

The Perirenal Fat Thickness Was Associated with Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus

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Purpose: Obesity is an important risk factor for nonalcoholic fatty liver disease (NAFLD). Perirenal fat and paranephric fat were seldom studied in NAFLD. We aimed to explore the relationship between perirenal fat thickness (PrFT) and paranephric fat thickness (PnFT) and NAFLD in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: A total of 493 diabetic patients including 231 NAFLD patients were enrolled in our study from September 2019 to December 2020. Patients with NAFLD were categorized into three subgroups according to the severity and fibrosis risk of NAFLD. Anthropometric indices and clinical characteristics were collected from clinical records. PrFT and PnFT were measured via ultrasound. Multivariate logistic regression analysis was used to assess the association between PrFT, PnFT and presence, severity and advanced fibrosis risk of NAFLD.

Results: Compared with non-NAFLD patients, those with NAFLD had significantly higher PrFT and PnFT. The PrFT and PnFT were independently associated with presence of NAFLD and the PrFT was independently associated with the advanced fibrosis risk of NAFLD after adjusting confounding factors.

Conclusion: The PrFT was independently associated with the presence and advanced fibrosis risk of NAFLD in patients with T2DM.

Keywords: nonalcoholic fatty liver disease, perirenal fat thickness, paranephric fat thickness, type 2 diabetes mellitus

Introduction

Nonalcoholic fatty liver disease (NAFLD), characterized by excessive fat accumulation in the liver, is the most common chronic liver disease. The global prevalence of NAFLD is estimated at 25%,¹ among which 35.5% in China.² Initially, NAFLD was considered as a relatively benign disease, but a minority of patients can progress to more severe stages such as cirrhosis, hepatocellular carcinoma, leading to liver failure and even liver transplantation.³ As a result, NAFLD has rapidly become a health-care burden to the society.^{1,4} While there is no valid treatment for NAFLD.⁵

NAFLD has been recognized as hepatic manifestation of metabolic syndrome, closely related to type 2 diabetes mellitus (T2DM), visceral obesity and insulin resistance.^{6,7} NAFLD is associated with an approximate doubling of risk of T2DM.⁸ The global prevalence of NAFLD among patients with T2DM ranges from 55.5% to 59.7%.^{9,10} Patients with NAFLD and T2DM also have a higher risk of progressing nonalcoholic steatohepatitis, suggesting there is a bidirectional interplay between NAFLD and T2DM.¹¹

It is well established that obesity increases the risk of NAFLD.^{12–16} The obesity indices in clinical studies included BMI,^{12,13} waist circumference¹⁴ and visceral obesity.^{15,16} However, not all obese patients develop NAFLD and, more importantly, NAFLD can occur in nonobese and even lean individuals, especially in Asian populations. Previous study indicated that 40% of global NAFLD patients were non-obese and approximately 20% were lean.¹⁷ It is reported that the majority of lean NAFLD patients were characteristic of excess visceral adiposity and insulin resistance.^{18,19} It is

suggested that high visceral-to-subcutaneous fat ratio values predicted increased NAFLD risk.²⁰ Chiyanika C conducted one study using prospectively acquired data and suggested that increased visceral adipose tissue (VAT) may be a vital driver to the development of NAFLD irrespective of BMI category.¹⁶ In addition, there is an established relationship between visceral fat and liver steatosis.²¹ In a large cohort study, larger areas of VAT were associated with higher risk of incident NAFLD. While larger areas of SAT were associated with regression of NAFLD.¹⁵

As part of visceral fat, perirenal fat is an ectopic fat pad located in the retroperitoneal space, surrounding the kidneys.²² Perirenal fat, wrapped by a complete renal fascia, has a complete system of blood supply, lymph fluid drainage and innervation. All this makes perirenal fat like an internal organ. As a mixture of brown adipose tissue (BAT) and white adipose tissue (WAT), perirenal fat can synthesis and secrete many adipokines, such as leptin, adiponectin and so on. While paranephric fat lies posterolaterally to each kidney and is anatomically adjacent to perirenal fat. In addition, paranephric fat is not wrapped by renal fascia and is relatively farther and forms the final layer of fat and fasciae associated with the kidney.²³ Histologically speaking, paranephric fat is a typical WAT depot, while perirenal fat is a mixture of WAT and BAT. Several studies demonstrated that accumulation of perirenal fat and para-perirenal fat were associated with renal function, atherosclerosis and cardiovascular disease.^{24–26} However, studies about the relationship between perirenal fat and paranephric fat and NAFLD are limited. One study involved 286 patients in Japan revealed that measurement of para- and perirenal sonographic fat thickness is positively associated with fatty liver grade.²⁷ Therefore, this study aimed to explore the relationship between the perirenal fat and paranephric fat and presence, severity and fibrosis risk of NAFLD in patients with T2DM, respectively.

