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Transabdominal ultrasonography of the pancreas is superior to that of the liver for detection of ectopic fat deposits resulting from metabolic syndrome

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Abstract

The aim of our study was to investigate the rate of nonalcoholic fatty pancreas disease (NAFPD) in the south China province of Fujian and its relationship to nonalcoholic fatty liver disease (NAFLD) and metabolic parameters.

NAFPD is frequently identified on transabdominal ultrasound examination. The incidence of NAFPD varies from 16% to 69.7% depending on the country.

A total of 256 subjects were recruited. Each was assessed by abdominal sonography to diagnose NAFLD and NAFPD. The ages, sexes, heights, weights, blood pressure, and detection of peripheral blood biochemical indices (cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], and glucose) were recorded. The relationships among metabolic parameters and NAFPD or NAFLD were evaluated, and the positive rates of NAFLD and NAFPD in the general population were compared.

The age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), cholesterol, triglycerides, HDL, LDL, and glucose were significantly associated with NAFPD and NAFLD but the positive rate of NAFPD was significantly higher than that of NAFLD. The BMI, age, and NAFLD were the independent risk factors of NAFPD. The sex distribution, weight, SBP, DBP, BMI, LDL, HDL, triglycerides, glucose, cholesterol, NAFPD, and NAFLD were different significantly between metabolic syndrome and normal subjects.

NAFPD and NAFLD can reflect the body metabolism, but NAFPD has a higher detection rate.

Abbreviations: BMI = body mass index, CVD = cardiovascular disease, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, MetS = metabolic syndrome, MRI = magnetic resonance imaging, NAFLD = nonalcoholic fatty liver disease, NAFPD = nonalcoholic fatty pancreas disease, PDAC = pancreatic ductal adenocarcinoma, SBP = systolic blood pressure.

Keywords: metabolic syndrome, nonalcoholic fatty liver disease, nonalcoholic fatty pancreas disease, ultrasonography

1. Introduction

With the constant development of the economy, the rate of overnutrition is rising in the general population and an increasing number of people suffer from metabolic syndrome (MetS). According to an epidemiology study, the prevalence of MetS in the 35 to 59 years old Chinese population increased from 10.1% to 12.1% over a period of 5 years.[1] Mean body mass index (BMI) has increased by 0.4 to 0.5 kg/m^2 per decade worldwide. An estimated 1.46 billion adults worldwide had a BMI of ≥25 kg/m^2 in 2008.[2] MetS is related to obesity, cardiovascular disease (CVD), diabetes mellitus, and even social deprivation.[3]

In a traditional study of MetS, the degree of fatty infiltration in the liver has been used as a common method to reflect the metabolism in the body, and even used to assess MetS indirectly.[4] Besides the liver, ectopic fat can also accumulate in other organs such as muscles, heart, and pancreas. In recent years, a number of studies have shown that the prevalence of pancreas steatosis, also called nonalcoholic fatty pancreas disease (NAFPD), is common and associated closely with MetS.[5,6]

Frequently, the pancreas shows hyperechogenicity in routine transabdominal ultrasound examinations. NAFPD is associated with obesity,[7] CVD,[8] pancreatitis,[9] and even pancreatic cancer.[10] Pancreatic fatty infiltration is a risk factor for pancreatic precancerous lessons such as intraepithelial neoplasia.[11]

Tomita and colleagues found the ratio of fatty degeneration in pancreases with pancreatic ductal adenocarcinoma (PDAC) was higher than for pancreases without PDAC (72% vs 44%).[12] The rate of NAFPD and NAFLD varied according to different studies.[13] Lee et al found that 29.9% of fatty pancreas patients had a normal liver but only 2.2% fatty liver patients had a normal pancreas.[5] Aleshina et al found the frequency of pancreatic steatosis was 70% in overweight children whereas the frequency

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of hepatic steatosis was 46.6%.[14] Other studies revealed that the ratios of NAFLD were higher than those of NAFPD.[15,16] The aim of this study was to compare the prevalence of NAFPD and NAFLD and to investigate the relationships between the 2 diseases and MetS.

