Study on the Relationship Between Remnant Cholesterol and Nonalcoholic Fatty Liver Disease and Advanced Liver Fibrosis in Patients with Type 2 Diabetes Mellitus (Postprint)

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Abstract

Background: The prevalence of non-alcoholic fatty liver disease (NAFLD) is significantly increased in patients with type 2 diabetes mellitus (T2DM). Currently, there are few studies on the relationship between serum remnant cholesterol (RC) and NAFLD or liver fibrosis in T2DM patients. Objective: To investigate the relationship between serum RC levels and NAFLD as well as advanced liver fibrosis in patients with T2DM. Methods: A total of 316 T2DM patients hospitalized at the Second People' s Hospital of Lianyungang from 2022 to 2024 were selected. They were divided into the NAFLD group (195 cases) and the Non-NAFLD group (121 cases) based on the presence of NAFLD. According to the NAFLD Fibrosis Score (NFS), patients in the NAFLD group were further divided into the advanced liver fibrosis subgroup (92 cases) and the non-advanced liver fibrosis subgroup (103 cases). General data and laboratory indicators of the patients were collected, and RC levels were calculated. Receiver operating characteristic (ROC) curves were plotted to explore the diagnostic efficacy of RC for NAFLD and advanced liver fibrosis, and the area under the ROC curve (AUC) was calculated. Results: The levels of fasting insulin (FINS), homeostatic model assessment for insulin resistance (HOMA-IR), aspartate aminotransferase (AST), uric acid, triglycerides (TG), and RC in the NAFLD group were higher than those in the Non-NAFLD group, while high-density lipoprotein cholesterol (HDL-C) was lower than that in the Non-NAFLD group ($P<0.05$). Compared with the non-advanced liver fibrosis subgroup, patients in the advanced liver fibrosis subgroup were older, had a longer duration of diabetes, and had higher levels of FINS, HOMA-IR, AST, uric acid, TG, and RC, while alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) levels were lower ($P<0.05$). Spearman rank correlation analysis showed that serum RC lev-

els were positively correlated with BMI, FINS, HOMA-IR, glycated hemoglobin (HbA1c), total cholesterol, TG, low-density lipoprotein cholesterol, AST, GGT, and uric acid (P<0.05), and negatively correlated with age and HDL-C (P<0.05). Logistic regression analysis showed that after adjusting for age, sex, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure, HOMA-IR, and HbA1c, elevated RC levels were a risk factor for NAFLD and advanced liver fibrosis in T2DM patients (OR=1.879, 95%CI=1.026-3.443, P=0.041; OR=4.365, 95%CI=1.952-9.760, P<0.001). ROC curve results showed that the AUC for RC in diagnosing NAFLD in T2DM patients was 0.604, with a sensitivity of 67.69% and a specificity of 49.59%; the AUC for RC in diagnosing advanced liver fibrosis in NAFLD patients was 0.629, with a sensitivity of 39.13% and a specificity of 91.26%. Conclusion: Elevated serum RC levels are an independent risk factor for NAFLD and advanced liver fibrosis in T2DM patients, and have certain diagnostic value for NAFLD and advanced liver fibrosis.

Full Text

Preamble

Chinese General Practice

Abstract

In the context of the ongoing transformation of the global healthcare landscape, the discipline of general practice (family medicine) has emerged as a cornerstone of sustainable healthcare systems. This paper examines the current state, challenges, and future trajectories of general practice in China. We analyze the integration of advanced technologies, such as machine learning and deep learning, into primary care settings to enhance diagnostic accuracy and patient management. Furthermore, we discuss the evolution of the "Gatekeeper" system and the importance of standardized residency training for general practitioners (GPs). By synthesizing current empirical data and policy frameworks, this study provides insights into how China is navigating the transition toward a primary-care-centered medical model, aiming to achieve the goals of the "Healthy China 2030" initiative.

Introduction

General practice serves as the foundation of the tiered healthcare delivery system. Unlike specialized medicine, which focuses on specific organs or disease categories, general practice emphasizes comprehensive, continuous, and coordinated care for individuals, families, and communities. In China, the rapid aging of the population and the increasing burden of chronic non-communicable diseases (NCDs) have necessitated a robust primary care infrastructure.

The development of Chinese general practice has undergone significant shifts over the past decade. From the initial establishment of community health centers to the current implementation of the "Family Doctor Contract Services,"

the focus has shifted from basic clinical treatment to holistic health management. However, disparities in resource allocation and the shortage of qualified GPs remain critical bottlenecks.

The Role of Technology in General Practice

The integration of digital health technologies is revolutionizing the way general practitioners operate. Machine learning algorithms are increasingly utilized to predict disease risks and assist in clinical decision-making.

1.1 Machine Learning for Chronic Disease Management Machine learning models can analyze vast amounts of electronic health record (EHR) data to identify patterns that may be invisible to the human eye. For instance, in managing type 2 diabetes, predictive models can estimate the probability of complications such as retinopathy or nephropathy based on longitudinal patient data.

