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The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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ORIGINAL ARTICLE

Retrospective Study Influencing factors for hepatic fat accumulation in patients with type 2 diabetes mellitus

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Author contributions: Wu MJ and Fang QL contributed equally to this study; Du X and Shi BM developed the study concept and design; Wu MJ and Fang QL mainly implemented the study; Wu MJ, Lu W, Zou SY, Zhu Y, and Fang QL registered the study patients and performed physical examination and medical treatments; Wu MJ and Zhu Y were responsible for measuring plasma lipid parameters; Wu MJ and Du X drafted the manuscript and performed statistical analyses; Wu MJ, Fang QL, and Du X interpreted the data and critically revised and completed the manuscript; all authors read and approved the submitted manuscript.

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease has become the most common chronic liver disease worldwide, which originates from the accumulation of triglyceride (TG) in the liver. Patients with type 2 diabetes mellitus (T2DM) are considered to have a predisposition to hepatic steatosis. However, the influencing factors for hepatic fat accumulation in T2DM patients remain unclear.

AIM

To investigate the influencing factors for hepatic fat accumulation in T2DM patients.

METHODS

We enrolled 329 T2DM patients admitted to the Endocrinology Department of the First Affiliated Hospital of Soochow University, who underwent MR mDIXON-Quant examination to quantify the hepatic fat fraction (HFF). According to body mass index (BMI), the patients were divided into normal weight, overweight, and obese groups. The differences in general statistics, biochemical parameters, islet function, and HFF were compared among the three groups. The associations between HFF and other parameters and the influences of various parameters on the severity of hepatic fat accumulation were analyzed.

RESULTS

The HFF of T2DM patients gradually increased in the normal weight, overweight, and obese groups (P < 0.05). Spearman correlation analysis showed that in T2DM patients, HFF was negatively correlated with age and high-density lipoprotein cholesterol (P < 0.05), whereas it was positively correlated with BMI, waist-hip ratio, fasting plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase, bilirubin, glutamyl transpeptidase, lactate dehydrogenase, albumin (ALB), uric acid (UA), total cholesterol, TG, low-density lipoprotein



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Review Board of the First Affiliated Hospital of Soochow University, and written informed consent was obtained from all participating patients before the initiation of the study.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Data sharing statement: The

datasets analyzed in current study are not publicly available due to relevant ongoing studies, but may be available from the corresponding authors upon reasonable request.

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cholesterol (LDL-C), C-reactive protein, free triiodothyronine, fasting insulin, fasting C-peptide, and homeostasis model assessment of insulin resistance (P <0.05). Multiple linear regression analysis showed significant positive influences of BMI, ALT, LDL-C, UA, and ALB on HFF in T2DM patients (P < 0.05). Binary logistic regression analysis showed that BMI, ALT, ALB, and LDL-C were independent risk factors for moderate to severe fatty liver in T2DM patients, and obesity increased the risk of being complicated with moderate to severe fatty liver by 4.03 times (*P* < 0.05).

CONCLUSION

The HFF of T2DM patients increases with BMI. Higher BMI, ALT, ALB, and LDL-C are independent risk factors for moderate to severe fatty liver in T2DM patients.

Key Words: Type 2 diabetes mellitus; Non-alcoholic fatty liver disease; Hepatic steatosis; Obesity; MR mDIXON-Quant imaging; Cross-sectional study

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Core Tip: Previous studies have showed a bidirectional association between nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM), as the existence of one circumstance aggravates the development of the other. NAFLD originates from the accumulation of triglyceride in hepatocytes, which may consequently lead to further liver injury. This study precisely quantified hepatic fat content by MR mDIXON-Quant imaging, and found that higher body mass index, alanine aminotransferase, albumin, and low-density lipoprotein cholesterol were associated with severer hepatic steatosis in T2DM patients. The MR mDIXON-Quant imaging might play an important role in future research and clinical management of NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of diseases characterized by hepatic fat accumulation without the excessive alcohol consumption or any other definite secondary pathogenic factors, and it has become the most common chronic liver disease worldwide[1]. In recent years, NAFLD has been considered to be associated closely with a variety of extrahepatic chronic diseases such as metabolic syndrome and its components, coronary heart disease, and chronic kidney diseases^[2].

