abnormal lipid profile with a low LDL-C/Apo B ratio.

**Statistical Analysis**
The clinical characteristics of the participants grouped by DKD status were described by mean ± SD, median (25 and 75% interquartile) and frequencies (percentages) for the normally and skewed distributed continuous variables and the categorical variables, respectively. We adopted Student’s t-test to compare differences in normally distributed data, the Mann–Whitney test to compare differences in skewed distributed data and the chi-square test to compare categorical data. Spearman’s bivariate correlation analyses were conducted to analyze the correlations of multiple lipid indices with DKD indicators. As the LDL-C/Apo B ratio was the only parameter related to DKD, multivariate logistic regression analyses were performed to investigate the impact of the LDL-C/Apo B ratio on DKD. Furthermore, the differences in the proportion and odds ratio (OR) were compared among group A, B, C and D by the chi-square test and multivariate logistic regression analyses. All analyses were performed using SPSS statistical software 18.0 (IBM SPSS Inc., USA). A value of \( p < 0.05 \) was defined as statistical significance.

**RESULTS**
**Clinical Characteristics of the Study Participants**
Among the recruited 936 T2D patients, patients combined with DKD accounted for 15.38%. As shown in Table 1, T2D patients with DKD had older ages, longer diabetic durations, higher systolic blood pressures, a higher prevalence of hypertension, higher prevalence of insulin, HbA1c levels and lipid indices other than LDL-C/Apo B ratio between patients with and without DKD (\( p > 0.05 \)).

**Relationships Between Lipid Indices and Kidney Damage Indices in Patients With T2D**
Table 2 shows that the LDL-C/Apo B ratio was positively correlated with eGFR (\( r = 0.146, p < 0.05 \)), and negatively correlated with cystatin C levels and UACR (\( r = -0.167, -0.120 \), both \( p < 0.05 \)). Cystatin C levels were significantly correlated with HDL-C levels, Apo B levels, HDL-C/Apo A1 ratios and Apo B/Apo A1 ratios (\( r = -0.102, 0.074, 0.084, -0.129 \) and 0.116, respectively, all \( p < 0.05 \)). UACR were positively correlated with TG levels and TG/HDL-C ratios (\( r = 0.127 \) and 0.123, both \( p < 0.05 \)). However, there were no significant correlations between kidney damage indices and total cholesterol (TC) levels and Apo A1 levels (all \( p > 0.05 \)).

**Association of the LDL-C/Apo B Ratio With DKD in Patients With T2D**
As the LDL-C/Apo B ratio was the only parameter correlated with all kidney damage indices, we thereby constructed multivariate logistic regression analyses to analyze the association between the LDL-C/Apo B ratio and DKD in patients with T2D. As illustrated in Table 3, DKD was significantly associated with the LDL-C/Apo B ratio [OR (95% CI), 0.560 (0.409-0.766)] in the basal unadjusted model 0. Even in the fully adjusted model 2, the LDL-C/Apo B ratio was still independently associated with DKD [OR (95% CI), 0.481 (0.275-0.843)].

**Proportion and ORs of DKD Based on Subgroup Analyses**
There were significant differences in the proportion of patients with DKD among Group A, B, C and D (8.7%, 21.3%, 12.8% and 19.7%, respectively, \( p \) for trend < 0.05). In Table 4, compared with Group A, the ORs of DKD in Group B, C and D were 2.850 (1.705-4.763), 1.557 (0.855-2.837) and 2.597 (1.538-4.385), respectively. After adjusting for other clinical factors, the ORs of DKD in Group B, C and D were 2.205 (1.136-4.280), 2.315 (1.078-4.974) and 3.513 (1.762-7.004) vs Group A, respectively (Figure 1).