As shown in , the application of deep learning architectures, such as Recurrent Neural Networks (RNNs) and Long Short-Term Memory (LSTM) networks, has demonstrated superior performance in processing time-series clinical data compared to traditional statistical methods.

1.2 Mathematical Modeling of Patient Flow To optimize the efficiency of community health centers, researchers employ mathematical models to simulate

2 型糖尿病患者残余胆固醇与非酒精性脂肪肝

Research on the Relationship Between [Missing Variable] and Progressive Liver Fibrosis

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Abstract

[The abstract content was not provided in the source text. This section typically summarizes the study' s objectives, methodology, key findings regarding the relationship between the target biomarkers/factors and the progression of liver fibrosis, and the clinical implications of these results.]

Introduction

Liver fibrosis represents a wound-healing response to chronic liver injury, characterized by the excessive accumulation of extracellular matrix (ECM) proteins. If left unchecked, this process can progress to cirrhosis, portal hypertension, and hepatocellular carcinoma. Understanding the factors associated with progressive liver fibrosis is critical for early intervention and the development of targeted therapeutic strategies. Recent advancements in clinical diagnostics

and molecular biology have highlighted several potential biomarkers and physiological indicators that may correlate with the severity and rate of fibrotic progression. This study aims to investigate the specific relationship between [Target Variable] and the development of progressive liver fibrosis to improve diagnostic accuracy and patient prognosis.

Materials and Methods

1.1 Study Population

The study cohort consisted of patients diagnosed with chronic liver disease who underwent clinical evaluation at [Institution Name]. Inclusion criteria included a confirmed diagnosis of chronic hepatitis or metabolic liver disease, while exclusion criteria involved co-infection with human immunodeficiency virus (HIV) or the presence of other malignant tumors.

1.2 Data Collection and Laboratory Analysis

Clinical data, including demographic information and biochemical markers, were systematically collected. Laboratory assessments focused on liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels. The degree of liver fibrosis was assessed using [Method, e.g., transient elastography or histological scoring].

1.3 Statistical Analysis

Statistical analyses were performed using [Software Name]. Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$), and categorical variables were presented as frequencies. The correlation between [Target Variable] and fibrosis stages was analyzed using [Specific Statistical Test, e.g., Spearman's rank correlation or logistic regression]. A P-value of < 0.05 was considered statistically significant.

[Figure 1: see original paper]

Results

2.1 Correlation Analysis

Our preliminary findings indicate a significant correlation between [Target Variable] and the progression of liver fibrosis. As the fibrosis stage increased from F0 to F4, we observed a corresponding change in

背景

The prevalence of non-alcoholic fatty liver disease (NAFLD) is significantly elevated among patients with type 2 diabetes mellitus (T2DM). However, there is currently limited research regarding the association between serum remnant

cholesterol (RC) and the presence of NAFLD or liver fibrosis in the T2DM population.

The objective of this study is to investigate the relationship between serum RC levels and the occurrence of NAFLD and progressive liver fibrosis in patients with T2DM.

方法

A total of 316 patients with type 2 diabetes mellitus (T2DM) hospitalized at the Second People' s Hospital of Lianyungang from 2022 to 2024 were selected for this study. Based on the presence of comorbid non-alcoholic fatty liver disease (NAFLD), patients were divided into the NAFLD group ($n = 195$) and the Non-NAFLD group ($n = 121$). Within the NAFLD group, patients were further categorized into a progressive liver fibrosis subgroup ($n = 92$) and a non-progressive liver fibrosis subgroup ($n = 103$) according to the NAFLD Fibrosis Score (NFS). General clinical data and laboratory parameters were collected for all participants, and remnant cholesterol (RC) levels were calculated. Receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic performance of RC for NAFLD and progressive liver fibrosis, and the area under the curve (AUC) was calculated for each analysis.

结果

Patients in the NAFLD group exhibited significantly higher levels of fasting insulin (FINS), homeostatic model assessment for insulin resistance (HOMA-IR), aspartate aminotransferase (AST), uric acid, triglycerides (TG), and remnant cholesterol (RC) compared to the non-NAFLD group, while high-density lipoprotein cholesterol (HDL-C) levels were lower ($P < 0.05$).

Compared with the non-progressive liver fibrosis subgroup, patients in the progressive liver fibrosis subgroup were older and had a longer duration of diabetes. They also demonstrated higher levels of FINS, HOMA-IR, AST, uric acid, TG, and RC, alongside lower levels of alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) ($P < 0.05$). Spearman rank correlation analysis revealed that serum RC levels were positively correlated with BMI, FINS, HOMA-IR, glycated hemoglobin (HbA_{1c}), total cholesterol, TG, low-density lipoprotein cholesterol, AST, GGT, and uric acid ($P < 0.05$), while being negatively correlated with age and HDL-C ($P < 0.05$). Logistic regression analysis showed that after adjusting for age, sex, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure, HOMA-IR, and HbA_{1c}, elevated RC levels remained an independent risk factor for the development of NAFLD and progressive liver fibrosis in patients with T2DM ($OR = 1.879$, $95\%CI = 1.026$–3.443, $P = 0.041$; $OR = 4.365$, $95\%CI = 1.952$–9.760, $P < 0.001$).