Materials and Methods

Study Population and Study Design

We enrolled 493 patients with T2DM, who hospitalized at the Center for Endocrine Metabolism and Immune Disease Center at Beijing Luhe Hospital, Capital Medical University from September 2019 to December 2020. The diagnosis of T2DM was defined according to 1999 World Health Organization Criteria,²⁸ which including fasting blood glucose ≥ 7.0 mmol/L and/or 2-hour blood glucose during a 75-g oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6 th revision, 2008) as reflected in a priori approval by the institution's human research committee. The study protocol was approved by the Ethics Review Committee of Beijing Luhe Hospital. Informed consent was obtained from each patient included in the study.

Diagnosis, Severity and Advanced Fibrosis Risk of NAFLD

Each subject underwent abdominal ultrasonography by an experienced clinician who was blinded to the clinical presentation and laboratory results. Fatty liver was identified by characteristic echo patterns including a diffuse increase in the echogenicity of the liver compared to that of the spleen or kidney, according to ultrasonographic liver features and by reference to well-established criteria for the assessment and management of NAFLD in China.²⁹ Patients were excluded if they met the following criteria: with known secondary etiologies of hepatic fat accumulation such as excessive alcohol intake (> 20 g/day for women and > 30 g/day for men),³⁰ long-term use of steatogenic medications (such as corticosteroids, methotrexate, amiodarone and tamoxifen), virus hepatitis, monogenic hereditary disorders, autoimmune hepatitis, drug-induced liver disease, severe malnutrition and Wilson Disease. Furthermore, fatty liver was graded as mild, moderate and severe by total scores of 2, 3–4 and 5, respectively, with the scoring criteria³¹ as: ① liver size: normal = 0, enlarged = 1; ② edge angle of liver: acute = 0, obtuse = 1; ③ parenchyma echo: normal (equal to the spleen) = 0, enhanced = 1, enhanced with far-field attenuation = 2; and ④ vessel display: clear = 0, unclear = 1. The fibrosis risk of NAFLD were commonly evaluated by NAFLD fibrosis score and FIB4 score. The advanced fibrosis risk of NAFLD is estimated by NAFLD fibrosis score:³² $\text{NAFLD fibrosis score} = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (x10}^9\text{/l)} - 0.66 \times \text{albumin (g/dl)}$. The cutoffs NAFLD fibrosis score for absence, intermediate, and presence of advanced fibrosis were < -1.455 , -1.455 to 0.676 , and > 0.676 , respectively. Using the two cutoff points, the absence and presence of advanced fibrosis could be detected with high accuracy (negative predictive value of 93%, positive predictive value of 90%). The FIB-4

score formula is $(\text{Age} \times \text{AST})/(\text{Plts} \times (\text{sqr}(\text{ALT})))$. The cutoffs for low, intermediate, and high probability of advanced fibrosis were <1.3 , 1.3 to 2.67 , and >2.67 , respectively.³³

Anthropometric Measurements and Laboratory Data

The clinical characteristics and anthropometric indices including age, gender, alcohol consumption, height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected through the medical records of each subject. The BMI was calculated as weight divided by the square of height (kg/m^2). The measure of perirenal fat thickness (PrFT) and paranephric fat thickness (PnFT) were measured via ultrasound. An auto-biochemical analyzer (Roche/Hitachi Cobas C501, Roche Diagnostic Corp., Indianapolis) was employed to determine the fasting blood glucose (FBG), serum concentrations of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), alanine aminotransferase (ALT), Aspartate aminotransferase (AST), blood creatinine (Cr), blood urea nitrogen (BUN), serum uric acid (SUA). Glycosylated hemoglobin (HbA1c) was quantified using high performance liquid chromatography (HPLC) with a D10 set (Bio-RAD, Hercules, California).

Measurement of Perirenal Fat Thickness and Paranephric Fat Thickness

The measure of PrFT and PnFT were performed as previously described by our team.²⁵ Briefly, PrFT and PnFT were measured by a single skilled operator, using a duplex Doppler apparatus (Model Preirus, HITACHI), with patients in the supine position. The operator was blind to the clinical data of all subjects. The probe was held vertical to the skin on the lateral aspects of the abdomen to obtain the optimal position. The pressure of the probe on the skin surface was as small as possible to prevent the fat layer from being compressed. The PrFT was determined from the renal fascia to the surface of the kidney. The PnFT was then determined from the inner side of the abdominal musculature to the renal fascia (Figure S1). The average of the ultrasound measurement values on both sides was defined as PrFT and PnFT.

Statistics

The statistical analysis was performed using statistical package R (version 3.5.2, available from <http://www.r-project.org>). Normal distribution of continuous variables was detected using histogram or Q-Q plot. Nearly normally distributed continuous variables were presented as mean \pm standard derivation and the differences were compared by student's *t* test. Categorical variables were presented as frequencies (proportions) and compared by Chi-square test. Tertiles of PrFT and PnFT were calculated. Univariate and Multivariate logistic regression analysis were used to evaluate the relationship between the PrFT and PnFT and presence, severity and advanced fibrosis risk of NAFLD in patients with T2DM, adjusting potential confounding variables. *P* values < 0.05 were considered statistically significant.