2. Materials and methods

This is a prospective study in which a total of 256 subjects who received a health checkup at the Second Affiliated Hospital of Fujian Medical University between January 2016 and June 2016 were screened by transabdominal ultrasound. The study was approved by the ethics committee of the hospital. All participants gave written informed consent. Subjects of this study with the following conditions or diseases were excluded: BMI $\geq$35 kg/m^2, alcohol consumption >20 g/d in the past year, chronic liver, pancreas, or kidney disease. Participants presence of any 3 of 5 risk factors constituted a diagnosis of MetS: BMI $\geq$25 kg/m^2; elevated triglycerides to 150 mg/dL (1.7 mmol/L); reduced HDL to <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women; elevated blood pressure, systolic $\geq$130 and/or diastolic $\geq$85 mm Hg or use of antihypertensive treatment; elevated fasting glucose $\geq$100 mg/dL (5.5 mmol/L) or treatment for diabetes mellitus.[17]

All subjects received abdominal sonographic examinations with the same machine (HI VISION Preirus, Hitachi joint-stock company, Tokyo, Japan) using a 3.5 MHz convex array transducer 12 hours after fasting. The liver echogenicity was classified into 4 grades[18]: level 0, normal liver echogenicity; level 1, a slight increase in liver echogenicity with no attenuation in the far field; level 2, a moderate increase in liver echogenicity with light attenuation in the far field and the diaphragm and vessels clearly visible; and level 3, a substantial increase in liver echogenicity with poor visualization of the diaphragm and the vessels. NAFLD was diagnosed when the liver appeared as level 1 to 3. The pancreas echogenicity was also classified into 4 grades[5,19]: level 0, the pancreas echogenicity was similar to the kidney parenchymal; level 1, pancreas echogenicity was slightly higher than in the kidney, but because the pancreas and kidney could not be displayed in the same screen, the radiologist compared the kidney with the liver and then compared the liver with the pancreas; level 2, a substantial increase in pancreas echogenicity but lower than the retroperitoneal fat echogenicity; and level 3, the pancreas echogenicity was similar to or higher than the retroperitoneal fat. NAFPD was diagnosed when the pancreas appeared as level 1 to 3. The ultrasound examinations were performed by 2 radiologists with one with more than 10 years' experience and the other had less than 2 years' experience in ultrasonography. If there was inconsistency in diagnosis, the senior radiologist made the final judgement. A kappa test was performed to check for consistency. The ages, sexes, heights, weights, systolic blood pressure (SBP), diastolic blood pressure (DBP), and detection of peripheral blood biochemical indices (cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], and glucose) were recorded within a week of the ultrasound examination.

2.1. Statistical analysis

SPSS software (version 21.0; SPSS) was used for statistical analysis. Spearman correlation test was used to identify the clinical and metabolic factors associated with NAFPD and NAFLD. Student *t* test was used to compare the continuous variables and Mann-Whitney *U* test was used to compare the grading variables between MetS and normal subjects. Multivariate logistic regression was performed to assess which independent risk factor has a major effect on the occurrence of NAFPD. The positive rates of NAFLD and NAFPD and sex distribution between MetS and normal subjects were compared using χ^2 tests. A value of $P < .05$ was defined as a statistical difference.

Table 1

The relationships among clinical and laboratory characteristics with NAFPD and NAFLD (*r*/*P*).

	NAFPD	NAFLD
Sex	NS	NS
Age	0.384/<0.001*	0.230/<0.001*
Height	0.180/0.004*	0.191/0.002*
Weight	0.417/<0.001*	0.458/<0.001*
SBP	0.298/<0.001*	0.311/<0.001*
DBP	0.184/0.011*	0.336/<0.001*
BMI	0.532/<0.001*	0.543/<0.001*
Cholesterol	0.200/0.001*	0.209/0.001*
LDL	0.202/0.001*	0.191/0.002*
HDL	−0.180/0.004*	−0.244/<0.001*
Glucose	0.339/<0.001*	0.482/<0.001*
Triglycerides	0.380/<0.001*	0.393/<0.001*

BMI = body mass index, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, NAFPD = nonalcoholic fatty pancreas disease, NS = no significance, SBP = systolic blood pressure.
* $P < .05$.