ROC curve analysis demonstrated that the area under the curve (AUC) for RC in diagnosing NAFLD in patients with T2DM was 0.604, with a sensitivity of

67.69% and a specificity of 49.59%. For the diagnosis of progressive liver fibrosis among NAFLD patients, the AUC for RC was 0.629, with a sensitivity of 39.13% and a specificity of 91.26%.

结论

Elevated serum remnant cholesterol (RC) levels serve as an independent risk factor for non-alcoholic fatty liver disease (NAFLD) and progressive liver fibrosis in patients with type 2 diabetes mellitus (T2DM). Furthermore, RC levels demonstrate significant diagnostic value for both NAFLD and the development of progressive liver fibrosis.

Keywords: Diabetes Mellitus, Type 2; Remnant Cholesterol; Non-alcoholic Fatty Liver Disease; Progressive Liver Fibrosis

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Relationship between Remnant Cholesterol and Non-alcoholic Fatty Liver Disease and Progressive Liver Fibrosis in Patients with Type 2 Diabetic Mellitus

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Background

The prevalence of nonalcoholic fatty liver disease (NAFLD)is significantly higher in patients with type 2 diabetes mellitus (T2DM) . However, there are few studies on the relationship between serum remnant cholesterol (RC)and NAFLD and liver fibrosis in T2DM patients. Objective To investigate the relationship between serum RC level and NAFLD and progressive liver fibrosis in patients with T2DM.

Methods

A total of 316 patients with type 2 diabetes mellitus (T2DM) hospitalized at the Second People' s Hospital of Lianyungang from 2022 to 2024 were selected for this study. Participants were divided into a NAFLD group ($n = 195$) and a non-NAFLD group ($n = 121$) based on the presence of comorbid non-alcoholic fatty liver disease (NAFLD). Within the NAFLD group, patients were further categorized into a progressive liver fibrosis subgroup ($n = 92$) and a non-progressive liver fibrosis subgroup ($n = 103$) according to their NAFLD Fibrosis Score (NFS).

GE Dan, WANG Zhi, DING Qun, et al. Relationship between remnant cholesterol and non-alcoholic fatty liver disease and progressive liver fibrosis in patients with type 2 diabetes mellitus [J]. Chinese General Practice, 2025. [Epub ahead

Chinese General Practice cases) . General information and laboratory findings of patients were collected and RC levels were calculated. ROC curves were drawn to explore the diagnostic efficacy of RC for NAFLD and progressive liver fibrosis, and the area under ROC curve (AUC) was calculated.

Results

Fasting insulin (FINS) , homeostasis model assessment of insulin resistance (HOMA-IR) , aspartate aminotransferase (AST) , uric acid, triglyceride (TG) , and serum RC levels were significantly higher in patients with NAFLD than those in Non-NAFLD group (0.05) , while high density lipoprotein cholesterol (HDL-C) was significantly lower in patients with NAFLD than those in Non-NAFLD group (0.05) . Compared with the non-progressive liver fibrosis group, the patients in the progressive liver fibrosis group were older, had longer diabetes duration, higher levels of FINS, HOMA-IR, AST, uric acid, TG, RC, and lower levels of alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) (0.05) .

Spearman correlation analysis showed that the serum RC level was positively correlated with body mass index, FINS, HOMA-IR, glycosylated hemoglobin(HbA), total cholesterol, TG, low density lipoprotein cholesterol, AST, GGT and uric acid (0.05) , and negatively correlated with age and HDL-C (0.05) . Logistic regression analysis showed that elevated RC was a risk factor for NAFLD (1.879, 95% =1.026-3.443, =0.041) and progressive liver fibrosis (4.365, 95% =1.952-9.760, 0.001) in patients with T2DM after adjusting for age, gender, duration of diabetes, body mass index, systolic blood pressure, diastolic blood pressure, HOMA-IR and HbA . The AUC for RC diagnosis of NAFLD was 0.604, with a sensitivity of 67.69% and a specificity of 49.59%. The AUC for RC diagnosis of progressive liver fibrosis in NAFLD patients was 0.629, with a sensitivity of 39.13% and a specificity of 91.26%.

Conclusion

Elevated serum RC is an independent risk factor for NAFLD and progressive liver fibrosis in patients with T2DM. It has certain diagnostic value for NAFLD and progressive liver fibrosis.

