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Prevalence and factors associated with nonalcoholic fatty pancreas disease and its severity in China

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Abstract

Pancreatic lipidosis (nonalcoholic fatty pancreas disease, NAFPD) causes insulin resistance and dysfunction of pancreatic β-cells, with the risk of type 2 diabetes mellitus (T2DM). However, the prevalence and pathogenic factors associated with NAFPD are not clear. The aim of the study was to explore the prevalence of NAFPD in a Chinese adult population, and investigate factors associated with NAFPD aggravation.

This was a cross-sectional study; 4419 subjects were enrolled for NAFPD screening and were divided into NAFPD (n = 488) and without NAFPD (n = 3930) groups. The sex, age, related concomitant diseases, general physical parameters, and serum glucose and lipid metabolism were compared between the 2 groups.

The overall NAFPD prevalence was 11.05%, but increased with age. In those <55 years NAFPD prevalence was lower in females than males ($P < .05$), but prevalence was similar >55 years. Nonalcoholic fatty liver disease (NAFLD), T2DM, homeostasis model assessment-insulin resistance index, total cholesterol, triglyceride, lipoprotein, adiponectin, and glucagon-like peptide 1 (GLP-1) were the independent risk factors for NAFPD ($P < .05$). Analaysis of mild NAFPD (MN) and severe NAFPD (SN) subgroups, according to the extent of fat deposition, suggested that NAFLD, triglyceride, lipoprotein, and adiponectin were independent risk factors for NAFPD aggravation ($P < .05$).

The NAFPD prevalence was about 11% in Chinese adults. Its development and progression was related to NAFLD, T2DM, insulin resistance, dyslipidemia, and GLP-1 levels. Severe NAFPD was associated with NAFLD and dyslipidemia.

Abbreviations: AUC = area under curve, BMI = body mass index, DM = diabetes mellitus, ELISA = enzyme-linked immunosorbent assay, GLP-1 = glucagon-like peptide 1, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment-insulin residence, IDF = International Diabetes Federation, IGR = impaired glucose regulation, LDL = low-density lipoprotein, MN = mild NAFPD, NAFLD = nonalcoholic fatty liver disease, NAFPD = nonalcoholic fatty pancreas disease, PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase, PPARα = peroxisome proliferator-activated receptor α, ROC = receiver-operating characteristic, SN = severe NAFPD, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglyceride.

Keywords: dyslipidemia, nonalcoholic fatty pancreas disease, type 2 diabetes mellitus

1. Introduction

Globally, diabetes mellitus (DM) is the third most common noncommunicable disease, after cardiovascular diseases and cancer. The World Health Organization (WHO) showed that there were 371 million DM patients in the world in 2012.[1] Changes in dietary patterns and lifestyles have made diabetes one of the major public health problems in China.[2] Pancreatic β-cell dysfunction and insulin resistance are 2 key links in the pathogenesis of diabetes, and their occurrence is closely related to the ectopic deposition of pancreatic lipids.[3–5] Pancreatic fat ectopic deposition disease, also known as nonalcoholic fatty pancreas disease (NAFPD), is a disease characterized by pancreatic fat infiltration or pancreatic islet cell steatosis. NAFPD is an independent risk factor for the pathogenesis of type 2 diabetes mellitus (T2DM) and impaired glucose regulation (IGR). But its etiology has not yet been determined. Animal and clinical studies have shown that a high-fat diet could cause NAFPD, resulting in impaired β-cell function, decreased insulin secretion, insulin resistance, and abnormal adipokine secretion.[3,6–8] Also, patients with NAFPD have an increased risk of developing T2DM.[9–11]

Studies concerning NAFPD, so far, have investigated different stages of glucose metabolism (prediabetes and diabetes) to find associations between the diseases.[9–11] But the severity of

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pancreatic fat deposition had not been studied. Therefore, this study explored the prevalence of NAFPD, and factors related to NAFPD and its severity in a Chinese population. We measured general characteristics, diseases, indicators of glucose and lipid metabolism, adipokines, inflammatory factors, and glucagon-like peptide-1 (GLP-1) levels in the population and measured the level of pancreatic fat deposition, attempting to find any relationship between them.

2. Methods

2.1. Patients

This study was a cross-sectional study from January 2015 to October 2017 in Ningbo Chinese Medical Hospital Affiliated to Zhejiang Chinese Medical University (Ningbo Chinese Medical Hospital). This study followed all applicable ethical rules and was approved by the Ethics Committee of Ningbo Chinese Medical Hospital. All subjects signed the informed consent form.

The inclusion criterium for the study was any adult (>18 years old) who attended the Ningbo Chinese Medical Hospital Affiliated to Zhejiang Chinese Medical University for medical examination or an outpatient visit who had responded to an advertisement from January 2015 to October 2017.