Results

A total of 493 patients with T2DM were enrolled in our study. The mean age is 57.63 ± 14.92 years and 48.7% of the patients were females. All the patients were classified into NAFLD group ($n = 231$) and Non-NAFLD group ($n = 262$) according the ultrasound imaging. The NAFLD group was further classified into mild ($n = 128$), moderate ($n = 80$) and severe group ($n = 23$) based on the ultrasound imaging by the same person.

The Clinical and Metabolic Characteristics of the Study Population

The clinical and the metabolic characteristics of the study population stratified by the presence and severity of NAFLD are shown in Table 1. We found that the presence and more severe NAFLD were prone to occurring in younger people ($P < 0.001$). In addition, the BMI, DBP, PrFT, PnFT, ALT and AST increased according the presence and progression of NAFLD. The BUN, HDL-c decreased according the presence and progression of NAFLD. While no differences were noted in gender, SBP, albumin, HbA1c, Cr, TC, the prevalence of current smoke, current drink, coronary heart disease and cerebrovascular disease among groups (Table 1).

Table I The General Clinical Characteristics of the Study Population According the Presence and Severity of NAFLD

Parameters	Non-NAFLD (N=262)	NAFLD		
		Mild (N=128)	Moderate (N=80)	Severe (N=23)
Gender (Female %)	141 (53.8)	70 (54.7)	46 (57.5)	16 (69.6)
Age (years)	61.94 ± 13.11	56.41 ± 13.94 ^a	50.38 ± 15.65 ^{ab}	40.57 ± 14.46 ^{abc}
BMI (kg/m ²)	25.09 ± 3.69	27.30 ± 3.62 ^a	28.53 ± 3.93 ^a	32.24 ± 4.50 ^{abc}
SBP (mmHg)	131.39 ± 18.44	130.20 ± 13.92	132.68 ± 16.25	132.57 ± 16.52
DBP (mmHg)	74.80 ± 11.52	78.95 ± 9.64 ^a	80.21 ± 11.11 ^a	84.17 ± 11.75 ^a
PrFT (cm)	0.88 ± 0.44	1.04 ± 0.43 ^a	1.10 ± 0.42 ^a	1.29 ± 0.44 ^a
PnFT (cm)	0.81 ± 0.34	1.04 ± 0.37 ^a	1.07 ± 0.38 ^a	1.37 ± 0.50 ^{abc}
Albumin (g/l)	41.00 ± 3.64	41.53 ± 3.48	42.15 ± 3.34	42.37 ± 3.44
ALT (U/L)	17.16 ± 9.46	26.48 ± 20.85 ^a	45.71 ± 46.40 ^{ab}	61.17 ± 30.72 ^{ab}
AST (U/L)	17.31 ± 11.22	21.28 ± 13.01	34.31 ± 37.52 ^{ab}	37.74 ± 18.47 ^{ab}
Platelet (×10 ⁹ /l)	201.50 ± 67.18	227.74 ± 53.88	242.82 ± 54.67 ^a	226.17 ± 38.40
HbA1c (%)	9.48 ± 2.35	9.68 ± 2.11	9.86 ± 1.73	9.88 ± 1.58
FBG (mmol/l)	8.53 ± 4.19	8.12 ± 3.24	8.96 ± 3.68	10.59 ± 4.44 ^b
Cr (umol/l)	74.92 ± 38.62	68.83 ± 19.04	67.79 ± 20.50	61.68 ± 15.59
BUN (mmol/l)	5.91 ± 2.74	5.12 ± 1.65 ^a	4.88 ± 1.68 ^a	4.17 ± 1.30 ^a
SUA (mmol/l)	355.35 ± 94.23	348.20 ± 94.11 ^a	366.03 ± 95.98 ^a	357.45 ± 88.87
TG (mmol/l)	1.49 ± 0.94	2.08 ± 1.50 ^a	2.42 ± 1.67 ^a	2.33 ± 1.23 ^a
TC (mmol/l)	4.38 ± 1.31	4.55 ± 1.33	4.65 ± 1.11	4.52 ± 1.18
HDL-c (mmol/l)	1.12 ± 0.29	1.03 ± 0.23 ^a	1.02 ± 0.18 ^a	0.90 ± 0.23 ^a
LDL-c (mmol/l)	2.77 ± 0.96	2.98 ± 1.04	3.06 ± 0.89	3.11 ± 0.98
Hypertension (%)	167 (64.0)	79 (61.7)	39 (49.4)	10 (43.5)
Coronary heart disease (%)	68 (26.5)	33 (26.2)	17 (21.8)	2 (9.1)
Cerebrovascular disease (%)	55 (21.4)	24 (19.2)	14 (18.2)	0 (0.0)
Current smoke (%)	98 (37.5)	52 (40.6)	39 (48.8)	11 (47.8)
Current drink (%)	69 (26.4)	43 (33.6)	17 (21.2)	7 (30.4)

Notes: ^a*P* < 0.05, vs non-NAFLD group, ^b*P* < 0.05, vs mild group, ^c*P* < 0.05, vs moderate group.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PrFT, perirenal fat thickness; PnFT, paranephric fat thickness; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycosylated hemoglobin; FBG, fasting blood glucose; Cr, blood creatinine; BUN, blood urea nitrogen; SUA, serum uric acid; TG, triglyceride; TC, total cholesterol; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol.