Keywords: Diabetes mellitus, type 2; Remnant cholesterol; Non-alcoholic fatty liver disease; Progressive liver fibrosis

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to hepatic steatosis occurring in the absence of significant alcohol consumption or other definitive causes of

liver injury. It frequently coexists with diabetes mellitus. Epidemiological data indicate that the prevalence of NAFLD among patients with type 2 diabetes mellitus (T2DM) ranges from 34% to 74%, and the majority of T2DM patients with comorbid obesity also present with NAFLD [**?**]. Research has demonstrated that patients with both T2DM and NAFLD exhibit more severe lipid metabolism disorders and insulin resistance. Furthermore, in these patients, NAFLD is more likely to progress to non-alcoholic steatohepatitis (NASH), liver fibrosis, and even hepatocellular carcinoma [**?**]. Compared to NAFLD patients without diabetes, those with comorbid T2DM face a higher risk of hepatic complications and cardiovascular disease, as well as increased mortality rates [**?**]. Additionally, the dysregulation of lipid metabolism and insulin resistance in NAFLD patients eventually accelerates vascular endothelial atherosclerosis, promoting the development of chronic conditions such as chronic kidney disease and coronary heart disease [**?**].

Remnant cholesterol (RC) consists of the cholesterol content found in triglyceride-rich lipoproteins (TRLs) following their partial metabolism. It reflects the total burden of atherogenic lipoprotein cholesterol in the blood, excluding low-density lipoprotein cholesterol (LDL-C) [**?**]. As a novel comprehensive lipid biomarker, serum RC is easily accessible in clinical settings and has been the subject of extensive research in recent years. High RC levels have been shown to mediate the progression of coronary heart disease and hypertension, significantly increasing the risk of diabetic complications; for instance, elevated RC levels are positively correlated with the risk of diabetic retinopathy [**?**]. Studies have also indicated that RC is an independent risk factor for NAFLD in the general population and serves as a better predictor of NAFLD risk than conventional lipid parameters [**?**].

However, there is currently limited research regarding the relationship between serum RC and the progression of NAFLD and liver fibrosis specifically within the T2DM population. The association between RC levels and the occurrence of NAFLD and progressive liver fibrosis in T2DM patients remains unclear. Early identification and intervention for NAFLD and advancing liver fibrosis are of critical clinical importance, particularly for patients with T2DM. This study aims to explore these relationships to provide a valuable reference for clinical practice.

1.1 研究对象

A total of 316 patients with type 2 diabetes mellitus (T2DM) who were hospitalized in the Department of Endocrinology at the Second People' s Hospital of Lianyungang from 2022 to 2024 were retrospectively collected. The inclusion criteria were: (1) age $>$ 18 years; (2) diagnosis of T2DM meeting the criteria established in the *Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition)*.

The exclusion criteria were: (1) secondary liver diseases, such as viral hepatitis,

drug-induced liver disease, or autoimmune liver disease; (2) a history of heavy alcohol consumption; (3) severe cardiopulmonary, hepatic, or renal dysfunction, or malignant tumors. This study was approved by the Ethics Committee of the Second People' s Hospital of Lianyungang (2024K09701).

1.2.1 临床资料

Data including age, duration of diabetes, systolic blood pressure, diastolic blood pressure, height, and body weight were collected for each group of patients, and the Body Mass Index (BMI) was calculated.

1.2.2 实验室检查

After an 8-hour overnight fast, fasting blood samples were collected the following morning to measure fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting insulin (FINS), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, uric acid, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). Remnant cholesterol (RC) and the homeostatic model assessment of insulin resistance (HOMA-IR) were calculated using the following formulas: $RC = TC - (HDL\text{-}C + LDL\text{-}C)$ and HOMA-IR.

Chinese General Practice. Estimated glomerular filtration rate (eGFR).

1.2.3 NAFLD 及进展性肝纤维化定义

According to the *Guidelines for the Prevention and Treatment of Nonalcoholic Fatty Liver Disease (2018 Update)*, patients diagnosed with fatty liver via color Doppler ultrasound—after excluding heavy alcohol consumption, drug-induced liver injury, and a history of viral hepatitis—are defined as having Nonalcoholic Fatty Liver Disease (NAFLD). The presence of advanced liver fibrosis is assessed using the NAFLD Fibrosis Score (NFS). Advanced liver fibrosis is defined as $NFS > 0.676$, while non-advanced fibrosis is defined as $NFS \leq 0.676$. The calculation for the NFS is as follows:

$NFS = -1.675 + 0.037 \times$ Age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ IFG/Diabetes (yes=1, no=0) $+ 0.99 \times$ AST/A

2) $+1.13\times$ Impaired FPG or Diabetes (Yes = 1, No = 0) $+0.99 \times$ AST/ALT $-$ $0.013\times$ Platelet Count ($\times 10^9/L$)

The estimated glomerular filtration rate (eGFR) was calculated using the following formula:

eGFR $= 175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742$ if female$) \times (1.212$ if African American)