The exclusion criteria were as follows: pancreatic exocrine diseases, pancreatic lesions, and other pancreatic diseases; heavy drinkers, defined as drinking >280 g alcohol/wk for men and >140 g/wk for women;[10] patients using lipid-lowering drugs, such as statins and fibrates,[12–14] and patients using antidiabetic drugs that affect serum adipocytokine or endogenous GLP-1 levels, such as metformin, thiazolidinediones, GLP-1 receptor agonists and dipeptidyl peptidase 4 (DPP4) inhibitors; patients with various conditions such as infection, trauma, serious bleeding, severe brain, and kidney complications; and patients with a variety of acute complications of diabetes such as diabetic ketosis, hypertonic diabetic coma, other diabetic comorbidities (such as cancer, disease of immune system, or hematologic system). (5) Pregnant or lactating, menstrual women.

2.2. Diagnostic criteria

All the ultrasound data were jointly collected by 2 qualified and experienced ultrasound physicians. A high-resolution ultrasound (LOGIQ7, GE Healthcare, USA) and 3.5 MHz linear sensor were used.

2.3. NAFPD

The criteria for diagnosis of NAFPD were based on the literature:[15] the parenchymal echogenicity of the pancreas was compared with the spleen as a control. NAFPD was diagnosed if the pancreas showed a plump morphorlogy, with increased volume and fuzzy edges. The echogenicity for the head, body, and tail of the pancreas were similar and stronger than that of the spleen. The area of enhanced echogenicity was >80%, and pancreatic fibrosis was excluded. The 2 grades of NAFPD were as follows: mild—parenchymal echogenicity of the pancreas was moderately to extremely enhanced; the margin of the pancreatic body was moderately fuzzy; and the border of the pancreatic ducts were moderately fuzzy. Severe—parenchymal echogenicity of the pancreas was extremely enhanced; the margin of the pancreatic body was extremely fuzzy; and the border of the pancreatic ducts were extremely fuzzy.

2.4. NAFLD

The diagnosis of NAFLD was according to the 2007 Asia-Pacific guidelines on NAFLD:[16] Two or more of the following abnormal findings were diagnosed as fatty liver: the local echogenicity of the liver was increased and the distant echogenicity was decreased. The parenchymal echogenicity of the liver was dense, and stronger than that of the kidney. Intrahepatic vessels and biliary structures were unclear.

2.5. T2DM

The American Diabetes Association standards (2010) were adopted for diagnosis of T2DM:[17] fasting plasma glucose (FPG) ≥7.0 mmol/L, plasma glucose of 2 hours post glucose-load (2 hPG) ≥11.1 mmol/L.

2.6. Hypertension

Hypertension was diagnosed according to the 2010 Chinese guidelines for the management of hypertension,[18] if the systolic pressure was ≥140 mm Hg and (or) diastolic pressure was ≥90 mm Hg at the time of visit without taking any antihypertensive drugs.

2.7. Overweight and obestiy

The 2009 International Diabetes Federation (IDF) standard was used for diagnosis of obesity [19] and central obesity.[20] The body mass index (BMI) was calculated as body weight (kg) × height $(m)^{-219}$ and overweight was defined as 25 $kg/m^2 \leq$ BMI <28 kg/m^2, obesity was defined as BMI ≥28 kg/m^2. Central obesity was defined as Chinese men with a waist ≥85 cm, or women with a waist ≥80 cm.

2.8. Clinical data collection

The patients' sex and age were recorded. Their height and weight were measured at fasting state by 2 independent specialists in the physical examination center and the mean value was adopted. Regular physical exercise was recorded if undertaken ≥3 times/wk. Current smoking was defined as at least 1 pack per month, for half a year.

2.9. Laboratory data collection

Four milliliters of fasting blood were collected after 12 hours of fasting from the enrolled subjects, and the serum was obtained. The total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting blood glucose (FBG) were determined by an automatic biochemical analyzer (AU5400, Olympus, USA). An enzyme-linked immunosorbent assay (ELISA) was used to measure the fasting serum C-peptide (DRG, EIA1293), serum leptin (LP, R&D MAB398, BAM398), adiponectin (APN, R&D MAB10651, BAM1065), tumor necrosis factor-α (TNF-α, R&D MAB610, BAF210), and fasting active GLP-1 level (abcam ab23472, ab48291).

Two milliliters of blood was taken and the glycosylated hemoglobin (HbA1c) [21] was determined by affinity chromatography microcolumn assay.

The homeostasis model assessment-insulin residence (HOMA-IR) index [22] was calculated according to the value of FBG and fasting C peptide levels using the HOMA2 calculator 2.2.3

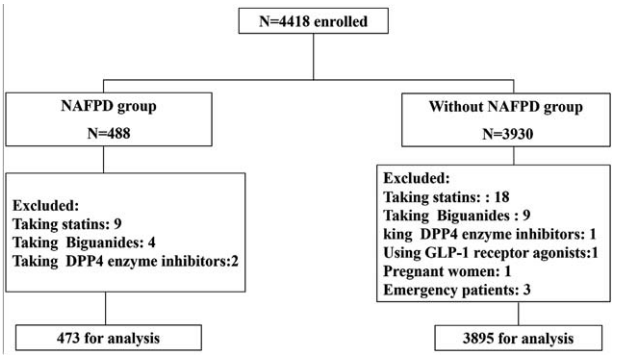

Figure 1. Flow chart of the enrolled patients.

version (provided by the Diabetes Center at Oxford University, UK).