**DISCUSSION**
In the current study, we evaluated the associations between multiple lipid indices with the risk of DKD in patients with T2D. We found that patients with DKD had a lower level of LDL-C/Apo B ratio than patients without DKD. The LDL-C/Apo B ratio was significantly associated with eGFR, UACR and cystatin C. We also demonstrated that the LDL-C/Apo B ratio is independently related to the prevalence of DKD. Moreover, we revealed that even in patients with normal lipid profiles, a low level of LDL-C/Apo B ratio was relevant to an increased risk of DKD.
Hyperlipidemia is a well-recognized risk factor for DKD in patients with T2D. Hyperlipidemia can facilitate apoptosis of podocytes, a specialized kidney epithelial cell, thus damaging the integrity of the glomerular filtration barrier and eventually causing the onset of proteinuria (16). In addition to podocytes, hyperlipidemia can also promote glomerulosclerosis, interstitial fibrosis and accelerate the progression of proteinuria by affecting glomerular endothelial cells and mesangial cells and promoting the accumulation of collagen and fibronectin (17). Renal tubular injury is a vital component of DKD, and even precedes the occurrence of glomerular injury (18). Hyperlipidemia can cause renal tubular injury when combined with proteinuria by the mechanism that albumin can act as a carrier of fatty acids and promote the deposition of fatty acids in kidney (19). Additionally, ectopic deposition of lipids in kidney can induce local oxidative stress and inflammation via generating excess adipokines and activating a variety of signaling pathways (20).

### TABLE 1 | Clinical characteristics of the study participants.

| Variables | Total n=936 | Without DKD n=792 | With DKD n=144 | p value |
|-----------|-------------|--------------------|----------------|---------|
| Age (years) | 57.65 ± 13.80 | 55.59 ± 13.20 | 68.98 ± 9.65 | <0.001 |
| Male, n (%) | 533 (56.9) | 458 (57.8) | 75 (52.1) | 0.202 |
| Diabetic duration (years) | 6.0 (1.0-10.0) | 5.0 (1.0-10.0) | 10.0 (8.6-20.0) | <0.001 |
| Smoking history, n (%) | 85 (9.1) | 68 (8.6) | 17 (11.8) | 0.210 |
| BMI (kg/m²) | 25.62 ± 3.94 | 25.63 ± 4.04 | 25.55 ± 3.36 | 0.842 |
| Hypertension, n (%) | 345 (36.9) | 260 (32.8) | 85 (59.0) | <0.001 |
| SBP (mmHg) | 134 (123-147) | 132 (123-145) | 142 (126-157) | <0.001 |
| DBP (mmHg) | 81.37 ± 11.04 | 81.43 ± 10.50 | 81.08 ± 13.69 | 0.726 |
| Statins medications, n (%) | 242 (25.9) | 182 (23.0) | 60 (41.7) | 0.001 |
| Metformin, n (%) | 415 (44.3) | 350 (44.2) | 65 (45.1) | 0.856 |
| Acarbose, n (%) | 82 (8.8) | 68 (8.6) | 14 (9.7) | 0.632 |
| Insulin-secretagogues, n (%) | 284 (30.3) | 239 (30.2) | 45 (31.3) | 0.844 |
| DPP-4 inhibitors, n (%) | 44 (4.7) | 35 (4.4) | 9 (6.3) | 0.389 |
| SGLT-2 inhibitors, n (%) | 66 (7.1) | 52 (6.6) | 14 (9.7) | 0.213 |
| Diuretics, n (%) | 76 (8.1) | 54 (6.8) | 22 (15.3) | 0.001 |
| Statins medications, n (%) | 58 (6.2) | 35 (4.4) | 23 (16.0) | <0.001 |
| HbA1c (%) | 9.32 ± 2.16 | 9.35 ± 2.14 | 9.14 ± 2.27 | 0.284 |
| LDL-C/Apo B (mmol/mmol) | 0.88 ± 0.27 | 0.87 ± 0.27 | 0.90 ± 0.29 | 0.204 |
| HDL-C/Apo A1 (mmol/mmol) | 1.03 (0.93-1.13) | 1.03 (0.93-1.13) | 1.02 (0.92-1.12) | 0.909 |
| UACR (mg/g) | 16.25 (8.10-47.65) | 13.60 (7.70-31.98) | 141.45 (24.15-897.55) | <0.001 |
| DBP (mmHg) | 5.23 (4.32-6.62) | 5.11 (4.20-6.26) | 7.13 (5.32-9.16) | <0.001 |
| BMI (kg/m²) | 56.0 (47.0-67.0) | 54.0 (46.0-63.0) | 86.0 (88.0-116.0) | <0.001 |
| Serum UA (umol/L) | 301.0 (241.0-375.0) | 290.5 (232.3-354.8) | 380.0 (313.0-472.0) | <0.001 |
| Apo A1 (mmol/L) | 0.83 (0.67-1.02) | 0.78 (0.64-0.93) | 1.33 (1.15-1.65) | <0.001 |
| Apo B (mmol/L) | 1.06 (0.97-1.19) | 1.07 (0.97-1.20) | 1.06 (0.94-1.19) | 0.115 |
| Cr (umol/L) | 52.8 ± 0.01 | 51.1 ± 0.01 | 54.3 ± 0.01 | <0.001 |
| Creatinine (mg/L) | 77 (8.2) | 64 (8.1) | 13 (9.0) | 0.741 |
| SBP (mmHg) | 102.93 ± 29.22 | 110.58 ± 23.22 | 58.60 ± 19.31 | <0.001 |
| eGFR (ml/min/1.73m²) | 4.34 (3.72-5.01) | 4.36 (3.74-5.03) | 4.27 (3.57-4.96) | 0.121 |
| TG (mmol/L) | 0.53 (0.93-1.31) | 1.12 (0.96-1.31) | 1.12 (0.92-1.30) | 0.360 |
| HDL-C (mmol/L) | 3.23 ± 0.88 | 3.27 ± 0.86 | 2.61 ± 1.00 | 0.071 |
| Apo A1 (mmol/L) | 0.94 (0.75-1.09) | 0.94 (0.75-1.09) | 0.93 (0.77-1.07) | 0.281 |
| Apo B (mmol/L) | 1.06 (0.97-1.19) | 1.07 (0.97-1.20) | 1.06 (0.94-1.19) | 0.115 |
| HDL-C (mmol/L) | 1.44 (0.88-2.72) | 1.43 (0.86-2.72) | 1.59 (0.94-2.82) | 0.239 |
| LDL-C/Apo B (mmol/mmol) | 2.88 (2.56-3.3) | 2.91 (2.59-3.34) | 2.74 (2.38-3.08) | <0.001 |
| Triglycerides (mmol/L) | 1.77 ± 0.01 | 1.77 ± 0.01 | 1.77 ± 0.01 | 0.909 |
| Age (years) | 66 (7.1) | 52 (6.6) | 14 (9.7) | 0.001 |
| n | 345 (36.9) | 260 (32.8) | 85 (59.0) | <0.001 |