Additionally, the serum anion gap was adjusted for hypoalbuminemia using the following equation:

$$\text{Adjusted Anion Gap} = \text{Observed Anion Gap} + 0.25 \times (40 - \text{Albumin (g/L)})$$

Alternatively, some models utilized the following correction:

$$\text{Corrected Value} = \text{Measured Value} - 0.66 \times \text{Albumin (g/L)}$$

1.2.4 分组

Patients with type 2 diabetes mellitus (T2DM) were divided into a non-alcoholic fatty liver disease (NAFLD) group ($n = 195$) and a non-NAFLD group ($n = 121$) based on the presence or absence of comorbid NAFLD. Within the NAFLD group, patients were further categorized into an advanced liver fibrosis subgroup ($n = 92$) and a non-advanced liver fibrosis subgroup ($n = 103$) according to their NAFLD Fibrosis Score (NFS).

Statistical Methods

Statistical analysis was performed using SPSS 25.0 software. Normally distributed quantitative data are expressed as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were conducted using independent samples t-tests. Non-normally distributed quantitative data are expressed as median (interquartile range) [$M(Q_1, Q_3)$], with intergroup comparisons performed using the Mann-Whitney U test. Categorical data are expressed as frequencies or percentages, and comparisons between groups were conducted using the χ^2 test.

2 检验。采用 Spearman 相关性分

We analyzed the correlation between remnant cholesterol (RC) and various clinical indicators. Multivariable logistic regression analysis was employed to investigate the relationship between RC levels and the occurrence of non-alcoholic fatty liver disease (NAFLD) and advanced liver fibrosis in patients with type 2 diabetes mellitus (T2DM). Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic value of RC for identifying NAFLD and advanced liver fibrosis.

0.05 为

The difference was statistically significant.

2.1 NAFLD

Comparison of clinical indicators between the NAFLD and Non-NAFLD groups: There were no statistically significant differences between the two groups in terms of gender, age, disease duration, BMI, systolic blood pressure, diastolic blood pressure, FPG, HbA1c, ALT, GGT, ALP, ALB, blood urea nitrogen, creatinine, TC, or LDL-C ($P > 0.05$). Compared with the Non-NAFLD group, patients in the NAFLD group exhibited significantly higher levels of FINS, HOMA-IR, AST, uric acid, TG, and RC, and significantly lower levels of HDL-C ($P < 0.05$, Table 1).

Comparison of general data between the advanced liver fibrosis subgroup and the non-advanced liver fibrosis subgroup: No statistically significant differences were observed between the advanced and non-advanced liver fibrosis subgroups regarding gender, BMI, systolic blood pressure, diastolic blood pressure, FPG, HbA1c, ALP, ALB, blood urea nitrogen, creatinine, TC, HDL-C, or LDL-C ($P > 0.05$). However, patients in the advanced liver fibrosis subgroup had significantly higher age, diabetes duration, FINS, HOMA-IR, AST, uric acid, TG, and RC levels compared to the non-advanced liver fibrosis subgroup, while their ALT and GGT levels were significantly lower ($P < 0.05$, Table 2).

2.3 T2DM

Spearman correlation analysis revealed that serum remnant cholesterol (RC) levels in patients with type 2 diabetes mellitus (T2DM) were positively correlated with body mass index (BMI), fasting insulin (FINS), HOMA-IR, HbA1c, total cholesterol (TC), triglycerides (TG), LDL-C, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), uric acid, and the risk of non-alcoholic fatty liver disease (NAFLD) (all $P < 0.05$). Conversely, RC levels were negatively correlated with age and HDL-C ($P < 0.05$). To further explore the relationship between serum RC, NAFLD, and progressive liver fibrosis in T2DM patients, binary logistic regression analysis was performed. In Model 1, using the presence of NAFLD as the dependent variable (assigned as: yes = 1, no = 0) and RC as the independent variable (measured value) without adjusting for other variables, the results indicated that RC is a significant factor influencing the occurrence of NAFLD in T2DM patients ($P < 0.05$).

In Model 2, after adjusting for sex (assigned as: male = 1, female = 0) and age (measured value), the results remained consistent, showing that RC is a significant factor for NAFLD in T2DM patients ($P < 0.05$). Model 3 further adjusted for BMI, duration of diabetes, systolic blood pressure, diastolic blood pressure, HOMA-IR, and HbA1c (all as measured values) based on Model 2. The results demonstrated that RC remains an independent factor influencing the development of NAFLD in patients with T2DM ($P < 0.05$), as shown in .

Among patients with NAFLD, binary logistic regression analysis was conducted using the occurrence of progressive liver fibrosis as the dependent variable (assigned as: yes = 1, no = 0) and RC as the independent variable (measured

value).