2.10. Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBM Corporation, Armonk, NY). Normality of distribution was evaluated using the Kolmogorov–Smirnov test. Variables with a normal distribution were compared using analysis of variance (ANOVA) and post hoc testing, and values are presented as means ± standard deviation. For variables with an abnormal distribution, the *Kruskal–Wallis* test was used for comparisons, and values are presented as medians (interquartile range). Categorical variables are presented as frequencies and were analyzed using the χ^2 or Fisher exact test, as appropriate. Logistic regression analysis was used for univariate analysis. The variants of $\alpha = 0.05$ were entered into the equation, and the variants of $\alpha = 0.1$ were eliminated. Two-sided P values $\leq .05$ were considered to be statistically significant.

3. Results

3.1. Prevalence of NAFPD

There were 4418 subjects enrolled on the study. A total of 488 NAFPD cases were diagnosed, and 3930 subjects were without NAFPD. This was a detection rate of 11.05%. After excluding various patients from the analysis, 473 subjects were in the NAFPD group and 3895 in the without NAFPD group as shown in the flow chart (Fig. 1).

Overall, 2287 subjects were male, and 2131 subjects were female, with a male/female ratio of 1.07:1. Among them, 1433 cases were <45 years, and 1492 cases were 45 to 54 years old; the number of males in these 2 age groups was higher than females ($P < .05$), 1493 cases were >54 years old, there was no significant difference between males and females in this age group ($P > .05$), as shown in Table 1. The 488 subjects with NAFPD included 277 males and 211 females. The prevalence in males was higher than that of females ($P < .05$). When analyzed as different age groups, we found that under 55 years, the prevalence of NAFPD was higher in males than females, but the prevalence in females increased after 55 years, so above 55 years there was no significant difference in prevalence between the 2 sexes.

The age of the subjects ranged from 35 to 66 years, and the average age of the NAFPD patients was 49.51 ± 9.15 years, the average age of without NAFPD subjects was 47.21 ± 6.93 years, the average age of the NAFPD patients was higher than the without NAFPD subjects, and the difference was statistically significant ($t = -5.300$, $P < .001$). The prevalence of NAFPD was 7.61% (109/1433) in the group <45 years, 10.19% (152/1492) in the group 45 to 54 years old, and 15.20% (227/1493) in the group >54 years, indicating that the prevalence of NAFPD increased with increasing age of the subjects, as shown in Figure 2A

The rates of T2DM and NAFLD were both higher in NAFPD patients than in without NAFPD subjects, and the differences were statistically significant ($P < .05$). There were 393 cases (80.8%) with mild pancreatic fat deposits and 95 cases (19.2%) with severe pancreatic fat deposits in NAFPD patients, which were subdivided into mild NAFPD group (MN) and severe NAFPD group (SN). The rates of T2DM and NAFLD in the MN group were lower than in the SN group, and the differences was statistically significant ($P < .05$), as shown in Table 1 and Figure 2B–C.

3.2. Analysis of general body index, serum glucose metabolism index, and lipid metabolism index in NAFPD patients

Fifteen subjects were excluded from the 488 cases diagnosed with NAFPD for factors that may have influenced the serum measurements, including 9 subjects using statins, 4 subjects using biguanides, and 2 subjects using DPP4 inhibitors, so a total of 473 NAFPD patients participated in the statistical analysis. Among the without NAFPD group, 33 subjects were excluded (including 18 subjects using statins, 9 subjects using biguanides, 1

Table 1

Comparison of NAFPD prevalence in males and female of different ages and with different concomitant diseases.

Grouping		Detection [%(NAFPD/SU)]					
		Male	Female	χ^2	*P*	OR	95% CI
Age group	Total	12.11 (277/2287)	9.90 (211/2131)	5.486	.021	1.254	1.037–1.516
	<45 y old	9.22 (65/705)	6.04 (44/728)	5.140	.028	1.579	1.061–2.350
	45–54 y old	12.20 (97/795)	8.61 (60/697)	5.092	.028	1.475	1.051–2.071
	>54 y old	14.61 (115/787)	15.16 (107/706)	0.094	.771	0.956	0.719–1.272
		NAFPD	NO-NAFPD				
Concomitant disease	T2DM	44.47 (217/488)	8.68 (341/3930)	503.905	<.001	8.428	6.830–10.400
	NAFLD	63.93 (312/488)	21.04 (827/3930)	417.368	<.001	6.651	5.445–8.125
		MN	SN				
	T2DM	39.69 (156/393)	56.84 (54/95)	9.176	.003	1.432	1.157–1.773
	NAFLD	60.56 (238/393)	90.53 (86/95)	30.791	<.001	1.495	1.349–1.657

NAFLD = nonalcoholic fatty liver disease, NAFPD = nonalcoholic fatty pancreas disease, T2DM = type 2 diabetes mellitus.