Normally distributed values in the table are given as the mean ± SD, skewed distributed values are given as the median (25 and 75% interquartiles), and categorical variables are given as frequency (percentage).

T2D, type 2 diabetes; DKD, diabetic kidney disease; BMI, body mass index; SBP/DBP, systolic/diastolic blood pressure; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT-2 inhibitors, sodium-glucose co-transporter-2 inhibitors; CCB, calcium channel blockers; ARB, angiotensin receptor blockers; HbA1c, glycosylated hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; Serum UA, serum uric acid; eGFR, estimated glomerular filtration rate; UACR, urine albumin/creatinine ratio; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.
patients with T2D (22). In a longitudinal study involving a large Japanese population, the TG/HDL-C ratio was positively associated with the increase of proteinuria and the decline of eGFR (23). In contrast, no associations were observed between lipid indices and DKD markers in other studies (24–26). UACR, eGFR and cystatin C, respectively reflecting glomerular filtration barrier, glomerular filtration function and tubular function, all are important indicators of kidney function (27). In this study, we observed that both TG and TG/HDL-C ratio were only positively associated with UACR, while Apo B/Apo A1 ratio was only positively associated with cystatin C, which indicated that these lipid indices were insufficient to comprehensively assess renal injury in patients with T2D. These inconsistencies among these studies and our study may be attributed to differences in the included population, uses of statin. In this study, the LDL-C/Apo B ratio was significantly correlated with kidney injury indices, suggesting that LDL-C/Apo B ratio was most closely correlated with DKD among multiple lipid indices.