Numerous epidemiological studies have revealed a bidirectional and complex association between NAFLD and type 2 diabetes mellitus (T2DM). Patients with NAFLD have an almost twofold greater risk of developing T2DM than ordinary people^[3], and the incidence of T2DM even increases with the severity of NAFLD diagnosed by ultrasound examination^[4]. While the prevalence of NAFLD is nearly 25% in the world, the prevalence in T2DM patients is > 72%[5]. Moreover, NAFLD patients with T2DM are more likely to progress from simple hepatic steatosis to steatohepatitis and liver fibrosis[5,6].

According to the classic two-hit theory, the accumulation of triglyceride (TG) in the liver is the first step of NAFLD pathogenesis[7]. MR mDIXON-Quant imaging is a new imaging technique that can directly and precisely measure the hepatic fat content[8], and has been rarely used in the clinical research of NAFLD with T2DM. Therefore, in the present study, this technique was used to measure the hepatic fat fraction (HFF) of T2DM patients. The patients were divided into three groups by their body mass index (BMI), and the parameters of body measurement, biochemical indexes, islet function, and HFF were analyzed to explore the influencing factors for hepatic fat accumulation



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in T2DM patients.

MATERIALS AND METHODS

Patients

A cross-sectional study was carried out among T2DM patients hospitalized at the Endocrinology Department of the First Affiliated Hospital of Soochow University, Suzhou, China between January 2017 and March 2018. Patients meeting the following criteria were excluded: (1) Type 1 diabetes, gestational diabetes, or special types of diabetes, and patients with acute diabetic complications; (2) History of malignant tumors; (3) Viral hepatitis, drug-induced hepatitis, or other severe liver diseases; (4) Severe renal diseases or a history of unexplained creatinine elevation; (5) Acute infections or other acute inflammatory diseases; (6) Severe cardiovascular and cerebrovascular diseases such as coronary heart diseases, heart failure, and stroke; (7) Hyperthyroidism, hypothyroidism, or any other endocrine abnormalities excluding diabetes mellitus; (8) Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus; (9) Hemochromatosis or any other congenital liver metabolic diseases; and (10) Alcohol consumption > 30 g/d for men and > 20 g/d for women. A total of 329 T2DM patients were randomly enrolled. The procedure of subject selection is shown in Figure 1.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University, and each patient gave signed informed consent.

Basic information collection and anthropometry

Basic information including age, course of diabetes mellitus, complicating diseases, and history of medication were obtained on the day of hospitalization, and body measurements were arranged in the next morning after an overnight fast. Each patient was required to complete measurement of height, weight, waist circumference (WC), and hip circumference (HC) with bare feet and underwear alone. BMI was calculated as weight divided by height squared (kg/m²), and waist to hip ratio (WHR) was calculated as WC divided by HC.

Laboratory analyses and parameter calculation

Blood samples from an antecubital vein were collected in a quiet state in the morning after an overnight fast (12 h). The blood samples were placed at room temperature for 30 min, and then partly centrifuged at 3500 r/\min for 10 min to extract the serum. Glycosylated hemoglobin (HbA_{1c}) was determined by high performance liquid chromatography (HLC-723G8; Tosoh Company, Japan). The analyses of biochemical parameters including fasting plasma glucose (FPG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), lipase, hydroxybutyrate dehydrogenase, alkaline phosphatase, lactate dehydrogenase (LDH), creatine kinase, γ-glutamyl transpeptidase (GGT), albumin (ALB), globulin, uric acid (UA), creatinine (Cr), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) were completed with an automated biochemical analyzer (7600; Hitachi Company, Japan). Hormones including fasting insulin (FINS), fasting C-peptide (FCP), fasting glucagon (FGC), thyroid stimulating hormone, free thyroxine, and free triiodothyronine (FT3) were analyzed by chemiluminescent immunoassay (AIA-2000ST; Tosoh). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as FPG multiplied by FINS then divided by 22.5.

Quantification of liver fat content

Each subject underwent MR mDIXON-Quant imaging with a Lonwin Magneto 1.5T superconducting magnetic resonance instrument. During examination, the patients were routinely scanned in the sagittal, coronal, and transverse planes, and the data of the axial mLIVE sequence were subsequently collected. The fraction of hepatic TG was presented on the abdominal image reconstructed with the in-built workstation. Specific measuring procedures are as follows. A section of hepatic parenchyma that was far from the edge of the liver and avoiding the large vessels or bile ducts was chosen as the region of interest (ROI). The average HFF of ROI was automatically demonstrated. The average HFF of three ROIs randomly selected from the left, middle and right lobes was taken as the final HFF of each patient. Patients with HFF of 5.5%-





Figure 1 Flowchart of subject selection.

