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

Shilin Li, MS, Liyang Su, BS, Guorong Lv, MS*, Weihong Zhao, BS, Jianhui Chen, BS

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/m² per decade worldwide. An estimated 1.46 billion adults worldwide had a BMI of ≥25 kg/m² 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.[1] 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...
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 ≥25 kg/m², alcohol consumption >20g/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 ≥25 kg/m²; 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 ≥130 and/or diastolic ≥85 mm Hg or use of antihypertensive treatment; elevated fasting glucose ≥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 χ² tests. A value of P < 0.05 was defined as a statistical difference.

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 (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
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 a great 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. 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 proteasome 3, miR-21, and hepatokines. NAPFD 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 NAPFD independently of age, sex, and other risk factors. These findings are similar to our results.

The pathogenesis of NAPFD is not clear. It is associated with genetics and diet according to present research. Maternal obesity can induce NAFLD in offspring and an obesogenic diet can significantly increase pancreatic triglycerides, pancreatic mRNA expression, and biological clock/molecular core circadian genes. A few years ago, some scholars also proposed that molecular mechanisms involving MetS may be causing permanents changes in the expression of hypothalamic circuits regulating energy homeostasis and the circadian clock. 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 NAPFD. Our study revealed that NAPFD correlated with MetS parameters such as BMI, blood pressure, cholesterol, triglycerides, and glucose.

Incipient NAPFD 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, 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. Therefore, it is particularly important to perform early diagnosis and interventions for NAPFD.

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 NAPFD 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 NAPFD and NAFLD. Our results showed that patients with NAFLD also often suffer from NAPFD; however, many patients with NAPFD 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. Generation of adipocytes may be easier than infiltration of triglycerides into hepatocytes. The size of an adipocyte is more suitable for scarring 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 NAPFD has a higher sensitivity than NAFLD, NAPFD 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. 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 examination.

Magnetic resonance imaging (MRI) and sonographic examination of the pancreas both have high specificity. 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.

References

[1] Wang ZW, Wang X, Li X, et al. Prevalence and trend of metabolic syndrome in middle-aged Chinese population. Zhonghua Liu Xing Bing Xue Za Zhi 2009;30:596-600.

[2] Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011;377:557-67.

[3] Blanquet M, Debost-Legrand A, Gerbaud L, et al. Metabolic syndrome and social deprivation: results of a French observational multicentre survey. Fam Pract 2016;33:17-22.

[4] Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014;2:901-10.

[5] Lee JS, Kim SH, Jun DW, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroenterol 2009;15:1869-75.

[6] Catanzano R, Cuffari B, Italia A, et al. Exploring the metabolic syndrome: nonalcoholic fatty pancreas disease. World J Gastroenterol 2015;22:7660-75.

[7] Fernandez-Santos C, Evangelista Carneiro R, de Souza Mendonca L, et al. Rosiglitazone aggravates nonalcoholic fatty pancreatic disease in C57BL/6 mice fed high-fat and high-sucrose diet. Pancreas 2009;38: e80-6.

[8] Wang CY, Ou HY, Chen MF, et al. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. J Am Heart Assoc 2014;3:e00297.

[9] Smits MM, van Geenen EJ. The clinical significance of pancreatic steatosis. Nat Rev Gastroenterol Hepatol 2011;8:169-77.

[10] Wang H, Maitra A, Wang H. Obesity, intrapancreatic fatty infiltration, and pancreatic cancer. Clin Cancer Res 2015;21:3369-71.

[11] Rebourzs Y, Gaujoux S, d'Assignies G, et al. Obesity and fatty pancreatic infiltration are risk factors for pancreatic preneoplastic lesions (PanIN). Clin Cancer Res 2015;21:3522-8.

[12] Tomita Y, Azuma K, Nonaka Y, et al. Pancreatic fatty degeneration and fibrosis as predisposing factors for the development of pancreatic ductal adenocarcinoma. Pancreas 2014;43:1032-41.

[13] Lesmana CR, Pakasi LS, Inggriani S, et al. Prevalence of non-alcoholic fatty pancreas disease (NAFDP) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. BMC Gastroenterol 2015;15:174.

[14] Alekhina E, Novikova VP, Grueva VA, et al. Hepatic steatosis and fatty pancreas—2 targets of metabolic syndrome in children. Eksp Klin Gastroenterol 2014;8:16-20.

[15] Ou HY, Wang CY, Yang YC, et al. The association between nonalcoholic fatty pancreas disease and diabetes. PLoS One 2013;8:e62561.

[16] Della Corte C, Mosca A, Majo F, et al. Nonalcoholic fatty pancreas disease and nonalcoholic fatty liver disease: more than ectopic fat. Clin Endocrinol 2015;83:656-62.

[17] Alberini KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.

[18] Ahn JM, Paik YH, Min SY, et al. Relationship between controlled attenuation parameter and hepatic steatosis as assessed by ultrasound in alcoholic or nonalcoholic fatty liver disease. Gut Liver 2016;10:295-302.

[19] Marks WM, Filly RA, Callen PW. Ultrasonic evaluation of normal pancreatic echogenicity and its relationship to fat deposition. Radiology 1980;137:475-9.

[20] National Guideline Centre (UK). Non-Alcoholic Fatty Liver Disease: Assessment and Management. London: 2016.

[21] Toonen EJ, Mirea AM, Tack CJ, et al. Activation of proteinase 3 contributes to non-alcoholic fatty liver disease (NAFLD) and insulin resistance. Mol Med 2016;22:202-14.

[22] Benhamouche-Trouillet S, Postic C. Emerging role of miR-21 in non-alcoholic fatty liver disease. Gut 2016;65:1781-3.

[23] Lebensztejn DM, Fiszak-Jackiewicz M, Bialokoz-Kalinowska I, et al. Heparotinones and non-alcoholic fatty liver disease. Acta Biochim Pol 2016;63:459-67.

[24] Britton KA, Fox CS. Ectopic fat depots and cardiovascular disease. Circulation 2011;124:e37-41.

[25] Mirrakhimov AE. Nonalcoholic fatty pancreatic disease and cardiometabolic risk: is there is a place for obstructive sleep apnea? Cardiovasc Diabetol 2014;13:29.

[26] Carter R, Mouradidaran A, Soeda J, et al. Non-alcoholic fatty pancreas disease pathogenesis: a role for developmental programming and altered circadian rhythms. PLoS One 2014;9:e89505.

[27] Orozco-Solis R, Matos Rj, Guzman-Quevedo O, et al. Nutritional programming in the rat is linked to long-lasting changes in nutrient sensing and energy homoeostasis in the hypothalamus. PLoS One 2010;5:e13537.

[28] Tushuizen ME, Bunck MC, Pourwels PJ, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. Diabetes Care 2007;30:2916-21.

[29] Mathar A, Zyzromsky NJ, Pitt HA, et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg 2009;208:989-96.

[30] Pinnick KE, Collins SC, Londos C, et al. Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. Obesity 2008;16:522-30.

[31] Colli A, Prati D, Fraquelli M, et al. The use of a pocket-sized ultrasound device improves physical examination: results of an in- and outpatient cohort study. PLoS One 2015;10:e0122181.

[32] Yoon JH, Lee JM, Lee KH, et al. Pancreatic steatosis and fibrosis: quantitative assessment with preoperative multiparametric MR imaging. Radiology 2016;279:140-50.

[33] Granger LA, Hilferty M, Francis T, et al. Variability in the ultrasonographic appearance of the pancreas in healthy dogs compared to dogs with hyperadrenocorticism. Vet Radiol Ultrasound 2015;56:540-8.