3. Results

A total of 256 subjects were included; there were 82 men (32%) and 174 women (68%), and the mean age was 48.2 ± 14.9 years. Two radiologists with good consistency in classifying liver and pancreas echogenicity (kappa of liver = 0.741, kappa of pancreas = 0.802) performed the evaluations. Among the 256 subjects, 121 (47.3%) were diagnosed as having NAFPD, 78 (30.5%) were diagnosed as having NAFLD, and the positive rate of NAFPD was significantly higher than that of NAFLD ($P < .001$). Both NAFPD and NAFLD were significantly associated with age, height, weight, SBP, DBP, BMI, cholesterol, triglycerides, HDL, LDL, and glucose, but sex was not associated with NAFPD and NAFLD (Table 1). Multivariate logistic regression revealed that BMI, age, and NAFLD were the independent risk factors of NAFPD (Table 2). NAFPD and NAFLD also had good consistency (odds ratio = 6.21, $P < .001$). There were 46 participants who fulfilled the criterion of MetS. The sex distribution, weight, SBP, DBP, BMI, LDL, HDL, triglycerides, glucose, cholesterol, NAFPD, and NAFLD were different significantly between MetS and non-MetS subjects. Patients with MetS were older than non-MetS subjects, but the difference was not significant (mean age 51.6 vs 47.5 years old, $P = .058$). There was no significant difference of height between MetS and non-MetS subjects (Table 3).

4. Discussion

The MetS is a major and increasing clinical and social issue worldwide. MetS is mainly caused by overnutrition or metabolic diseases which influence the metabolism of glucose and fat and appear as hyperglycemia, obesity, hyperlipidemia, and hypertension. MetS is a leading risk factor for cardiovascular morbidity and mortality. Ectopic fat accumulation is an important

Table 2

Multivariate logistic regression analysis testing the association between NAFPD and risk factors.

	Odds ratio (95% CI)	*P* value
Age	1.05 (1.02, 1.08)	.001*
Sex	1.15 (0.42, 3.18)	.787
Height	1.00 (1.00, 1.01)	.315
Weight	0.94 (0.86, 1.03)	.177
SBP	1.01 (0.99, 1.04)	.307
DBP	0.99 (0.95, 1.03)	.684
BMI	1.55 (1.20, 2.00)	.001*
Triglyceride	0.63 (0.21, 1.90)	.417
LDL	0.37 (0.03, 4.11)	.422
HDL	0.21 (0.02, 2.48)	.215
Glucose	1.23 (0.96, 1.57)	.098
Cholesterol	3.04 (0.28, 32.78)	.360
NAFLD	6.21 (3.03, 12.73)	<.001*
MetS	4.55 (1.39, 14.92)	.012*

BMI = body mass index, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, MetS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, NAFPD = nonalcoholic fatty pancreas disease, SBP = systolic blood pressure.
* $P < .05$.

Table 3

Comparison of risk factors between MetS and non-MetS subjects.

	MetS (n = 46)	non-MetS (n = 210)	*P* value
Age, y (mean, SD)	51.6, 12.9	47.5,15.2	.058
Sex, (male, female)	22, 24	59, 151	<.001*
Height, m (mean, SD)	1.62, 0.08	1.61, 0.07	.453
Weight, kg (mean, SD)	67.3, 10.7	55.6,9.2	<.001*
SBP, mm Hg (mean, SD)	142.80, 20.81	121.58,16.55	<.001*
DBP, mm Hg (mean, SD)	86.73, 10.21	74.03, 10.35	<.001*
BMI, kg/m^2 (mean, SD)	25.76,3.57	21.51,3.16	<.001*
LDL, mmol/L (mean, SD)	3.08,1.14	2.57,0.82	.005*
HDL, mmol/L (mean, SD)	1.12, 0.42	1.47,0.45	<.001*
Triglycerides, mmol/L (mean, SD)	2.21, 1.52	0.98, 0.57	<.001*
Glucose, mmol/L (mean, SD)	6.77,3.17	4.92,1.35	<.001*
Cholesterol, mmol/L (mean, SD)	5.19,1.47	4.47,0.97	.003*
NAFPD, level (mean, range)	1.28, 0–3	0.62, 0–3	<.001*
NAFLD, level (mean, range)	1.09, 0–2	0.25, 0–2	<.001*

BMI = body mass index, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, MetS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, NAFPD = nonalcoholic fatty pancreas disease, SBP = systolic blood pressure.
* $P < .05$.

pathophysiologic abnormality of MetS. Excess of adipose tissue, especially visceral, is the basis for the establishment of MetS. Liver was previously considered as the most-influenced organ of ectopic fat accumulation, and great a number of studies have been carried out in the past decades. It has been reported that the prevalence of NAFLD is more than 20% of the general population in Europe and North America and is higher in the Middle East and South Asia. It is significantly associated with obesity, type 2 diabetes mellitus, CVD, and other conditions.[20] Liver steatosis will develop into fibrosis and even cirrhosis if patients do not control the progress of the disease.