10.0%, 10.1%-25.0%, and > 25.0% were diagnosed as having mild, moderate, and severe fatty liver, respectively.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 25.0. After normality testing of each continuous variable, variables with a normal distribution are presented as the mean \pm SD, while variables with a skewed distribution are presented as median with interquartile range. There was no lack of research data, so during statistical analyses there was no need to deal with the missing values.

In the group comparison, variables with a normal distribution were compared by one-way analysis of variance, and then compared in pairs with the Fisher's least significant difference test. Variables with a skewed distribution were processed by the logarithm transformation based on 10 to meet a normal distribution, and then compared by the methods above, while those still distributed askew after the logarithmic transformation were compared by the nonparametric Kruskal-Wallis test. Spearman correlation analysis was used to find out the associations between HFF and other variables. Multiple linear regression analysis was used to determine the linear correlations between HFF and other variables. Binary logistic analysis was used to explore the independent influencing factors for moderate to severe fatty liver in patients with T2DM. Before linear regression and logistic regression analyses, collinearity analysis was conducted to screen out variables with a variance inflation factor > 10, under which circumstance only one of the collinear variables would be selected for regression analysis. Univariate regression analysis was performed for variables that were significantly correlated with HFF in Spearman correlation analysis, and variables with P < 0.1 in the univariate regression analysis were further enrolled in the multivariate regression analysis.

All the reported *P* values were two-tailed, and only those < 0.05 were considered statistically significant.

RESULTS

Group comparisons

We enrolled 329 T2DM patients with an average age of 53.19 ± 15.19 years. In accordance with the BMI classification standard for Chinese adults proposed by the Chinese Working Group on Obesity in 2001, the participants were stratified into the following groups: Normal weight group with a BMI of $18.5-23.9 \text{ kg/m}^2$, overweight group with a BMI of $24.0-27.9 \text{ kg/m}^2$, and obese group with a BMI $\ge 28.0 \text{ kg/m}^2$. The normal weight group included 127 patients with a mean age of 54.72 ± 13.40 years, the overweight group included 123 patients with a mean age of 55.98 ± 15.03 years, and the obese group included 79 patients with a mean age of 46.41 ± 16.25 years. Comparisons of general statistics, metabolic parameters, hormones, and HFF among groups are shown in Table 1.