The Association of PrFT and PnFT with Presence of NAFLD

Compared to non-NAFLD patients, those with NAFLD had significantly higher PrFT (1.08 cm vs 0.88 cm, *P* < 0.001, Figure 1A) and PnFT (1.09 cm vs 0.81 cm, *P* < 0.001, Figure 1B). When all patients were divided into three groups according to tertiles of PrFT and PnFT value, the data showed that the prevalence of NAFLD increased with the increased PrFT and PnFT (Figure 1C and D). To further explore the association between PrFT and PnFT and NAFLD, we conducted univariate and multivariate logistic regression analysis. Univariable logistic regression demonstrated that gender, age, BMI, waist circumference, DBP, AST, ALT, platelet, Cr, BUN, SUA, TG, HDL-c, LDL-c were significantly associated with the presence of NAFLD (Table S1). In the multivariate logistic regression, both higher PrFT (OR = 2.15, *P* = 0.012, Table 2) and PnFT (OR = 2.76, *P* = 0.006, Table 2) were independently associated with higher odds for NAFLD after adjusting age, gender, BMI, waist circumference, DBP, drink, TG, TC, HDL-c, LDL-c and HbA1c (Table 2).

The Association of PrFT and PnFT with Severity of NAFLD

To further explore the PrFT and PnFT with the severity of NAFLD, patients with NAFLD were further stratified into three subgroups including mild, moderate and severe group. We found that patients with severe NAFLD had higher PrFT and PnFT than mild NAFLD (*P* = 0.026 and *P* < 0.001, Figure 2A and B, respectively). In addition, we also compared the proportion of severity of NAFLD according to the tertiles of PrFT and PnFT. The proportion of severe NAFLD did

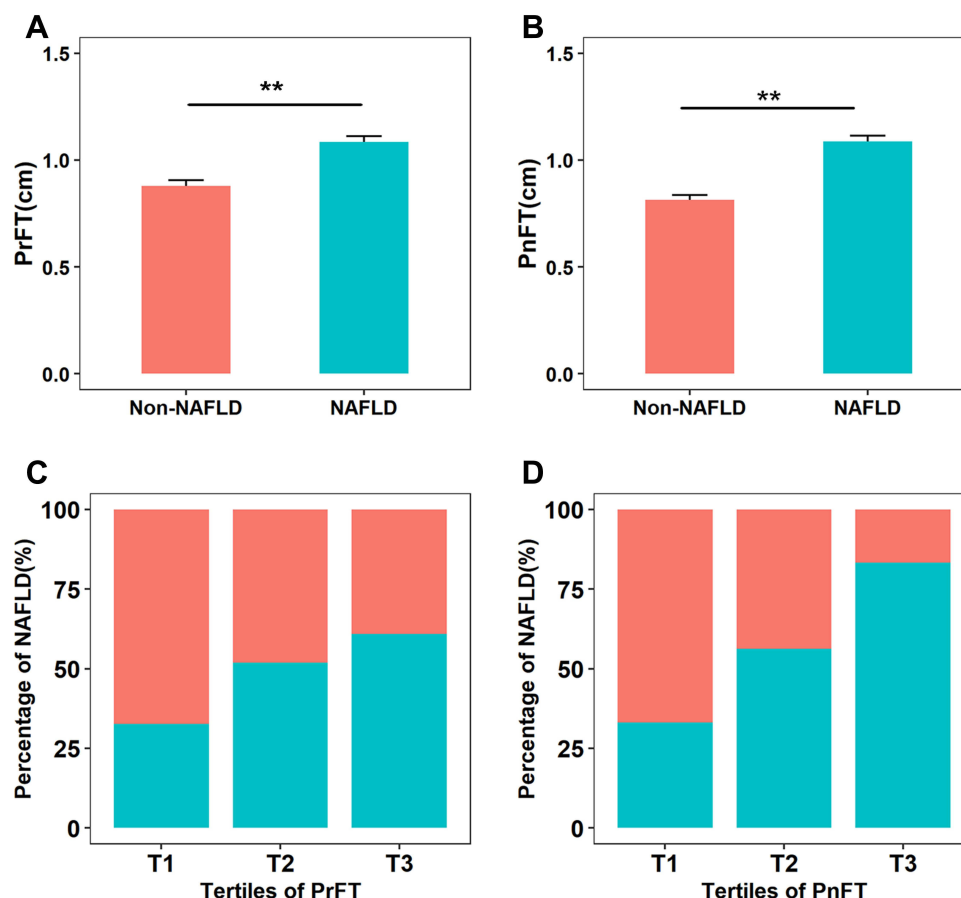


Figure 1 The relationships between perirenal fat thickness and paranephric fat thickness and the presence of NAFLD. **(A)** perirenal fat thickness, **(B)** paranephric fat thickness, **(C and D)** the percentage of patients with NAFLD (bluish-green) in different perirenal fat thickness and paranephric fat thickness ranging from T1 (low) to T3 (high). ** $P < 0.01$.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; PrFT, perirenal fat thickness; PnFT, paranephric fat thickness.