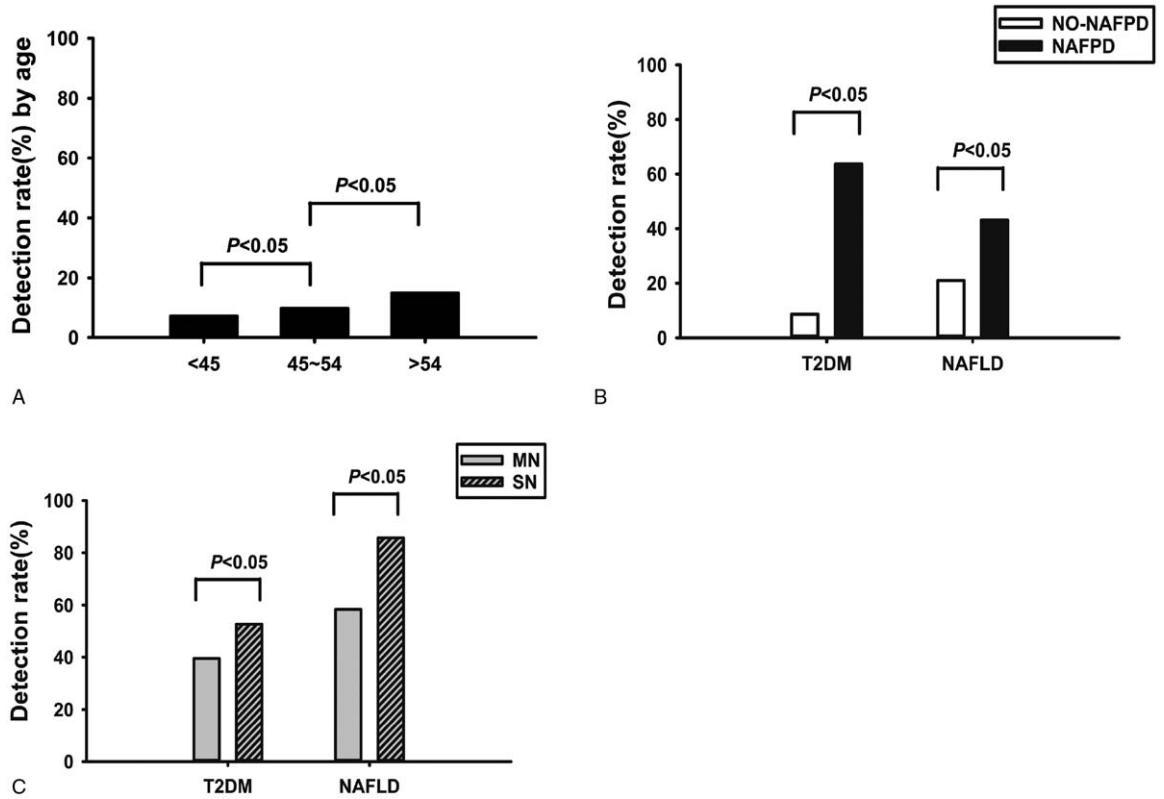

Figure 2. Comparison of NAFPD diagnoses between different age groups (A); the prevalence of T2DM and NAFLD in the 2 different groups (B); and in the mild NAFLD (MN) and severe NAFLD (SN) subgroups (C).

Table 2

Comparison of general conditions and laboratory indexes between the 2 groups.

	Without NAFPD (n = 3895)	NAFPD (n = 473)	*P*
Age	47.91 ± 8.10	49.16 ± 8.12	.002
Sex (male, n, %)	1992, 51.14%	271, 57.3%	.011
BMI, kg/m^2	23.12 ± 1.85	24.93 ± 2.83	<.001
HOMA-IR	1.24 ± 0.50	1.76 ± 0.70	<.001
HbA1c, %	5.59 ± 1.44	6.86 ± 1.72	<.001
TG, mmol/L	1.51 ± 0.54	1.94 ± 0.91	<.001
TC, mmol/L	4.27 ± 0.92	4.90 ± 0.97	<.001
HDL, mmol/L	1.31 ± 0.26	1.29 ± 0.29	.166
LDL, mmol/L	2.43 ± 0.67	2.45 ± 0.76	.530
APN, μg/mL	14.16 ± 6.06	9.62 ± 4.61	<.001
LP, ng/mL	13.76 ± 6.23	20.31 ± 9.83	<.001
GLP-1, pmol/mL	13.32 ± 5.95	8.76 ± 4.65	<.001
TNF-α, ng/mL	14.48 ± 6.09	14.46 ± 6.03	.958
NAFLD, %	815, 20.92%	301, 63.64%	<.001
T2DM, %	318, 8.16%	199, 42.07%	<.001
Hypertension, %	680, 17.46%	91, 19.24%	.337
Overweight and obestiy, %	503, 12.91%	235, 49.68%	<.001
Central obesity, %	728, 18.69%	248, 52.43%	<.001
Regular physical exercise (≥3 times/wk), %	997, 25.60%	103, 21.78%	.071
Current smoking, %	885, 22.72%	110, 23.26%	.794

APN = adiponectin, BMI = body mass index, GLP = glucagon-like peptide, HbA1c = hemoglobin A1C, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assement-insulin residence, LDL = low density lipoprotein, LP = leptin, NAFLD = nonalcoholic fattly liver disease, NAFPD = nonalcoholic fatty pancreas disease, T2DM = type 2 diabetes mellitus, TG = triglyceride, TNF = tumor necrosis factor.

subject using DPP4 inhibitor, 1 subject using GLP-1 receptor agonist, 1 pregnant woman, and 3 emergency patients), so a total of 3895 without NAFPD subjects participated in the statistical analysis. There were 271 males and 202 females in the NAFPD group, and 1992 males and 1905 females in the without NAFPD group.