Table 1 Comparison of clinical and laboratory characteristics among the three groups						
Variable	Normal weight group	Overweight group	Obese group	P value		
Cases	127	123	79	-		
Age (yr)	$54.72 \pm 13.40^{\circ}$	55.98 ± 15.03 ^c	46.41 ± 16.25 ^{a,b}	< 0.001		
Height (cm)	$164.66 \pm 8.36^{\circ}$	165.78 ± 8.09 ^c	169.32 ± 9.37 ^{a,b}	0.001		
Weight (cm)	60.00 (13.00) ^{b,c}	71.00 (10.00) ^{a,c}	87.00 (16.00) ^{a,b}	< 0.001		
BMI (kg/m ^b)	21.97 (2.63) ^{b,c}	25.81 (1.80) ^{a,c}	29.76 (3.47) ^{a,b}	< 0.001		
WC (cm)	$83.18 \pm 7.81^{b,c}$	92.43 ± 6.47 ^{a,c}	103.73 ± 9.20 ^{a,b}	< 0.001		
HC (cm)	$91.52 \pm 7.41^{b,c}$	98.96 ± 6.51 ^{a,c}	106.89 ± 8.18 ^{a,b}	< 0.001		
WHR	0.91 (0.06) ^{b,c}	0.95 (0.07) ^{a,c}	0.97 (0.06) ^{a,b}	< 0.001		
HFF (%)	7.02 (2.39) ^{b,c}	8.51 (4.91) ^{a,c}	13.03 (11.69) ^{a,b}	< 0.001		
FPG (mmol/L)	6.42 (3.55) ^{b,c}	7.59 (2.73) ^{a,c}	8.44 (3.74) ^{a,b}	< 0.001		
HbA _{1c} (%)	9.64 ± 2.23	9.38 ± 2.10	9.48 ± 2.11	0.639		
FINS (uU/mL)	9.55 (9.70) ^{b,c}	11.80 (8.40) ^a	12.10 (8.60) ^a	0.014		
FCP (ng/mL)	0.85 (0.90) ^{b,c}	1.20 (1.10) ^{b,c}	1.60 (1.50) ^{a,b}	< 0.001		
FGC (pg/mL)	104.50 (51.90)	96.50 (51.40)	97.50 (54.90)	0.239		
HOMA-IR	2.62 (3.11) ^{b,c}	4.05 (3.31) ^a	4.57 (3.01) ^a	< 0.001		
ALT (U/L)	18.80 (12.30) ^c	22.10 (14.50) ^c	36.80 (43.00) ^{a,b}	< 0.001		
AST (U/L)	18.10 (6.40) ^c	20.40 (8.70) ^c	27.00 (22.30) ^{a,b}	< 0.001		
DBIL (mmol/L)	3.90 (1.90)	3.90 (2.50)	4.50 (2.10)	0.078		
IBIL (mmol/L)	9.60 (4.70) ^c	10.30 (6.00)	10.60 (5.50) ^a	0.018		
TBIL (mmol/L)	13.30 (6.10) ^c	14.10 (8.10)	15.50 (8.20) ^a	0.031		
LPS (U/L)	30.20 (16.70) ^c	29.60 (10.60) ^c	27.10 (9.50) ^{a,b}	0.045		
HBDH (U/L)	30.20 (16.70)	29.60 (10.60)	27.10 (9.50)	0.786		
ALP (U/L)	82.70 (33.30)	82.40 (34.30)	81.40 (29.30)	0.487		
LDH (U/L)	165.00 (39.00) ^c	169.00 (43.00)	179.00 (53.00) ^a	0.027		
CK (U/L)	70.70 (44.40)	75.50 (58.10)	77.60 (51.70)	0.230		
GGT (U/L)	20.80 (17.50) ^{b,c}	26.30 (33.10) ^{a,c}	37.70 (39.60) ^{a,b}	< 0.001		
ALB (g/L)	41.40 (5.30) ^c	42.20 (3.90) ^c	43.20 (4.00) ^{a,b}	0.007		
GLB (g/L)	25.70 (5.20)	26.30 (4.60)	26.50 (4.50)	0.379		
A/G	1.60 (0.40)	1.60 (0.40)	1.60 (0.30)	0.206		
UA (µmol/L)	280.00 (109.00) ^{b,c}	334.00 (94.00) ^{a,c}	384.00 (137.00) ^{a,b}	< 0.001		
Cr (µmol/L)	56.00 (21.00) ^b	61.00 (19.00) ^a	59.00 (20.00)	0.016		
TC (mmol/L)	4.40 ± 0.85	4.58 ± 1.32	4.64 ± 1.18	0.273		
TG (mmol/L)	1.06 (0.64) ^{b,c}	1.45 (1.13) ^{a,c}	1.86 (1.46) ^{a,b}	< 0.001		
LDL-C (mmol/L)	2.46 (0.95) ^c	2.66 (1.15)	2.89 (1.05) ^a	0.006		
HDL-C (mmol/L)	1.31 (0.42) ^{b,c}	1.14 (0.27) ^a	1.12 (0.36) ^a	< 0.001		
CRP (mg/L)	1.07 (2.60) ^{b,c}	1.59 (2.30) ^a	2.16 (3.00) ^a	< 0.001		
TSH (mIU/L)	2.19 (1.58)	2.50 (1.88)	2.21 (1.60)	0.127		
FT3 (pmol/L)	2.42 ± 0.42	2.49 ± 0.48	2.56 ± 0.46	0.109		
FT4 (pmol/L)	1.15 ± 0.29	1.12 ± 0.29	1.10 ± 0.26	0.463		

 $^{\mathrm{a}}P$ < 0.05 compared with the normal weight group.

$^{b}P < 0.05$ compared with the overweight group.

^cP < 0.05 compared with the obese group. BMI: Body mass index; WHR: Waist to hip ratio; HFF: Hepatic fat fraction; FPG: Fasting plasma glucose; HbA_{1c}: Glycosylated hemoglobin; FINS: Fasting insulin; FCP: Fasting C-peptide; FGC: Fasting glucagon; HOMA-IR: Homeostasis assessment of insulin resistance; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; TBIL, Total bilirubin; LPS: Lipase; HBDH: Hydroxybutyrate dehydrogenase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; CK: Creatine kinase; GGT: γ-glutamyl transpeptidase; ALB: Albumin; GLB: Globulin; A/G: Albumin to globulin ratio; UA: Uric acid; Cr: Creatinine; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CRP: C-reactive protein; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine.