not increase according the tertiles of PrFT ($P = 0.144$, Figure 2C), but increased according the tertiles of PnFT ($P = 0.016$, Figure 2D). Univariable logistic regression demonstrated that age, BMI, waist circumference, DBP, AST, ALT, platelet, FBG, BUN, HDL-c were significantly associated with the severity of NAFLD (Table S2). Subsequently, we conducted multivariate logistic regression to assess the independent effect of PrFT and PnFT on the severity of NAFLD. Our results revealed that higher PrFT and PnFT were significantly associated with high risk of severe NAFLD (OR = 8.42, $P = 0.002$, OR = 8.96, $P = 0.002$, respectively, Table 3) after adjusting age, gender, DBP, HDL-c and FBG.

Table 2 Independent Effect of Perirenal Fat Thickness and Paranephric Fat Thickness on the Presence of NAFLD

	PrFT (cm)		PnFT (cm)	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1	2.94 (1.94–4.52)	< 0.001*	7.59 (4.44–13.39)	< 0.001*
Model 2	3.82 (2.38–6.28)	< 0.001*	7.05 (3.94–13.06)	< 0.001*
Model 3	2.15 (1.15–4.08)	0.017*	2.76 (1.35–5.79)	0.006*

Notes: Model 1: adjusted no factors. Model 2: adjusted for age and gender. Model 3: adjusted for age, gender, body mass index, waist circumference, diastolic blood pressure, drink, triglyceride, total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol and glycosylated hemoglobin. * P values < 0.05.

Abbreviations: PrFT, perirenal fat thickness; PnFT, paranephric fat thickness.

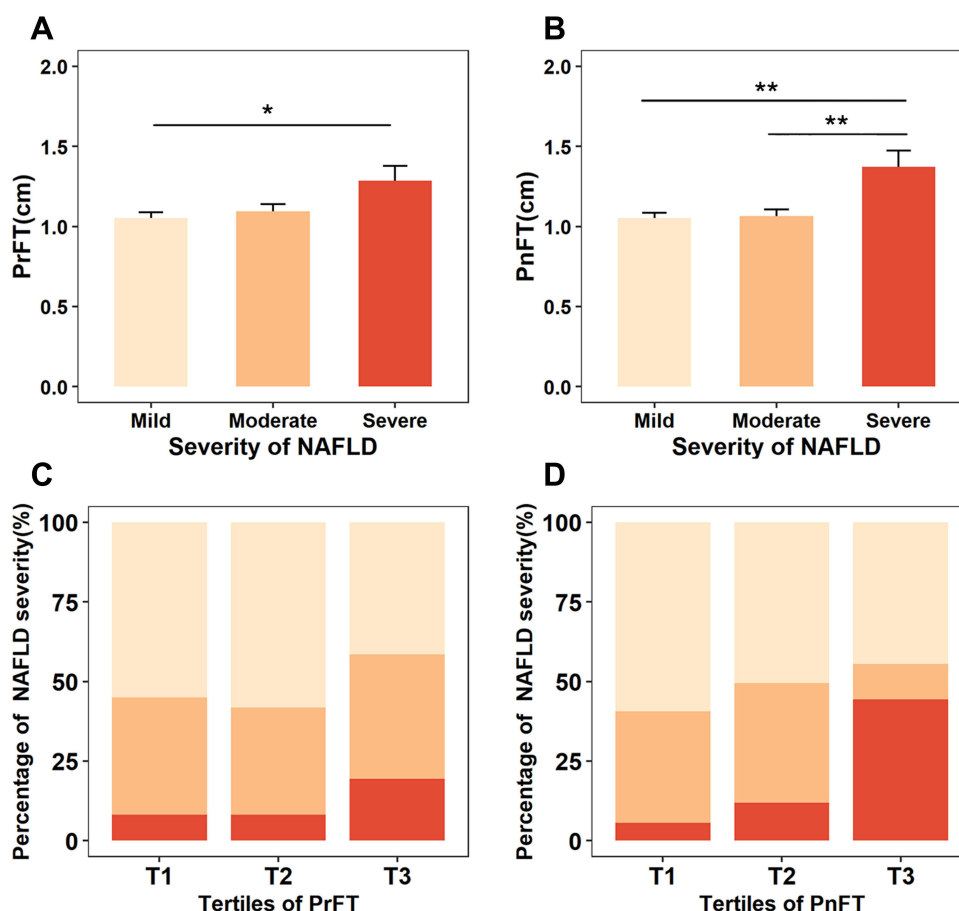


Figure 2 The relationships between perirenal fat thickness and paranephric fat thickness and the severity of NAFLD. (A) perirenal fat thickness, (B) paranephric fat thickness, (C and D) comparisons of the severity of NAFLD among tertiles of perirenal fat thickness and paranephric fat thickness ranging from T1 (low) to T3 (high). * $P < 0.05$, ** $P < 0.01$.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; PrFT, perirenal fat thickness; PnFT, paranephric fat thickness.