Univariate analysis found that the age, BMI, HOMA-IR, levels of TC, TG, and LP in the NAFPD group were higher than in the without NAFPD group, whereas the levels of APN and GLP-1 were lower than those in the without NAFPD group, and the difference was statistically significant ($P < .05$). Age and levels of HDL, LDL, and TNF-α were not significantly different from those in the without NAFPD group ($P > .05$), as shown in Table 2.

3.3. Factors related to the pathogenesis of NAFPD

With NAFPD as the dependent variable (NAFPD = 1, without NAFPD = 0), 12 indicators had statistically significant differences between the NAFPD group and without NAFPD group including age, sex, and others as independent variables. After assignment of count data: sex (male = 1, female = 0), occurrence of NAFLD (yes = 1, no = 0), occurrence of T2DM (yes = 1, no = 0), both binary logistic regression analysis and multivariate logistic regression analysis were carried out. The results showed that sex, concomitant NAFLD, concomitant T2DM, HOMA-IR, TC, TG, APN, LP, and GLP-1 entered the regression equation, sex (male), occurrence of NAFLD, occurrence of T2DM, HOMA-IR, TC, TG, and LP were positively correlated with NAFPD ($P < .05$, OR >1), and APN was negatively correlated with NAFPD ($P < .05$, OR <1), as shown in Table 3. This indicated that males with NAFLD or T2DM, elevated HOMA-IR index, elevated serum

Table 3

Logistic regression analysis for risk factors of NAFPD.

	Binary logistic regression			Multivariate logistic regression			ROC curve analysis		
	OR	95% CI	*P*	OR	95% CI	*P*	AUC	Sensitivity	Specificity
Age	1.006	0.991–1.021	.455	0.994	0.979–1.010	.455	—	—	—
Sex	1.362	1.050–1.765	.020	0.734	0.566–0.952	.020	—	—	—
NAFLD	2.784	2.120–3.656	<.001	0.359	0.274–0.472	<.001	—	—	—
T2DM	3.662	2.700–4.983	<.001	0.273	0.201–0.370	<.001	—	—	—
Overweight and obestiy	2.584	1.798–3.714	<.001	0.690	0.504–0.943	.020	—	—	—
Central obesity	1.450	1.060–1.983	.020	0.387	0.269–0.556	<.001	—	—	—
BMI	1.037	0.954–1.127	.392	0.964	0.887–1.048	.392	—	—	—
HOMA-IR	1.259	1.009–1.570	.041	0.794	0.637–0.991	.041	0.753	0.829	0.598
HbA1c	0.993	0.910–1.084	.876	1.007	0.922–1.099	.876	—	—	—
TG	1.359	1.142–1.616	.001	0.736	0.619–0.876	<.001	0.631	0.425	0.875
TC	1.281	1.117–1.469	<.001	0.781	0.681–0.896	<0.001	0.691	0.662	0.702
APN	0.864	0.841–0.887	<.001	1.158	1.127–1.190	<0.001	0.729	0.552	0.776
LP	1.097	1.080–1.114	<.001	0.912	0.897–0.926	<.001	0.703	0.499	0.917
GLP-1	0.885	0.863–0.908	<.001	1.130	1.101–1.159	<.001	0.739	0.751	0.682

APN = adiponectin, BMI = body mass index, GLP = glucagon-like peptide, HbA1c = hemoglobin A1C, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assement-insulin residence, LDL = low density lipoprotein, LP = leptin, NAFLD = nonalcoholic fattly liver disease, NAFPD = nonalcoholic fatty pancreas disease, T2DM = type 2 diabetes mellitus, TG = triglyceride, TNF = tumor necrosis factor.

levels of TC, TG, LP, and decreased serum levels of APN and GLP-1 were independent risk factors for the pathogenesis of NAFPD.

3.4. Reciever-operating characteristic (ROC) curve analysis of APN, LP, and TG in NAFPD patients

The ROC curves of APN, LP, and TG levels in NAFPD and without NAFPD groups are shown in Figure 3, the area under curve (AUC), sensitivity, and specificity are shown in Table 3. The AUC of HOMA-IR, APN, LP, and GLP-1 were all >0.7 ($P < .05$), indicating that these 4 indicators were discriminative to the occurrence of NAFPD. The AUC of TG and TC were both <0.7 ($P < .05$), and their discriminative power was not within the acceptable range.

3.5. Analysis of indicators of NAFPD with different degrees of pancreatic fat deposition

The NAFPD patients were divided into 2 subgroups according to the extent of pancreatic fat deposition, namely, the MN group and the SN group. There were 224 males and 158 females in the MN group, and 47 males and 44 females in the SN group; there was no significant difference in sex between the 2 groups ($\chi^2 = 1.468$, $P = .240$). Independent samples *T* tests were performed on relevant factors, and the results showed that levels of BMI, HOMA-IR, HbA1c, TG, and LP in the SN group were higher than those in the MN group, and the levels of APN and GLP-1 were lower than those in the MN group, and the difference was statistically significant ($P < .05$). There was no significant difference in age, TC, HDL, LDL, and TNF-α level between both groups ($P > .05$), as shown in Table 4.