> In terms of anthropometric data, body weight, WC, HC, WHR, and HFF of T2DM patients gradually increased in the normal weight, overweight, and obese groups (P < 0.01). With regard to metabolic parameters and islet function, FPG increased while HbA_{1c} remained stable with BMI rising among the three groups. FINS, FCP, and HOMA-IR in the normal weight group were significantly lower than those in the other groups (P < 0.05). FCP in the overweight group was significantly lower than that in the obese group (P < 0.01). There were no significant differences in FGC among the three groups (P > 0.05). ALT, AST, GGT, ALB, and UA were significantly higher in the obese group than in the other groups (P < 0.01), and GGT, UA, and Cr were significantly higher in the overweight group than in the normal weight group (P < 0.05). With respect to lipid profile, TG increased gradually in the normal weight, overweight, and obese groups (P < 0.01). HDL-C in the normal weight group was significantly higher than that in the other groups, while LDL-C was significantly lower than that in the obese group (P < 0.01). There were no significant differences in thyroid function among the three groups (P > 0.05).

Spearman correlation analysis of HFF with other variables

Table 2 shows that the HFF of T2DM patients was negatively correlated with age and HDL-C (r = -0.136 and -0.251, P < 0.05), and positively correlated with BMI, WHR, FPG, FINS, FCP, HOMA-IR, ALT, AST, DBIL, IBIL, TBIL LDH, GGT, ALB, UA, TC, TG, LDL-C, CRP, and FT3 (*r* = 0.493, 0.227, 0.281, 0.133, 0.385, 0.247, 0.459, 0.385, 0.154, 0.251, 0.234, 0.126, 0.413, 0.217, 0.305, 0.193, 0.478, 0.269, 0.251, and 0.157, *P* < 0.05).

Multivariate linear regression analysis of HFF with other variables

Multivariate linear regression analysis showed that ALT (β = 0.437, *P* < 0.001), BMI (β = 0.246, P < 0.001), LDL-C ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), UA ($\beta = 0.108$, P = 0.025), and ALB ($\beta = 0.121$, P = 0.007), P = 0.007), P = 0.007, P = 00.091, P = 0.039) had significant positive linear correlations with HFF in T2DM patients (Table 3).

Analysis of influencing factors for moderate to severe fatty liver in T2DM patients

Among 329 T2DM patients, 97 were diagnosed with moderate fatty liver, and 21 with severe fatty liver. In multivariate binary logistic regression analysis, increased BMI was a significant independent risk factor for severer hepatic steatosis. The odds ratio (OR) of moderate to severe fatty liver was 2.29 times higher in overweight patients and 5.03 times higher in obese patients than in patients with normal weight (P < 0.05). Meanwhile, increased ALT (OR = 1.029, P < 0.001), ALB (OR = 1.105, P = 0.006), and LDL-C (OR = 1.710, P = 0.004) were other independent risk factors for moderate to severe fatty liver in T2DM patients (Table 4).

DISCUSSION

Among the spectrum of NAFLD, although most patients with non-alcoholic fatty liver (NAFL) are at a low risk of adverse prognosis[9], about 25% of them may progress to nonalcoholic steatohepatitis (NASH)[10], in which case, patients are more likely to develop liver fibrosis, cirrhosis, failure, or even carcinoma[11]. Meanwhile, the ectopic accumulation of fat in the liver leads to increasing gluconeogenesis, decreasing glycogen synthesis, and inhibition of the insulin signaling pathway^[12], and finally destroys the homeostasis of glucose metabolism. The increase in hepatic fat content is closely related to the progressive pre-diabetic phase in people without diabetes^[13]. Furthermore, glucose metabolic disorder and complications of cardiovascular, retinal, renal, and neurological disorders are more severe in T2DM patients with NAFLD[14]. Therefore, screening and evaluation of NAFL in T2DM patients may help clinical physicians to manage the intensity of metabolic treatment, formulate treatment plan,