However, when further adjusting for obesity parameters such as BMI and waist circumference, both PrFT and PnFT were not associated with high risk of severe NAFLD (OR = 3.60, $P = 0.093$, OR = 3.54, $P = 0.093$, respectively, Table 3).

The Association of PrFT and PnFT with Advanced Fibrosis Risk of NAFLD

To investigate the relationship between PrFT and PnFT and the advanced fibrosis risk of NAFLD. All the NAFLD patients were divided into three subgroups according to the NAFLD fibrosis score (absence of advanced fibrosis, indeterminate of advanced fibrosis, presence of advanced fibrosis). We found that PrFT was positively associated with NAFLD fibrosis score ($r = 0.198$, $P = 0.003$), but the PnFT was not associated with NAFLD fibrosis score ($r = 0.038$, $P = 0.575$). In addition, PrFT was higher in NAFLD patients with advanced fibrosis risk than those without advanced fibrosis risk ($P = 0.022$, Figure 3A). This trend is not obvious about PnFT in NAFLD patients with different fibrosis risk (Figure 3B). However, there is no obvious difference in the percentage of advanced fibrosis risk of NAFLD in the three groups according to the tertiles of PrFT and PnFT ($P = 0.107$ and $P = 0.074$, respectively, Figure 3C and D). Univariate logistic regression found that age, BMI, waist circumference, SBP, DBP, albumin, AST, ALT, platelet, FBG, Cr, BUN, TC, LDL-c, prevalence of hypertension, coronary heart disease and cerebrovascular disease were significantly associated with the advanced fibrosis risk of NAFLD (Table S3). Furthermore, we conducted multivariate logistic regression to assess the independent effect of PrFT and PnFT on the presence of advanced fibrosis risk in NAFLD patients. We revealed that increased PrFT was independently associated with advanced fibrosis risk in NAFLD patients (OR = 9.1, $P = 0.035$, Table 4) after adjusting age, gender, BMI, waist circumference, hypertension, FBG, TC and LDL-c. While the higher PnFT was not independently associated with advanced fibrosis risk in NAFLD patients (OR = 1.85, $P = 0.592$,

Table 3 Independent Effect of Perirenal Fat Thickness and Paranephric Fat Thickness on the Severity of NAFLD

	PrFT (cm)		PnFT (cm)	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1				
Mild	Ref.		Ref.	
Moderate	1.47 (0.75–2.86)	0.258	1.24 (0.59–2.59)	0.569
Severe	3.93 (1.37–11.28)	0.011*	6.72 (2.25–20.02)	< 0.001*
Model 2				
Mild	Ref.		Ref.	
Moderate	1.80 (0.85–3.81)	0.124	1.14 (0.50–2.57)	0.753
Severe	6.60 (1.90–22.86)	0.003*	6.31 (1.83–21.81)	0.004*
Model 3				
Mild	Ref.		Ref.	
Moderate	1.93 (0.66–3.34)	0.093	1.23 (0.53–2.86)	0.628
Severe	8.42 (2.19–32.30)	0.002*	8.96 (2.25–35.61)	0.002*
Model 4				
Mild	Ref.		Ref.	
Moderate	1.39 (0.60–3.19)	0.439	0.75 (0.30–1.89)	0.547
Severe	3.60 (0.81–16.01)	0.093	3.54 (0.81–15.50)	0.093

Notes: Model 1: adjusted no factors. Model 2: adjusted for age and gender. Model 3: adjusted for age, gender, diastolic blood pressure, high density lipoprotein-cholesterol and fasting blood glucose. Model 4: adjusted for age, gender, body mass index, waist circumference, diastolic blood pressure, high density lipoprotein-cholesterol and fasting blood glucose. * P values < 0.05.

Abbreviations: PrFT, perirenal fat thickness; PnFT, paranephric fat thickness.

Table 4) after adjusting age, gender, BMI, waist circumference, hypertension, FBG, TC and LDL-c. We also evaluated the fibrosis risk of NAFLD using the FIB4 score, but the sample of NAFLD patients with high probability of advanced fibrosis is very small. We combined the NAFLD patients with intermediate and high probability of advanced fibrosis into one group named intermediate-high group. There was no independent relationship between PrFT, PnFT and fibrosis risk of NAFLD evaluated by FIB4 score. The univariate and multivariate logistic regression were shown in supplemental materials (Tables S4 and S5).