In recent years, a large number of studies of NAFLD have been reported, which found that the mechanism of NAFLD has an association with the activation of proteinase 3,[21] miR-21,[22] and hepatokines.[23] NAFPD has some similar mechanisms to NAFLD. Researchers have found that diabetes and NAFLD, hypertension, and CVD have played an important role in the ectopic fat deposition in the pancreas. Diabetes and NAFLD are associated with NAFPD independently of age, sex, and other risk factors.[15,24,25] These findings are similar to our results.

The pathogenesis of NAFPD is not clear. It is associated with genetics and diet according to present research. Maternal obesity can induce NAFPD in offspring and an obesogenic diet can significantly increase pancreatic triglycerides, pancreatic mRNA expression, and biological clock/molecular core circadian genes.[26] A few years ago, some scholars also proposed that molecular mechanisms involving MetS may be causing permanent changes in the expression of hypothalamic circuits regulating energy homeostasis and the circadian clock.[27] Adipocytes can produce leptin as a regulator of body weight and insulin produced by pancreas can also regulate glycometabolism. This interconnection of peripheral signals with the central signaling controls the energy balance. Disturbance of the balance may result in MetS as well as NAFPD. Our study revealed that NAFPD correlated with MetS parameters such as BMI, blood pressure, cholesterol, triglycerides, and glucose.

Incipient NAFPD may not cause clinical symptoms and may have no significant effect on health. Nevertheless, with the pancreatic steatosis aggravation, it can lead to beta-cell dysfunction,[28] cause the occurrence of diabetes, and increase the risk of pancreatitis after it becomes serious. Pancreatic steatosis is associated with pancreatic cancer and can also promote dissemination and the lethality of pancreatic cancer.[29] Therefore, it is particularly important to perform early diagnosis and interventions for NAFPD.

NAFLD is usually regarded as an evaluation index in previous studies of MetS. Studies support the idea that NAFLD is a very important decisive factor and has a positive significance for diagnosis, prevention, and treatment of MetS. However, we found that the positive rate of NAFPD was significantly higher than that of NAFLD ($P < .001$), and we summarized the effects of age, sex, BMI, and several common biochemical indicators of metabolic disease for NAFPD and NAFLD. Our results showed that patients with NAFLD also often suffer from NAFPD; however, many patients with NAFPD did not suffer from NAFLD.

Whether ectopic fat more easily or earlier infiltrates into the pancreas remains to be further studied. Other studies have shown that liver steatosis mainly increases triglyceride levels in the liver and pancreas steatosis is mainly characterized by an increase in the number of adipocytes within the pancreas.[30] Generation of adipocytes may be easier than infiltration of triglycerides into hepatocytes. The size of an adipocyte is more suitable for scattering ultrasound beams, used to form the ultrasound image of parenchymatous organs than intracellular triglycerides. This may be the reason for the different sonographic findings between the liver and pancreas. Because diagnosis of NAFPD has a higher sensitivity than NAFLD, NAFPD may be more suitable for evaluation of MetS but additional studies are necessary.

The most common abdominal examination is ultrasonography and even a pocket-sized ultrasound can discover most abdominal problems.[31] Ultrasound can clearly show pancreas morphology when patients have adequate preparation and oral consumption of ultrasound contrast agents can be used when the images are interfered with by digestive gas. The pancreas is more difficult to obtain a biopsy from because of the high rate of severe complications, and is more difficult to obtain a pathological diagnosis from compared with the liver, kidney, and other organs. Thus, its evaluation is more dependent on radiological and biochemical examination.

Magnetic resonance imaging (MRI) and sonographic examination of the pancreas both have high specificity.[32] However,

MRI is not included in regular examinations because of its high price and lack of availability. In animal studies, sonographic examination is the only applicable imaging examination method.[33] Therefore, pancreas ultrasound has very high practicability and can become a useful method in indirect evaluation of MetS. Further studies are needed.

There are some limitations of our study. The diagnosis of NAFPD was conducted only by the method of ultrasound and it may be interfered by intra-gastrointestinal gas, obesity, and the experience of examiners. Pathology examination of pancreas was not applied for most of the patients because pancreatic biopsy has not been suggested and regularly performed in clinical practice.

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