Table 2 Spearman correlation analysis of hepatic fat fraction with other variables					
Variable	r	<i>P</i> value			
Age	0.136	0.013			
BMI	0.493	< 0.001			
WHR	0.227	< 0.001			
FPG	0.281	< 0.001			
FINS	0.133	0.016			
FCP	0.385	< 0.001			
HOMA-IR	0.247	< 0.001			
UA	0.305	< 0.001			
ALT	0.459	< 0.001			
AST	0.385	< 0.001			
DBIL	0.154	0.005			
IBIL	0.251	< 0.001			
TBIL	0.234	< 0.001			
LDH	0.126	0.022			
GGT	0.413	< 0.001			
ALB	0.217	< 0.001			
TC	0.193	< 0.001			
TG	0.478	< 0.001			
LDL-C	0.269	< 0.001			
HDL-C	-0.251	< 0.001			
CRP	0.251	< 0.001			
FI3	0.157	0.005			

BMI: Body mass index; WHR: Waist to hip ratio; FPG: Fasting plasma glucose; FINS: Fasting insulin; FCP: Fasting C-peptide; HOMA-IR: Homeostasis assessment of insulin resistance; UA: Uric acid; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; TBIL, Total bilirubin; LDH: Lactate dehydrogenase; GGT: γ -glutamyl transpeptidase; ALB: Albumin; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CRP: C-reactive protein; FT3: Free triiodothyronine.

Table 3 Multivariate linear regression analysis of hepatic fat fraction with other variables in type 2 diabetes mellitus patients						
Variable	В	SE	β	t	P value	95%CI
ALT	0.080	0.008	0.437	9.455	< 0.001	0.063-0.096
BMI	0.409	0.083	0.246	4.925	< 0.001	0.246-0.573
LDL-C	1.040	0.380	0.121	2.737	0.007	0.292-1.788
UA	0.008	0.003	0.108	2.253	0.025	0.001-0.014
ALB	0.135	0.065	0.091	2.070	0.039	0.007-0.263

ALT: Alanine aminotransferase; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; UA: Uric acid; ALB: Albumin; CI: Confidence interval.

> monitor disease progression, and prevent or delay the development of chronic complications.

> In the present study, MR mDIXON-Quant imaging was used to precisely quantify the hepatic fat content in T2DM patients. We found that the HFF of T2DM patients gradually increased in the normal weight, overweight, and obese groups. We also found that lipid metabolism disorder and insulin resistance deteriorated in obese

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Table 4 Multivariate binary logistic regression analysis of independent influencing factors for moderate to severe fatty liver in type 2 diabetes mellitus natient

Variable		В	SE	Wald	<i>P</i> value	OR	95%CI
BMI	< 24						
	24-27.99	0.830	0.329	6.361	0.012	2.294	1.203-4.373
	≥ 28	1.615	0.379	18.121	< 0.001	5.027	2.390-10.572
ALT		0.028	0.007	15.643	< 0.001	1.029	1.014-1.043
ALB		0.099	0.036	7.480	0.006	1.105	1.029-1.186
LDL-C		0.537	0.185	8.389	0.004	1.710	1.189-2.459

BMI: Body mass index; ALT: Alanine aminotransferase; ALB: Albumin; LDL-C: Low-density lipoprotein cholesterol; CI: Confidence interval.

T2DM patients. The multivariate linear regression analysis showed that HFF had a significantly positive linear correlation with BMI, and the binary logistic regression analysis showed that overweight and obesity increased the risk of moderate to severe fatty liver by 2.29 times and 5.03 times, respectively, in T2DM patients. All the above suggest that the increase in BMI played an important role in the aggravation of hepatic fat accumulation, which is consistent with the opinion of obesity serving as a significant risk factor for NAFLD in previous studies. In a retrospective longitudinal study including 4.12 million metabolically healthy people in the UK, the overweight and obese populations had a 3.3 and 6.9 times higher risk of developing NAFLD, respectively, than those with normal weight[15]. Another cohort study including 77425 metabolically healthy individuals in South Korea found a dose-effect relationship between baseline BMI and incidence of NAFLD in both sexes[16]. In the classic doublehit theory, the insulin resistance of adipose tissues leads to imbalance of lipolysis, resulting in excess free fatty acids being transported to the liver[17]. Under normal circumstances, the free fatty acids in the liver are either involved in mitochondrial β oxidation or esterified to synthesize TG[18]. When the synthesis of TG overbalances its release in the form of very low-density lipoprotein, the rest forms lipid droplets in hepatocytes, which is the first hit in the development of NAFLD. The molecular changes caused by hepatic steatosis may make the liver vulnerable to the second hit, which usually means oxidative stress and cytokine-mediated liver injury [7]. Compared with obese people with normal glucose metabolism, the insulin resistance deteriorates in obese T2DM patients. As a result, strict and precise weight management plays a vital role in inhibiting the pathogenesis and development of NAFLD in T2DM patients.