Discussion

Obesity is a well-known risk factor for development of NAFLD.^{12,13} Increasing evidence indicated that the visceral fat, especially ectopic fat surrounding internal organs, appears to be a more important indicator of metabolic disturbances. However, as part of visceral fat, perirenal fat and paranephric fat were seldom studied in relation to the association with NAFLD and T2DM. The results of the present study show that both the PrFT and PnFT were independently associated with the presence of NAFLD. In addition, PrFT was also independently associated with the advanced fibrosis risk of NAFLD in patients with T2DM.

In our study, we found that NAFLD patients had significantly higher PrFT and PnFT than Non-NAFLD patients, which was consistent with previous study.³⁴ We revealed that both PrFT and PnFT were independently associated with presence of NAFLD after adjusting confounding factors. Similarly, Nicola Vitturi concluded that perirenal fat and paranephric fat were related to the presence of NAFLD after adjusting for age, sex and waist circumference in logistic regression.³⁴ Satsuki Kawasaki investigated the usefulness of para- and perirenal sonographic fat thickness (UFT) for quantitative estimation of fatty liver in patients with T2DM and reported a positive correlation between UFT and fatty liver infiltration.²⁷ Thus, measurement of UFT or PrFT in our study maybe useful methods for the quantification of fatty liver. PrFT and PnFT, surrounding the kidneys, were ectopic fat in the abdominal cavity and parts of visceral fat. A number of studies have explored the relationship between visceral fat and NAFLD. Chan-Hee Jung conducted a cross-sectional study including 7465 Korean adults and reported that high visceral-to-subcutaneous fat ratio values predicted increased risk for NAFLD.²⁰ Chiyanika

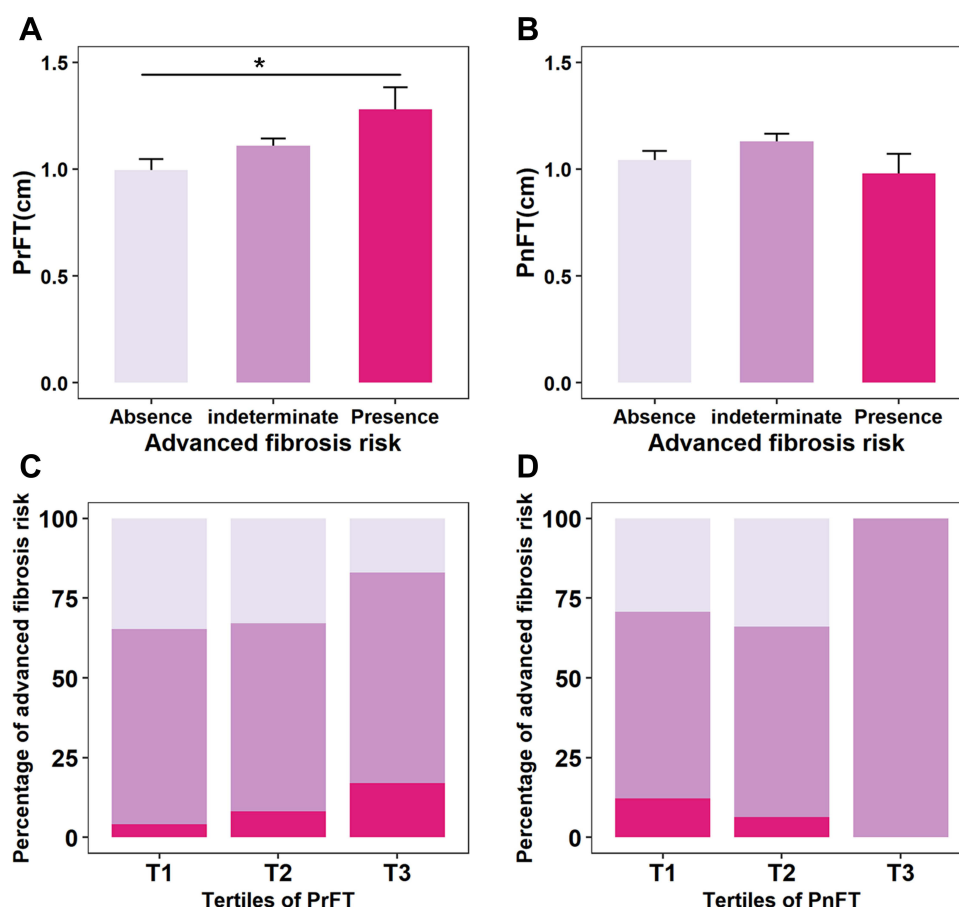


Figure 3 The relationships between perirenal fat thickness and paranephric fat thickness and the fibrosis risk of NAFLD evaluated by NAFLD fibrosis score. **(A)** perirenal fat thickness, **(B)** paranephric fat thickness, **(C and D)** comparisons of the fibrosis risk of NAFLD among tertiles of perirenal fat thickness and paranephric fat thickness ranging from T1 (low) to T3 (high). Absence, absence of advanced fibrosis risk, Indeterminate, indeterminate of advanced fibrosis risk, Presence, presence of advanced fibrosis risk. **P* values < 0.05.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; PrFT, perirenal fat thickness; PnFT, paranephric fat thickness.

