Ectopic fat deposition and its related abnormalities of lipid metabolism followed by nonalcoholic fatty pancreas

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ABSTRACT

Background and Objectives: The positive energy balance between caloric intake and caloric output increasing storage of triglycerides (TG) in adipocytes has made nonalcoholic fatty liver disease (NAFLD) one of the major public health problems in China. Excessive lipid deposition in the pancreas is referred to as nonalcoholic fatty pancreas disease (NAFPD). Early assessment of pancreatic fat infiltration will have an increasing role in the clinical management of the metabolic dysregulation and prevention pancreatic complications. Subjects and Methods: We retrospectively collected data of inpatients with NAFPD from EUS database between September 2012 and August 2020 at our endoscopic center. The prevalence of NAFPD and factors associated with its development were statistically analyzed. The echogenicity of the pancreas was compared to that of the left renal cortex during the EUS examination by using an existing criterion. Results: Four thousand, seven hundred and four consecutive individuals underwent EUS were enrolled. The prevalence of NAFPD was 1.2\% (57/4704). Factors independently associated with NAFPD on multivariate analysis were increasing TG (odds ratios [OR] 4.65, \textit{P} = 0.014), NAFLD (OR 16.76, \textit{P} = 0.005) and decreasing apolipoprotein A-1 (OR 0.002, \textit{P} = 0.0127). We found no association between NAFPD and age, sex, total cholesterol or hypertension. Conclusions: We found a meaningful relationship between NAFLD, dyslipidemia, and NAFPD in Chinese. We hypothesized that NAFPD was strongly correlated with ectopic fat deposition and its related abnormalities of lipid metabolism. Early diagnosis of NAFLD provides opportunities to control the progression of NAFPD.

Key words: apolipoprotein A-1, EUS, metabolic syndrome, nonalcoholic fatty liver disease, nonalcoholic fatty pancreas disease

INTRODUCTION

Changes in dietary patterns and lifestyles have made nonalcoholic fatty liver disease (NAFLD) one of the...
major public health problems in China, the imbalance of lifestyles between caloric intake and caloric output makes excessive energy mainly to be stored in hepatocytes in the form of triglycerides (TG).\[^1,2\] Excessive lipid deposition in the pancreas is referred to as nonalcoholic fatty pancreas disease (NAFPD). Similar to the condition in the liver, NAFPD can progress to nonalcoholic steato-pancreatitis, and this process can also be reversed by weight loss.\[^3\] Although hepatic fat is localized mainly intracellularly, pancreatic fat is connected to the presence of adipocytes which infiltrate its parenchyma. Fat infiltration and accumulation into different organs results in organ damage and failure.\[^4\] Fatty tissue also increasing plasma levels of cytokines could induce inflammatory reaction and fibrosis,\[^3,5\] it has been also suggested that NAFPD might be associated with pancreatic cancer.\[^6 - 9\] Additionally, patients with NAFPD background have a higher mortality rate when they have pancreatic cancer or acute pancreatitis.\[^10,11\] Therefore, we believe that the assessment of pancreatic fat infiltration will have an important role in the clinical management of the metabolic dysregulation and pancreatic complications.

Studies about the prevalence of NAFPD show different rates of NAFPD between 2.7% and 30.7% in China.\[^12-14\] EUS can avoid the interference of bowel gas to identify echotexture and pancreatic duct abnormalities, which makes it one of the best methods for the evaluation of pancreatic tissue. In addition, diagnosing NAFPD by comparison of echogenicity of the pancreas with that of the adjacent organs (left kidney) in the same window on EUS is possible.\[^15,16\] Computed tomography (CT) and magnetic resonance imaging (MRI) have also been reported to diagnose NAFPD,\[^6,14\] but this was not the case in our study. The aim of this study was to assess the correlation between NAFPD diagnosed by EUS and the known metabolic risk factors.

**SUBJECTS AND METHODS**

**Data sources**

In this retrospective study, we investigated inpatients of 18 years and older who were diagnosed with NAFPD or normal pancreas (NP) through EUS between September 1, 2012, and August 31, 2020, at our hospital in Shanghai. All cases with documented hyperechoic pancreas, pancreatic fat infiltration, or NAFPD were identified from a EUS database. Clinical, endoscopic, imaging, and biochemical data were collected in electronic medical files. Demographic characteristics, past medical history, and laboratory measurements were compared between group with NAFPD and group with NP to determine the risk factors for NAFPD. All EUS procedures were performed using a linear echoendoscope (EG-580 UT, Fujifilm Optical Co Ltd., Japan) with a frequency of 7.5 MHz by three experienced endosonographers.