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**TABLE 2 |** Relationships between lipid indices and kidney damage indices in patients with T2D.

| Lipid indices | Cystatin C | UACR | eGFR |
|---------------|------------|------|------|
|               | r | p value | r | p value | r | p value |
| TG            | -0.150 | 0.668 | 0.127 | <0.001 | 0.046 | 0.190 |
| TC            | -0.130 | 0.210 | 0.024 | 0.311 | 0.119 | 0.245 |
| HDL-C         | -0.102 | 0.004 | -0.027 | 0.420 | 0.026 | 0.454 |
| LDL-C         | 0.074 | 0.028 | -0.032 | 0.347 | -0.077 | 0.329 |
| Apo A1        | -0.043 | 0.227 | 0.015 | 0.669 | 0.025 | 0.483 |
| Apo B         | 0.084 | 0.017 | 0.050 | 0.143 | -0.013 | 0.718 |
| TG/HDL-C      | 0.017 | 0.621 | 0.123 | <0.001 | 0.031 | 0.376 |
| LDL-C/Apo B   | -0.237 | <0.001 | -0.120 | <0.001 | 0.146 | <0.001 |
| HDL-C/Apo A1  | -0.129 | <0.001 | -0.045 | 0.191 | 0.051 | 0.152 |
| Apo B/Apo A1  | 0.116 | 0.001 | 0.031 | 0.362 | -0.039 | 0.267 |

$r$: spearman’s correlation coefficient

T2D, type 2 diabetes; UACR, urine albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.

**TABLE 3 |** Multivariate logistic regression analysis to identify the association of LDL-C/Apo B ratio with DKD.

| Models | B | SE | Wald | p | OR | 95% CI |
|--------|---|----|------|---|----|-------|
| Model 0 | -0.580 | 0.160 | 13.193 | <0.001 | 0.560 | 0.409-0.766 |
| Model 1 | -0.620 | 0.205 | 9.124 | 0.003 | 0.538 | 0.360-0.804 |
| Model 2 | -0.731 | 0.286 | 6.546 | 0.011 | 0.481 | 0.275-0.843 |

Model 0: unadjusted model.
Model 1: adjusted for age, male, diabetic duration, smoking history, BMI, hypertension, SBP, DBP.
Model 2: additionally adjusted for HbA1c, antidiabetic treatments, antihypertensive treatments, statins medications.

**TABLE 4 |** ORs (95% CIs) of DKD according to the four subgroups.

| Variable | Group A | Group B | Group C | Group D | p value |
|----------|---------|---------|---------|---------|---------|
| LDL-C/Apo B ratio range | 2.881-7.387 | 0.732-2.879 | 2.881-7.387 | 0.732-2.879 | – |
| Number | 289 | 240 | 179 | 228 | – |
| DKD | 25 (8.7) | 51 (21.3) | 23 (12.8) | 45 (19.7) | <0.001 |
| Model 0 | 1-reference | 2.850 (1.705-4.763) | 1.557 (0.855-2.837) | 2.597 (1.538-4.385) | <0.001 |
| Model 1 | 1-reference | 2.190 (1.167-4.113) | 2.235 (1.066-4.884) | 3.743 (1.955-7.167) | 0.001 |
| Model 2 | 1-reference | 2.205 (1.136-4.280) | 2.315 (1.078-4.974) | 3.513 (1.762-7.004) | 0.006 |

Group A: normal lipid profile with a high LDL-C/Apo B ratio (> 2.880); Group B: normal lipid profile with a low LDL-C/Apo B ratio (< 2.880); Group C: abnormal lipid profile with a high LDL-C/Apo B ratio (> 2.880); Group D: abnormal lipid profile with a low LDL-C/Apo B ratio (< 2.880).