C suggested that VAT may be a vital driver of NAFLD based on a prospectively acquired data.¹⁶ Another large cohort study indicated that VAT was longitudinally associated with higher risk of incident NAFLD.¹⁵ In terms of severity of NAFLD, we did not get positive result about PrFT, PnFT and NAFLD. However, previous study has reported that para- and perirenal sonographic fat thickness is positively associated with fatty liver infiltration.²⁷ In our study, although 231 patients with NAFLD, only 23 (10%) NAFLD patients were classified into severe group. The relative low proportion of severe group may partly explain this negative result. Larger sample in the future study is needed and necessary to confirm the results.

Our study also found that the PrFT was independently associated with the advanced fibrosis risk of NAFLD. Previous studies revealed that presence of diabetes, abdominal obesity, increased waist circumferences, higher AST or ALT levels, higher VAT area, and C-peptide levels were independent risk factors associated with liver fibrosis.^{20,35–39} However, a systematic review and meta-analysis study including 13 studies with a total of 11,043 participants concluded that obesity may not be an independent factor for advanced fibrosis in NAFLD patients.⁴⁰ The obesity standard based on BMI in the 13 studies may partly explain this result. Therefore, central or visceral obesity, instead of generalized obesity maybe more closely related to the advanced fibrosis risk of NAFLD.

The mechanisms underlying the association between PrFT or PnFT and the presence, severity and fibrosis risk of NAFLD are not fully studied yet. But, some plausible explanations about visceral fat on NAFLD have been proposed. One main mechanism is that excess visceral fat was prone to lipolysis, resulting in increased free fatty acids and TG accumulation in the liver. All above may activate NF- κ B pathway and increase diacylglycerol (DAG) content in the liver,⁴¹ which induce chronic inflammation, hepatic insulin resistance and hepatic steatosis.^{42,43} Another possible mechanism is that lipid accumulation

Table 4 Independent Effect of Perirenal Fat Thickness and Paranephric Fat Thickness on the Fibrosis Risk of NAFLD Evaluated by NAFLD Fibrosis Score

	PrFT (cm)		PnFT (cm)	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1				
Absence	Ref.		Ref.	
Indeterminate	1.93 (0.94–3.96)	0.072	1.76 (0.82–3.75)	0.146
Presence	5.00 (1.49–16.8)	0.009*	0.63 (0.16–2.47)	0.509
Model 2				
Absence	Ref.		Ref.	
Indeterminate	2.55 (0.88–7.35)	0.083	5.24 (1.6–17.06)	0.006*
Presence	11.76 (2.11–65.63)	0.005*	4.73 (0.63–35.24)	0.129
Model 3				
Absence	Ref.		Ref.	
Indeterminate	1.64 (0.49–5.53)	0.427	3.06 (0.79–11.87)	0.106
Presence	9.10 (1.16–71.15)	0.035*	1.85 (0.20–17.44)	0.592

Notes: Absence, absence of advanced fibrosis risk; Indeterminate, indeterminate of advanced fibrosis risk; Presence, presence of advanced fibrosis risk. Model 1: adjusted no factors. Model 2: adjusted for age and gender. Model 3: adjusted for age, gender, body mass index, waist circumference, hypertension, fasting blood glucose, total cholesterol and low density lipoprotein-cholesterol. *P values < 0.05.

Abbreviations: PrFT, perirenal fat thickness; PnFT, paranephric fat thickness.

leads to adipocytes death and dysfunction, producing more inflammatory adipokines and cytokines, such as interleukin 6 and tumor necrosis factor- α , which promoting NAFLD progression and fibrosis.^{43–45} In summary, insulin resistance, chronic inflammation and lipotoxicity were involved in the pathogenesis of NAFLD progression.^{46–52}

Some limitations existed in this study. First of all, this study was a single center study and sample was relatively small, limiting the generalization of our findings in other population. Larger sample in the future study is needed and necessary. Secondly, this was a cross-sectional study, it is difficult to ascertain a causal relationship between PrFT and PnFT and NAFLD. Further studies are needed to illuminate the mechanism of PrFT and PnFT and NAFLD.

Conclusion

We found that both the PrFT and PnFT were independently associated with the presence of NAFLD after adjusting confounding factors and the PrFT was independently associated with the advanced fibrosis risk of NAFLD after adjusting confounding factors in patients with T2DM. The measure of the PrFT maybe a useful tool to reflect the development and progression of NAFLD in clinical practice.

Data Sharing Statement

Data used to support the findings of this study is available from the Dong Zhao upon request.

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Disclosure

The authors declare that there is no conflict of interest regarding the publication of this article.

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