With the extent of NAFPD as a dependent variable (MN = 1, SN = 2), binary logistic regression analysis and multiple logistic regressions were carried out with 8 indicators that had statistically significant differences between the 2 groups such as NAFLD, T2DM, and BMI as dependent variables. Among them, NAFLD, central obesity, and TG were positively correlated with the severity of NAFLD ($P < .05$, OR >1), and the level of APN was negatively correlated with the severity of NAFPD ($P < .05$, OR < 1), as shown in Table 5. This indicated that the

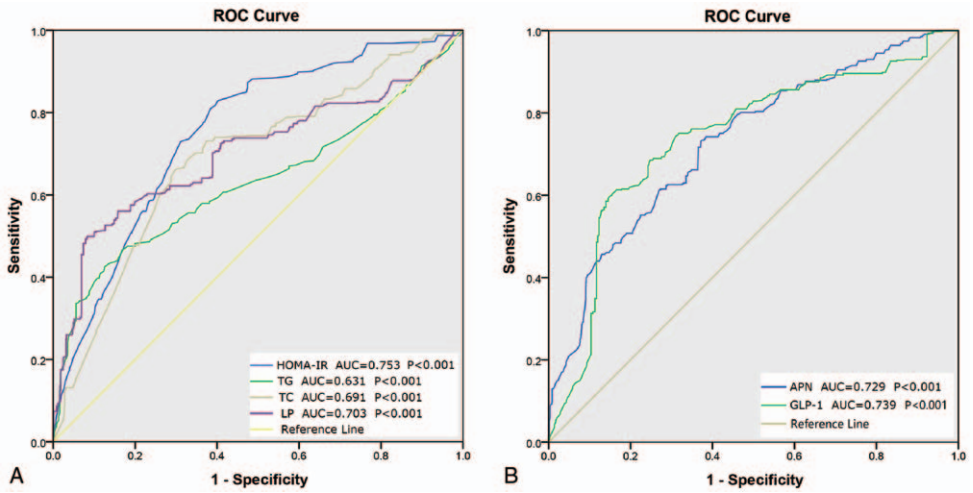

Figure 3. Receiver-operating characteristic (ROC) curve for HOMA-IR, TG, TC, and LP (A) ROC curve for APN and GLP-1 (B).

Table 4

Comparison of general conditions and laboratory indexes of NAFPD patients with different extents of pancreatic fat deposition (*mean ± SD*).

	MN (n = 382)	SN (n = 91)	*P*
Age	49.04 ± 7.92	49.64 ± 8.93	.532
Gender (male, n, %)	224, 58.64%	47, 51.65%	.240
BMI, kg/m^2	24.56 ± 2.61	26.48 ± 3.17	<.001
HOMA-IR	1.70 ± 0.67	2.02 ± 0.79	<.001
HbA1c, %	6.76 ± 1.65	7.27 ± 1.92	.023
TG, mmol/L	1.84 ± 0.86	2.34 ± 1.01	<.001
TC, mmol/L	4.88 ± 0.96	5.03 ± 1.04	.189
HDL, mmol/L	1.29 ± 0.27	1.31 ± 0.33	.507
LDL, mmol/L	2.44 ± 0.76	2.50 ± 0.76	.520
APN, μg/mL	10.05 ± 4.79	7.79 ± 3.23	<.001
LP, ng/mL	19.44 ± 9.69	23.94 ± 11.45	<.001
GLP-1, pmol/mL	8.93 ± 4.77	8.08 ± 4.09	.086
TNF-α, ng/mL	14.53 ± 6.12	14.19 ± 5.68	.627
NAFLD, %	223, 58.38%	78, 85.71%	<.001
T2DM, %	151, 39.53%	48, 52.75%	.022
Hypertension, %	71, 18.59%	20, 21.98%	.461
Overweight and obestiy, %	174, 45.55%	61, 67.03%	<.001
Central obesity, %	163, 42.67%	85, 93.41%	<.001
Regular physical exercise (≥3 times/wk), %	87, 22.77%	23, 25.27%	.612
Current smoking, %	86, 22.51%	17, 18.68%	.426

APN = adiponectin, BMI = body mass index, GLP = glucagon-like peptide, HbA1c = hemoglobin A1C, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assement-insulin residence, LDL = low density lipoprotein, LP = leptin, MN = mild NAFPD, NAFLD = nonalcoholic fattly liver disease, NAFPD = nonalcoholic fatty pancreas disease, SN = severe NAFPD, T2DM = type 2 diabetes mellitus, TG = triglyceride, TNF = tumor necrosis factor.

presence of NAFLD, central obesity, elevated TG levels, and decreased APN levels were independent risk factors for NAFPD exacerbation. ROC curves of APN, LP, and TG values of the MN group and SN group are shown in Figure 4, and the AUC, sensitivity and specificity of the 2 groups are shown in Table 5, the AUC of TG and APN were both <0.7 ($P < .05$), and the discrimination was not within the acceptable range.