Model 0: unadjusted model.
Model 1: adjusted for age, male, diabetic duration, smoking history, BMI, hypertension, SBP, DBP.
Model 2: additionally adjusted for HbA1c, antidiabetic treatments, antihypertensive treatments, statins medications.

with the increase of proteinuria and the decline of eGFR (23). In contrast, no associations were observed between lipid indices and DKD or DKD markers in other studies (24–26). UACR, eGFR and cystatin C, respectively reflecting glomerular filtration barrier, glomerular filtration function and tubular function, all are important indicators of kidney function (27). In this study, we observed that both TG and TG/HDL-C ratio were only positively associated with UACR, while Apo B/Apo A1 ratio was only positively associated with cystatin C, which indicated that these lipid indices were insufficient to comprehensively assess renal injury in patients with T2D. These inconsistencies among these studies and our study may be attributed to differences in the included population, uses of statin. In this study, the LDL-C/Apo B ratio was significantly correlated with kidney injury indices, suggesting that LDL-C/Apo B ratio was most closely correlated with DKD among multiple lipid indices.
A review published in 2020 suggested that hyperlipidemia may promote atherosclerosis independent of LDL-C concentration, which may be partly attributed to the presence of small dense LDL-C (sd-LDL-C) (28). LDL-C is a group of apolipoproteins with greater heterogeneity, and LDL-C with small particle size and high density is named as sd-LDL-C (29). Methods such as nuclear magnetic resonance and hypervelocity centrifugation can be used to evaluate sd-LDL-C, but these methods are not suitable for clinical practice due to high costs and lengthy processes (30). The LDL-C/Apo B ratio widely used in clinical and research studies has been identified as a surrogate marker for sd-LDL-C, and the smaller the LDL-C/Apo B ratio, the greater the proportion of sd-LDL-C (31). The present study found that even in patients with normal lipid profiles, having a low LDL-C/Apo B ratio significantly increased the risk of DKD in patients with T2D.

Compared with other LDL-Cs, less sd-LDL-Cs binding to LDL-C receptors result in sd-LDL-C staying in the circulation longer (32), and sd-LDL-Cs tend to be oxidized and modified to form oxidized LDL (33). Oxidized LDL, a marker of endothelial dysfunction and oxidative stress, can be excessively uptaken by multiple types of kidney cells, thus promoting glomerulosclerosis and kidney fibrosis, eventually accelerating the process of DKD (34). In addition, macrophages can be attracted by oxidized LDL, chemotaxis and phagocytosis oxidized LDL to form foam cells. Subsequently, the accumulation of foam cells in renal arterioles aggravates local renal hemodynamic disorders (35). Sodium-glucose co-transporter-2 inhibitors are a novel class of hypoglycemic agents recommended for type 2 diabetic patients with DKD by a group of guidelines, and a clinical study showed that the use of SGLT2 inhibitors could significantly reduce the level of sd-LDL-C in patients with T2D (36). These results together suggested that a low LDL-C/Apo B ratio was an important risk factor and a potential target for DKD in patients with T2D.

This study had several limitations. First, as this study was a cross-sectional study, the causal relationship between the LDL-C/Apo B ratio and DKD could not be fully elucidated. Second, the LDL-C/Apo B ratio was a proxy for evaluating sd-LDL-C rather than the gold standard, but the large sample size of this study compensated for this deficiency. Third, the generalizability of this study was limited by that this study was based on a Chinese population. Therefore, longitudinal and intervention studies are needed to address the above limitations.

In summary, the LDL-C/Apo B ratio was closely associated with the risk of DKD, and a lower LDL-C/Apo B ratio might be a potent risk factor and therapeutic target for prevention and treatment of DKD in patients with T2D. Even in type 2 diabetic patients with normal lipid profile, the LDL-C/Apo B ratio should be routinely assessed.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by The medical research ethics committee of Second Affiliated Hospital of Nantong University. The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

C-FL and Z-HC participated in the design of the study, data collection, analysis of the data, and drafting of the manuscript. X-QW and H-YH conceived of the study, participated in its design and revised the manuscript. W-SL and L-YH participated in data collection. All authors read and approved the final manuscript.

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