Subjects who met the following criteria were excluded: (1) subjects with a history of pancreatic or left kidney resection, or subjects with a history of gastrointestinal reconstruction such as Billroth surgical intervention; (2) subjects with space-occupying lesions in the pancreas or with advanced malignant diseases contraindicating this study; (3) subjects with a previous diagnosis of chronic pancreatic, liver, kidney disease, or severe immune system disorders; (4) subjects with acute inflammatory disease (such as acute pancreatitis or cholangitis); (5) heavy drinkers, defined as drinking 20 g daily (140 g weekly) for men and 10 g daily (70 g weekly) for women;\[^17\] (6) subjects with drug history of lipid-lowering agents within 1 year, such as statins, fibrates; and (7) all who did not undergo follow-up.

The study protocol was approved by the Clinical Research Ethics Committee of our hospital (NO. CHEC2011-069). All subjects gave informed written consent. Authors had access to the study data and reviewed and approved the final manuscript.

**Definitions**

Normal pancreas, nonalcoholic fatty pancreas disease, and nonalcoholic fatty liver disease

Because the pancreas can be compared directly with the left kidney in the same acoustic window [Figure 1], the EUS examination based on the comparison of the renal echogenicity versus pancreatic parenchymatous and hepatic echogenicity is used. NP was defined as the echogenicity of the pancreas was similar to that of

![Figure 1. Pancreas and left kidney in the same acoustic window. (a) Normal pancreas; (b) nonalcoholic fatty pancreas disease (P pancreas, K kidney)](image)

**Figure 1.** Pancreas and left kidney in the same acoustic window. (a) Normal pancreas; (b) nonalcoholic fatty pancreas disease (P pancreas, K kidney)
the left renal cortex, and the main pancreatic duct was clearly delineated, and fine, salt and pepper dots in the pancreatic parenchyma were clearly seen. NAFPD and NAFLD were shown as brighter echotexture than left kidney cortex echotexture. Additionally, pancreatic fat infiltration also bases on the aspects including blurring of the pancreatic duct and the absence of parenchymal “salt and pepper” dots,[18,19] hepatic fat infiltration also bases on deep attenuation or vessel blurring.[20] EUS was performed by one of the 3 endosonographers. These endosonographers agreed on the definition and criteria of NP, NAFPD, and NAFLD.

Hypertension, type 2 diabetes mellitus, and body mass index
Hypertension was defined as blood pressure ≥130/85 mmHg, Type 2 diabetes mellitus (T2DM) was defined as fasting plasma glucose ≥5.6 mmol/L, respectively, the definition can also be made when patients have received treatment for the these metabolic abnormalities;[21] body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Statistical analysis
Statistical analysis was conducted using SPSS software version 19 (IBM Corp, Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation (SD) and that of qualitative variables by frequency (percentage). Study subjects were divided into two groups, and their clinical and metabolic characteristics were compared using Student’s t-test (in continuous variables) or Chi-squared tests (in categorical variables). We used logistic regression models to estimate odds ratios (OR) and their 95% confidence intervals (95% CIs) for the independently association between NAFPD and these factors. A P < 0.05 was considered statistically significant.

RESULTS
Initially, a total of 4704 subjects were included, the most common finding of EUS was assessment or biopsy examination of solid pancreatic mass (62.2%). Other results included assessment of chronic pancreatitis (10.2%), pancreatic pseudocyst (8.2%), biliary abnormalities (5.8%), pancreatic-cystic lesions (5.4%), NP (n = 109, 2.3%), submucosal mass in the stomach (1.9%), NAFPD (n = 57, 1.2%), and other findings (2.8%). Indications for patients diagnosed with NAFPD by EUS included suspected pancreatic mass (15/57 26.3%), elevated CA199 (12/57, 21.1%), idiopathic acute pancreatitis (10/57, 17.5%), suspected ampullary tumor (7/57, 12.3%), elevated blood amylase (6/57, 10.5%), submucosal mass in the stomach (4/57, 7%), and abdominal pain, emaciation, or diarrhea of unknown cause (3/57, 5.3%). All of these patients underwent CT or MRI before EUS examination, NAFPD was diagnosed in only 10 patients. Indications for patients diagnosed with NP by EUS included elevated CA199 (23/109, 21.1%), suspected biliary abnormalities (17/109 15.6%), submucosal mass in the stomach (15/109,13.8%), abdominal pain of unknown cause (14/109, 12.8%), suspected pancreatic lesions (12/109, 11%), elevated blood amylase (10/109, 9.2%), idiopathic acute pancreatitis (10/109, 9.2%), and other reasons (8/109, 7.3%). In the final analysis, 109 patients, 43 (39.4%) males, the overall mean age of 52.3 years (SD, 12.9 years), were enrolled in the present study after excluding 57 subjects with various reasons [Figure 2]. None of the 40 NAFPD patients developed pancreatic cancer or acute pancreatitis during follow-up.