4. Discussion

The aim of this study was to investigate the prevalence of NAFPD in a Chinese population and to explore factors associated with the risk of NAFPD. The results showed that the overall prevalence of NAFPD was 11%. The prevalence of NAFPD was higher overall in males than in females, but although the prevalence was higher in males in subjects <55 years of age, there was no difference between males and females after 55 years. NAFLD, T2DM, HOMA-IR index, TC, TG, LP, APN, and GLP-1 were independent risk factors for NAFPD. Also, NAFLD, TG, LP, and APN were independent risk factors for NAFPD aggravation.

The result of this study showed a clear sex difference in NAFPD prevalence in subjects <55 years that was lost as the subjects aged. We speculated that this might be related to the role of estrogen in energy regulation and lipid metabolism. Dysfunction of lipid metabolism, caused by decreased estrogen in postmenopausal women, might be the reason of the significant increase in the prevalence of NAFPD in women after 55 years of age.[19] Other studies have also shown that sex differences were associated with the onset of NAFPD.[9,23] Among 4418 subjects, the average age of NAFPD patients was higher than without NAFPD subjects, and the prevalence of NAFPD increased with age. We inferred that this might be related to lipid metabolism dysfunction being aggravated by age-related slowing of metabolism and aggravation of ectopic fat deposition caused by prolonged dyslipidemia. Ectopic fat deposition is likely to be due to excessive TG-induced supersaturated fat storage of cells, preadipocyte differentiation, abnormal lipid synthesis, and degradation in mature adipocytes and the decreased lipid storage capacity of cells, which causes TG to deposit in nonfatty tissues and induce insulin resistance (IR).[24] Lipids are less harmful to health if they are deposited subcutaneously and in other parts of the body.[25,26] An epidemiological study in Asians showed that a simple increase in BMI did not increase the risk of T2DM without NAFLD and IR.[27] So, it could be concluded that the damage caused by obesity to the body occurs mostly in the presence of ectopic fat deposition, which is often accompanied by the appearance of IR. This study showed that T2DM and NAFLD rates were higher in NAFPD patients than those without NAFPD, and the T2DM and NAFLD rates in severe NAFPD patients were higher than in mild NAFPD patients. Thus, it can be seen that aggravation of pancreatic fat deposition is related to increased abnormal glucose metabolism and liver fat deposition. This was consistent with the conclusion of similar studies[4,5] that NAFPD was an independent risk factor for the onset of T2DM. According to the prevalence of NAFLD, we could infer that ectopic lipid deposition caused by abnormal lipid metabolism usually co-occurred in multiple organs, suggesting that IR caused by ectopic fat deposition in multiple organs might lead to further aggravation of glucose metabolic disorder.

Table 5

Logistic regression analysis of related factors of NAFPD with different extent of pancreatic fat deposition.

	Binary logistic regression			Multivariate logistic regression			ROC curve analysis		
	OR	95% CI	*P*	OR	95% CI	*P*	AUC	Sensitivity	Specificity
NAFLD	3.776	1.864–7.659	<.001	0.265	0.131–0.537	<.001	—	—	—
T2DM	1.445	0.779–2.680	.242	0.692	0.373–1.283	.242	—	—	—
Central obesity	17.220	6.606–44.888	<.001	0.058	0.022–0.151	<.001			
Overweight and obestiy	0.614	0.293–1.285	.196	1.629	0.778–3.409	.196	—	—	—
BMI	1.074	0.937–1.230	.305	0.931	0.813–1.067	.305	—	—	—
HOMA-IR	1.008	0.670–1.517	.969	0.992	0.659–1.493	.969	—	—	—
HbA1c	1.023	0.856–1.222	.805	0.978	0.818–1.169	.805	—	—	—
TG	1.483	1.091–2.016	.012	0.674	0.496–0.917	.012	0.657	0.725	0.547
APN	0.876	0.817–0.939	<.001	1.142	1.065–1.224	<.001	0.637	0.879	0.408
LP	1.028	0.998–1.058	.068	0.973	0.945–1.002	.068	—	—	—

APN = adiponectin, BMI = body mass index, HbA1c = hemoglobin A1C, HOMA-IR = homeostasis model assement-insulin residence, LP = leptin, NAFLD = nonalcoholic fattly liver disease, NAFPD = nonalcoholic fatty pancreas disease, T2DM = type 2 diabetes mellitus, TG = triglyceride.