We also found that ALT, ALB, LDL-C, and UA had significantly positive linear correlations with HFF. In binary logistic regression analysis, higher ALT, ALB, and LDL-C were also independent risk factors for moderate to severe fatty liver in T2DM patients. ALT is rich in the hepatic cytoplasm, which is most commonly used to indicate hepatic inflammation and injury, and in some cases is considered to reflect the severity of hepatic fat deposition[19]. Although ALT is not sufficient to serve as a biomarker for the diagnosis of NAFLD and NASH, it may serve as a clinical reference for the severity of NAFLD. ALB is a good indicator of nutritional status in the clinically stable population[20]. Several previous studies have suggested ALB as an independent risk factor for NAFLD[21,22]. In the case of overnutrition, the hepatic capacity of dealing with basic energy substrates such as carbohydrates and fatty acids is overloaded, leading to accumulation of toxic lipids^[23]. To some extent, the positive correlation between ALB and hepatic steatosis in our study may relate to its reflection on nutritional status.

UA is considered a natural scavenger of free radicals derived from nitrite peroxides in healthy people^[24], while when exposed to metabolic disorders, it may convert into a strong oxidant and induce the genesis of reactive oxygen species[25], which exacerbates hepatic steatosis. Moreover, UA can stimulate the synthesis of pro-inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor- α [26], and further stimulate the production of CRP in the liver [27]. Therefore, UA may associate with hepatic fat accumulation by inducing oxidative stress and chronic lowgrade inflammation. A domestic cross-sectional study including 183903 people in China who underwent physical examinations found that the prevalence of NAFLD in the non-obese population increased with LDL-C quartiles^[28]. In a further cohort



study of 16173 people, the cumulative incidence of NAFLD gradually increased with LDL-C quartiles, and the LDL-C level at the upper limit of normal range predicted the risk of developing NAFLD in non-obese individuals^[28]. Secretion of very low-density lipoprotein into the circulation increases with synthesis of TG in liver, in which case the proportion of small dense LDL particles also increases in the bloodstream^[29]. However, the inferences above are not sufficient to support the predictive influence of LDL-C on the development of NAFLD. In future, more research is needed to determine the relationship between them.

In addition, although insulin resistance is considered a basic characteristic promoting the development of NAFLD[30], there was no independent linear correlation between HOMA-IR and HFF in our study. This may be because HOMA-IR is not an appropriate indicator of insulin resistance in NAFLD patients[31]. It has been found that hepatic insulin clearance is impaired in NAFLD patients, as the hepatic insulin extraction decreases with the increase of intrahepatic TG content[31,32]. According to those authors, the level of plasma insulin did not represent the level of portal insulin, but rather the level of insulin remaining after the first hepatic pass[31]. Therefore, application of a glucose clamp technique in research or serum insulin/C-peptide release test in clinics may be more suitable for the accurate evaluation of islet function in NAFLD patients.

Among the various diagnostic methods for NAFLD, liver biopsy is always a golden standard for quantifying hepatic steatosis. While the pathological features are distributed diffusely in most chronic liver diseases, liver biopsy only assesses 1/50000 of the hepatic parenchyma, which means inevitable sampling differences[33]. Meanwhile, the risks and technical requirements of the invasive procedure limit the clinical application of liver biopsy. Ultrasound examination is the most commonly applied imaging technique for diagnosing NAFL. However, the diagnostic sensitivity decreases among NAFLD patients with HFF < 20%[34] and it is incapable of accurately evaluating the severity of hepatic steatosis in obese individuals. The diagnostic results of ultrasound examination depend on the accuracy of the instruments and professional skills of the operators, which results in poor repeatability. As a semi-quantitative technique for the measurement of NAFL, computed tomography has a high specificity for patients with moderate and severe fatty liver, although the risks of ionizing radiation make it inappropriate for long-term monitoring of NAFLD patients. Magnetic resonance spectroscopy (MRS) is commonly considered the most precise noninvasive method to quantify hepatic TG, but it is time-consuming and requires professional analysis of the results[35]. MR mDIXON-Quant imaging is a burgeoning technique for precisely measuring the hepatic liver content, which is non-invasive and rapid, and has a sensitivity of 95% and specificity of 100% in detecting hepatic steatosis [36]. It is reported that the quantification of hepatic TG by MR mDIXON-Quant imaging is highly correlated with that of MRS or histological analysis[37]. It avoids any invasive injury or radiation threat, takes a shorter period of time, has a high resolution, and diagnoses without any influence from the intensity of the magnetic field[35]. Above all, MR mDIXON-Quant imaging has high clinical value in the diagnosis and grading of NAFL, monitoring of NAFLD progression, and evaluation of treatment and prognosis, and might play an important role in future NAFLD research.