In Model 1, without adjusting for any variables, the results showed that RC is a significant factor influencing the occurrence of progressive liver fibrosis in NAFLD patients ($P < 0.05$). Model 2 adjusted for sex (male = 1, female = 0) and age (measured value), and the results again indicated that RC is a significant factor for progressive liver fibrosis in these patients ($P < 0.05$). Model 3 further adjusted for BMI, duration of diabetes, systolic blood pressure, diastolic blood pressure, HOMA-IR, and HbA1c based on Model 2. The results confirmed that RC is an independent factor influencing the development of progressive liver fibrosis in NAFLD patients ($P < 0.05$), as detailed in .

2.5 ROC

Diagnostic Value of Serum Remnant Cholesterol (RC) for NAFLD and Advanced Liver Fibrosis

To evaluate the diagnostic performance of serum remnant cholesterol (RC) in identifying non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM), as well as its ability to predict the occurrence of advanced liver fibrosis among NAFLD patients, Receiver Operating Characteristic (ROC) curves were constructed (see [Figure 1: see original paper] and [Figure 2: see original paper]).

The analysis revealed that when the optimal cutoff value for RC was set at 0.52, the diagnostic utility for NAFLD reached its peak. At this threshold, the area under the curve (AUC) was 0.604, with a corresponding sensitivity of 67.69% and a specificity of 49.59%.

Furthermore, regarding the progression to advanced liver fibrosis in patients already diagnosed with NAFLD, the optimal RC cutoff value was determined to be 0.91. At this level, RC demonstrated its highest diagnostic value for advanced fibrosis, yielding an AUC of 0.629, a sensitivity of 39.13%, and a high specificity of 91.26%.

3 讨论

NAFLD is a multisystem metabolic disease that shares a bidirectional causal relationship with type 2 diabetes mellitus (T2DM); together, these conditions synergistically promote the development of chronic diseases such as liver cirrhosis, coronary heart disease, and chronic kidney disease. Insulin resistance serves as one of the core mechanisms underlying the onset and progression of NAFLD, making the mitigation of insulin resistance a critical therapeutic target for the disease. Research has demonstrated that insulin resistance is closely associated with the degree of hepatic tissue damage in patients with NAFLD.

Comparison of General Data and Clinical Indicators

The clinical and biochemical characteristics of the study participants were compared between the Non-NAFLD group and the NAFLD group. The results, expressed as mean ± standard deviation ($\bar{x} \pm s$) or median (interquartile range), are summarized in .

Comparison of general data and examination indexes between NAFLD group and non-NAFLD group

Indicator	Non-NAFLD Group ($n = 121$)	NAFLD Group ($n = 195$)
Gender (Male/Female)	79/42	111/84
Age (years)	56 (50, 63)	58 (51, 66)
Duration of Disease (years)	6 (2, 10)	6 (2, 10)
BMI (kg/m^2)	25.4 ± 2.4	26.9 ± 2.7
SBP (mmHg)	135 (126, 147)	136 (128, 147)
DBP (mmHg)	85 ± 10	86 ± 10
FPG (mmol/L)	7.79 (6.54, 9.50)	7.92 (6.94, 9.93)
FINS ($\mu U/mL$)	5.97 (4.29, 8.39)	8.17 (6.08, 12.25)
HOMA-IR	2.31 (1.47, 3.17)	3.12 (2.15, 4.61)
HbA1c (%)	8.5 (7.6, 10.5)	8.9 (7.6, 10.5)
ALT (U/L)	21 (16, 31)	22 (15, 29)
AST (U/L)	20 (16, 25)	25 (19, 36)
GGT (U/L)	24 (18, 39)	28 (20, 42)
ALP (U/L)	78 (62, 95)	77 (65, 93)
ALB (g/L)	43.3 ± 3.8	$42.

b represents the t-value, while the remaining test statistics are expressed as Z-values; 1 mmHg = 0.133 kPa.

Results

Comparison of Clinical and Laboratory Indices Between Groups

The clinical characteristics and laboratory examination indices were compared between the non-progressive liver fibrosis group and the progressive liver fibrosis group. The data are presented as mean ±standard deviation ($\bar{x} \pm s$), median (interquartile range), or frequencies as appropriate.

As shown in , the non-progressive group consisted of 103 patients (60 males and 43 females) with a median age of 54 (44, 60) years and a median disease duration of 5 (2, 10) years. The progressive group included 92 patients (50 males and 42 females) with a median age of 62 (57, 69) years and a median disease duration of 8 (2, 10) years.

Significant differences were observed in several metabolic and biochemical markers. The progressive liver fibrosis group exhibited a higher Body Mass Index

(BMI) of 27.8 ± 2.5 kg/m^2 compared to 26.0 ± 2.7 kg/m^2 in the non-progressive group. Furthermore, the progressive group showed significantly elevated levels of fasting plasma glucose at 9.33 (7.28, 14.70) mmol/L and higher triglyceride (TG) levels at 3.40 (2.65, 4.59) mmol/L, compared to 7.07 (5.17, 9.91) mmol/L and 2.10 (1.76, 2.77) mmol/L in the non-progressive group, respectively.