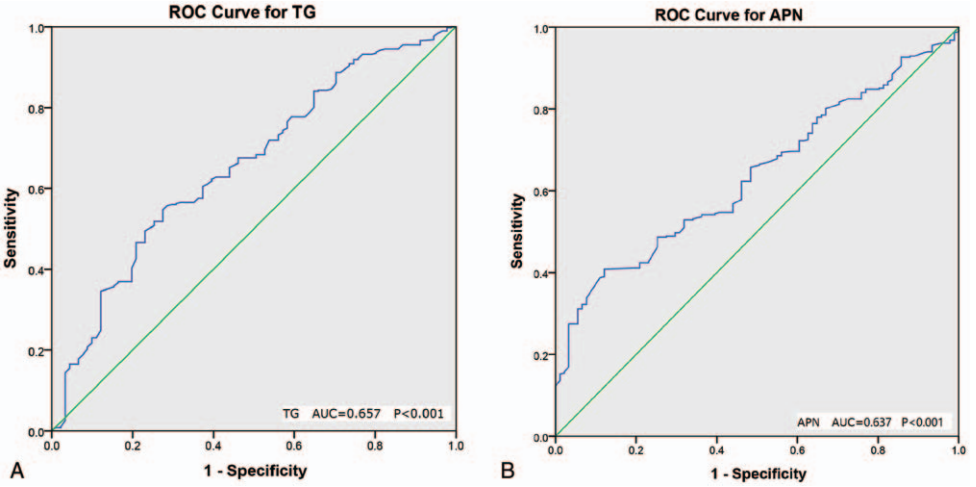

Figure 4. Receiver-operating characteristic (ROC) curve for severity of NAFPD and TG (A) or APN (B).

We found that patients with NAFPD also had increased insulin resistance, increased obesity (especially central obesity), serum lipid metabolism disorders and decreased GLP-1. With more severe NAFPD, the occurrence of central obesity and lipid metabolism disorder were further increased. So, male gender, NAFLD, T2DM, overweight and obestiy, increased central obesity, increased levels of HOMA-IR, TG, TC, LP, and decreased levels of APN and GLP-1 were independent risk factors for NAFPD. At the same time, NAFLD, increased central obesity, increased TG levels, and decreased APN levels were also independent risk factors for exacerbation of NAFPD. ROC curve analysis showed that HOMA-IR, APN, LP, and GLP-1 were all able to predict the onset of NAFPD, of these HOMA-IR had the highest sensitivity (0.829) and LP had the highest specificity (0.917). The results of this study on serum TG were similar to the results of Lee et al,[7] indicating that high serum TG was an important cause of NAFPD. APN and LP are adipokines that are closely related to IR. APN has an anti-inflammatory effect and was found to be decreased in the serum of obese and T2DM populations, and negatively correlated with IR index,[4] whereas LP is highly expressed in serum and adipose tissue of obese populations, and positively correlated with the increase in volume and number of adipocytes.[28] LP resistance induced by increased LP could cause a decrease in the effect of LP and then lead to enhancement of lipid esterification, which is an important mechanism of ectopic fat deposition. This study found that decreased APN and increased LP were independent risk factors for the onset of NAFPD and exacerbation of NAFPD, which were consistent with the results of similar studies, which further suggested that lipid metabolism disorder and abnormal secretion of adipokines are the basis of the pathogenesis of NAFPD, as well as an important factor that leads to IR and T2DM.

We also found that there was a decrease in serum GLP-1 levels in NAFPD patients compared with normal subjects. GLP-1 is a polypeptide hormone secreted by L cells in the terminal ileum and colon, that can promote insulin secretion through the incretin effect,[29] and can also increase the sensitivity of peripheral tissues to insulin by activating the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway or activating peroxisome proliferator-activated receptor α (PPARα) to reduce the synthesis of apolipoprotein CIII and then improve lipid metabolism,[30] which is closely related to glucose metabolism and lipid metabolism. The incretin effect is decreased in diabetic patients, and one study found that an obese population also had decreased incretin effect,[31,32] but whether this is related to the decrease of endogenous GLP-1 secretion in obese populations, remains in debate.[33,34] This study found that the fasting endogenous GLP-1 (7–37) levels in the NAFPD population was significantly lower than that in the healthy population, and GLP-1 was an independent risk factor for NAFPD. Therefore, we concluded that the decreased endogenous GLP-1 might be more prevalent in populations with ectopic fat deposition than in those with simple obesity. The inconsistent results in previous studies on obese populations might be because ectopic fat deposition was not considered, and data was included from studies of obese populations without ectopic fat deposition.

This study has some limitations. This was a single center study and did not use random sampling based on residents, so these results may not be applicable for the population as a whole. This means the prevalence of the study is potentially higher than actual. As a cross-sectional study, this study could only investigate the prevalence of NAFPD and suggest risk factors; the causal relationship between NAFPD and the risk factors could not be established. The population of subjects without NAFPD would have to be followed-up for a long time to investigate the incidence of NAFPD and the true risk of developing this disease in this population. In addition, this study didn't include factors such as socioeconomic status, which may also bias the research results.

In summary, our study showed that the occurrence of NAFPD increased with age, and there were gender differences. NAFLD, T2DM, overweight and obestiy, central obesity and HOMA-IR, TC, TG, LP, APN, and GLP-1 were all independent risk factor for the onset of the disease. Among them, NAFLD, central obesity, TG and APN were also independent risk factors for exacerbation of NAFPD. We concluded that lipid metabolism disorder was the basis for the pathogenesis of NAFPD, and the resulting abnormal secretion of adipokines and ectopic fat deposition in other areas could interact to cause IR and glucose metabolism disorder, which resulted in T2DM. Therefore, we should pay close attention to the degree of pancreatic fat deposition in people with central obesity and lipid metabolism disorders. And people who already have pancreatic fat deposition should be carefully screened for ectopic fat deposition in other areas. In addition,

the blood glucose of patients with NAFPD should be screened and followed up, to discover prediabetes, diabetes, and other related metabolic diseases.

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