The limitations of this study included the small number of study patients. Therefore, further studies with larger numbers of patients are needed to verify our findings.

CONCLUSION

This study demonstrated that the severity of hepatic fat accumulation mainly increases with BMI. Higher BMI, ALT, ALB, and LDL-C are significant independent risk factors for moderate to severe fatty liver in T2DM patients. Meanwhile, the MR mDIXON-Quant imaging can precisely measure hepatic TG in T2DM patients, and is important for future research and clinical practice in patients with T2DM and NAFLD.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD), the most common hepatic chronic disease worldwide, has been considered to have a complex association with type 2 diabetes



mellitus (T2DM). The existence of NAFLD disturbs the homeostasis of glucose metabolism, while patients with T2DM have a higher prevalence of hepatic steatosis, which is the origin of further adverse pathological changes.

Research motivation

In previous clinical studies focused on NAFLD, most diagnoses of hepatic steatosis were conducted using common imaging techniques such as ultrasound and computed tomography, which have limited diagnostic sensitivity and accuracy under certain circumstances. There is an urgent need for a rapid, non-invasive, and inexpensive technique to precisely quantify hepatic fat content and to grade the severity of hepatic steatosis for future NAFLD research.

Research objectives

We aimed to quantify the hepatic triglyceride (TG) content and then investigate the influencing factors for hepatic fat accumulation and the severity of fatty liver in T2DM patients.

Research methods

A cross-sectional study was conducted at the department of endocrinology, including 329 hospitalized T2DM patients divided into three groups according to their body mass index (BMI). MR mDIXON-Quant imaging was applied to quantify the hepatic fat fraction (HFF) of each patient, and fasting blood samples were obtained for further biochemical analysis. HFF, anthropometric data, and laboratory characteristics were compared among the three groups. Spearman correlation analysis and linear regression analysis were carried out to determine the associations between HFF and other variables, and binary logistic regression analysis was carried out to find out the influencing factors for severer hepatic steatosis in T2DM patients.

Research results

The HFF of T2DM patients gradually increased in the normal weight (BMI of 18.5-23.9 kg/m²), overweight weight (BMI of 24.0-27.9 kg/m²), and obese groups (BMI \ge 28.0 kg/m²). Spearman correlation analysis and multivariate linear regression analysis showed that BMI, alanine aminotransferase (ALT), albumin (ALB), low-density lipoprotein cholesterol (LDL-C), and uric acid had significant positive associations with HFF of T2DM patients. Multivariate binary logistic regression analysis showed that BMI, ALT, ALB, and LDL-C were independent risk factors for moderate to severe fatty liver in T2DM patients. Overweight and obesity increased the odds ratio of severer fatty liver by 2.29 times and 5.03 times, respectively, in T2DM patients.

Research conclusions

We quantified hepatic TG content and graded the severity of hepatic steatosis by MR mDIXON-Quant imaging technique. We found that in T2DM patients, hepatic fat accumulation is significantly associated with increasing BMI, ALT, ALB, and LDL-C. Higher BMI, ALT, ALB, and LDL-C are independent risk factors for moderate to severe non-alcoholic fatty liver in T2DM patients.

Research perspectives

Considering of the small size of subjects and the limitation of cross-sectional study, prospective studies with larger size of subjects are needed to verify our findings. However, we would like to recommend the MR mDIXON-Quant imaging as an excellent tool for the diagnosis and grading of non-alcoholic hepatic steatosis, which might play an important role in future research and clinical practice of NAFLD.

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