Regarding liver function and protein synthesis, the progressive group demonstrated lower serum albumin levels (41.2 ± 3.8 g/L vs. 43.8 ± 3.2 g/L) and lower Low-Density Lipoprotein Cholesterol (LDL-C) levels (2.75 ± 0.92 mmol/L vs. 3.21 ± 0.94 mmol/L). Other markers, including Total Cholesterol (TC) and various enzymatic activities, were also recorded and analyzed to evaluate the degree of hepatic

Correlation Analysis Between Remnant Cholesterol and Metabolic Indices in Patients with Type 2 Diabetes Mellitus

Abstract

This study investigates the correlation between Remnant Cholesterol (RC) and various clinical indices—including High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), and the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD)—in patients diagnosed with Type 2 Diabetes Mellitus (T2DM). Furthermore, we employ logistic regression analysis to identify the specific influencing factors for NAFLD within this patient population.

Introduction

Type 2 Diabetes Mellitus (T2DM) is frequently associated with dyslipidemia and metabolic complications, most notably Non-Alcoholic Fatty Liver Disease (NAFLD). While LDL-C has traditionally been the primary focus of lipid management, recent evidence suggests that Remnant Cholesterol (RC) may serve as a more significant marker for residual cardiovascular risk and metabolic dysfunction. This study aims to clarify the relationship between RC levels and other lipid profiles, and to evaluate the role of RC as a predictor for NAFLD in T2DM patients.

Correlation Analysis of RC and Lipid Indices

In patients with T2DM, lipid metabolism is often characterized by an elevation of triglyceride-rich lipoproteins. Remnant cholesterol, calculated as total cholesterol minus HDL-C and LDL-C, represents the cholesterol content within these atherogenic remnants. Our analysis demonstrates a significant correlation between RC and traditional lipid markers. Specifically, RC levels show a strong positive correlation with triglyceride levels and a complex inverse relationship with HDL-C.

The data indicates that as RC levels increase, there is a concomitant shift in the lipid subfractions, often preceding significant elevations in LDL-C. This suggests that RC may be a sensitive indicator of early metabolic derangement in diabetic subjects.

Prevalence of NAFLD in T2DM Patients

NAFLD is increasingly recognized as the hepatic manifestation of metabolic syndrome, and its prevalence is disproportionately high among the T2DM population. In this study, we observed that patients with higher RC levels exhibited a significantly higher prevalence of NAFLD compared to those in the lower RC quartiles. The accumulation of remnant lipoproteins appears to contribute to hepatic lipid deposition and subsequent insulin resistance, creating a feedback loop that exacerbates both T2DM and liver pathology.

[Figure 1: see original paper]

Logistic Regression Analysis of Influencing Factors for NAFLD

To determine the independent risk factors for the development of NAFLD in T

2 值

Wald

HOMA-IR 0.339 12.800 <0.001 1.404 1.166~1.691

Logistc regression analysis of influencing factors for progressive liver fibrosis in patients with NAFLD

2 值

Wald

RC 1.362 13.792 <0.001 3.903 1.902~8.009

RC 1.734 15.883 <0.001 5.663 2.414~13.287

Age | 0.114 | 31.224 | <0.001 | 1.120 | 1.077-1.166

RC 1.474 12.879 <0.001 4.365 1.952~9.760

Age 0.146 28.190 <0.001 1.158 1.097~1.222

BMI 0.388 19.437 <0.001 1.475 1.241~1.752

[FIGURE: 1-Specificity ROC curve for RC diagnosis of NAFLD in T2DM patients; 1-Specificity ROC curve for RC diagnosis of progressive liver fibrosis in NAFLD patients]. The results of this study demonstrate that patients with Type 2 Diabetes Mellitus (T2DM) combined with Non-Alcoholic Fatty Liver Disease (NAFLD) exhibit higher HOMA-IR levels. Furthermore, HOMA-IR

levels in the NAFLD with progressive liver fibrosis group were significantly higher than those in the non-progressive liver fibrosis group. These findings suggest that insulin resistance is closely associated with the severity of NAFLD and progressive liver fibrosis.

According to *Chinese General Practice*, these findings are consistent with previous research. Animal studies have confirmed that the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide can alleviate liver injury in rats with diabetes and NAFLD by improving lipid metabolism and insulin resistance. The *Guidelines for the Prevention and Treatment of Diabetes in China (2024 Edition)* also recommend that patients with T2DM and NAFLD prioritize GLP-1 receptor agonists that offer both hepatic and cardiovascular benefits. Dyslipidemia is a primary pathogenic factor for NAFLD, characterized mainly by decreased high-density lipoprotein cholesterol (HDL-C). The excessive accumulation of lipids in hepatocytes caused by disordered lipid metabolism is a key factor in the occurrence and progression of NAFLD. Our results show that HDL-C levels in patients with T2DM and NAFLD are lower than those in patients with T2DM alone. HDL-C possesses antioxidant properties and enhances cholesterol clearance; by reversing the cholesterol transport system, it promotes the clearance of dietary cholesterol and reduces serum cholesterol levels, playing a vital role in the pathogenesis of NAFLD. Serum remnant cholesterol (RC) is calculated from the lipid profile, defined as the cholesterol remaining after subtracting LDL-C and HDL-C from total cholesterol (TC). It is easily accessible in clinical settings without increasing the financial burden on patients. As a composite index, RC may be a more effective and reliable predictor of NAFLD compared to single lipid markers. A study based on a healthy non-diabetic population evaluated the relationship between serum RC and NAFLD, showing that higher RC levels were significantly associated with an increased risk of NAFLD in both adjusted and unadjusted models. In this study, the prevalence of NAFLD among T2DM patients was 61.7%, which is consistent with previous research indicating a positive correlation between serum RC levels and NAFLD risk. A longitudinal retrospective cohort study showed that even after adjusting for age, sex, blood pressure, blood glucose, and coronary heart disease, serum RC remained significantly positively correlated with the occurrence of NAFLD in the elderly Chinese population. In adolescent populations, patients with higher RC levels exhibit more severe hepatic fat accumulation than those with lower RC levels. Logistic regression analysis results showed that even after adjusting for sex, age, BMI, duration of diabetes, systolic blood pressure, diastolic blood pressure, HOMA-IR, and HbA_{1c}, elevated serum RC levels remained an independent risk factor for NAFLD and progressive liver fibrosis in T2DM patients. The possible mechanisms include: (1) insulin resistance leads to decreased lipoprotein lipase activity and a reduced ability to hydrolyze triglycerides (TG), resulting in impaired metabolism of triglyceride-rich lipoproteins (TRLs) and elevated RC levels, while the lipotoxicity of hyperlipidemia can further aggravate insulin resistance in the liver and peripheral tissues, forming a vicious cycle; (2) intestinal cholesterol absorption is significantly increased in diabetic patients, causing an

increase in RC; (3) a high-lipid microenvironment can inhibit the activity of hepatic endothelial cells, leading to mitochondrial dysfunction and the production of large amounts of reactive oxygen species (ROS), which results in hepatocyte apoptosis; (4) studies have shown that RC levels are associated with low-grade inflammation and may be related to tumor necrosis factor (TNF), interleukins 1, 6, and 8, and pro-atherogenic adhesion molecules, playing an important role in the occurrence and progression of NAFLD. ROC curve analysis in this study showed that the Area Under the Curve (AUC) for serum RC in diagnosing NAFLD and progressive liver fibrosis was > 0.6, suggesting that RC has a certain diagnostic efficacy for these conditions in T2DM patients. It can serve as an early screening indicator for NAFLD and progressive liver fibrosis, emphasizing the need for lipid management to reduce RC levels and mitigate the risk of disease progression. Correcting lipid metabolism disorders in diabetic patients can reduce the incidence and progression of NAFLD; notably, combination therapy with statins and ezetimibe can significantly lower RC levels compared to statin monotherapy, offering greater advantages in reducing diabetic complications. This study also found that serum uric acid levels were significantly elevated in patients with diabetes combined with NAFLD and progressive liver fibrosis, and serum RC was positively correlated with uric acid. Uric acid promotes NAFLD development by activating the NLRP3 inflammasome signaling pathway in hepatocytes, inducing chronic inflammation. Additionally, uric acid can induce insulin resistance, leading to lipid accumulation in hepatocytes. Hyperuricemia can damage the vascular endothelium through oxidative stress and inflammatory responses, promoting atherosclerosis and dyslipidemia; conversely, hyperlipidemia can affect the renal excretion of uric acid, further increasing its levels. Therefore, early interventions such as active control of blood glucose, lipids, and inflammation, along with reducing uric acid and improving insulin sensitivity, can delay the occurrence and progression of NAFLD and progressive liver fibrosis in diabetic patients to a certain extent.

This study has certain limitations. First, the retrospective nature of the study precludes the ability to clarify the causal relationship between serum RC and NAFLD or progressive liver fibrosis in diabetic patients. Second, this was a single-center study; future multi-center, large-sample prospective cohort studies are required to validate these conclusions.

In summary, serum RC levels in T2DM patients are closely associated with the occurrence of NAFLD and progressive liver fibrosis, demonstrating significant diagnostic value for these conditions. As a novel and clinically effective lipid biomarker, RC is simple to calculate and easily obtained. It can be utilized for the early identification of high-risk NAFLD populations. Reducing serum RC levels may represent an effective therapeutic strategy for improving NAFLD and progressive liver fibrosis in patients with diabetes.

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Qun was responsible for the study' s conception and design and is accountable for the overall work.

The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.