Table 1 shows the clinical characteristics of the groups with NAFPD and NP. There was no significant difference in age, sex, hypertension, and total cholesterol between the two groups. NAFLD was seen in 29.4% of the two research groups. Patients with NAFPD had a significantly higher frequency of NAFLD and T2DM (60% vs. 11.6% [P < 0.001] and 25% vs. 4.6% [P = 0.001], respectively). Patients with NAFPD had a significantly higher mean BMI and TG (26.5 [SD, 2.7] vs. 23 [SD, 3.1] kg/m² [P < 0.001] and 2.4 [SD, 1.9] vs. 1.4 (SD, 0.8) mmol/L [P = 0.003], respectively). In addition, apolipoprotein A-1 (ApoA-1) was significantly higher in those with NAFPD.

Table 1. Clinical and laboratory characteristics of the subjects

|                        | NAFPD (n=40) | Normal pancreas (n=69) | P  |
|------------------------|--------------|------------------------|----|
| Age (years)            | 52.0±12.1    | 52.5±13.3              | 0.848 |
| Gender, male (%)       | 19 (46.3)    | 24 (34.8)              | 0.19 |
| BMI (kg/m²)            | 26.5±2.7     | 23±3.1                 | <0.001 |
| NAFLD (%)              | 24 (60)      | 8 (11.6)               | <0.001 |
| Hypertension (%)       | 13 (32.5)    | 12 (17.4)              | 0.072 |
| T2DM (%)               | 10 (25)      | 3 (4.6)                | 0.001 |
| Total cholesterol (mmol/L) | 4.9±1.0    | 4.7±1.0                | 0.902 |
| Triglycerides (mmol/L) | 2.4±1.9      | 1.4±0.8                | 0.003 |
| ApoA-1 (g/L)           | 1±0.2        | 1.3±0.3                | <0.001 |

BMI: Body mass index; NAFLD: Nonalcoholic fatty liver disease; NAFPD: Nonalcoholic fatty pancreas disease; T2DM: Type 2 diabetes mellitus; ApoA-1: Apolipoprotein A-1

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was significantly lower in the NAFPD group compared with the NP group (1.0 [SD, 0.2] vs. 1.3 [SD, 0.3] g/L [P < 0.001]).

To investigate the effects of clinical variables on the risk of NAFPD, we performed logistic regression analysis, the statistical results are shown in Table 2. Patients with NAFLD have a 16.76 times greater chance to have NAFPD (95% CI, 2.33–120.76, P = 0.005), and those with higher TG had a 4.65-fold increased chance of having NAFPD (95% CI, 1.36–15.9, P = 0.014). However, patients with higher ApoA-1 had a decreased chance of having NAFPD (OR 0.002, 95% CI 0–0.50, P = 0.0127). BMI (OR 1.36, P = 0.156), and T2DM (OR 3.31, P = 0.599) were not associated with NAFPD.

**DISCUSSION**

To the best of our knowledge, this is the first study to compare NAFPD and NP via EUS examination in China. Our results explicitly indicate that NAFLD and dyslipidemia were strongly associated with NAFPD. There is an increasing evidence of the association between NAFPD and all the components of the metabolic syndrome (MetS) in animal models and humans.[14,18,22] Besides, MetS and its components (obesity, arterial hypertension, hypertriglyceridermia, the changes of high-density lipoprotein [HDL] cholesterol, and T2DM) are all significant factors of NAFPD development.[23] Our results demonstrated an increased prevalence of NAFPD in patients with hypertension, T2DM, high BMI, and high TG. However, this study could have been underpowered to detect a statistically significant independent risk association with these parameters of MetS in multivariate logistic regression analysis except high plasma TG. Fatty tissue has a central role in TG metabolism, hypertriglyceridermia is one of plasma lipoprotein profile of a viscerally obese individual with ectopic fat and dysfunctional adipose tissue.[24,25] Ectopic fat deposition with the essence of increased storage of TG in adipocytes is associated with a chronic low-grade inflammatory state of abdominal adipose tissue, which eventually leads to adipose tissue dysfunction, insulin resistance, lipid metabolism disorders and MetS.[21,25,26] It has been proved that fatty tissue dysfunction will eventually lead to abnormalities in lipid metabolism, such as hypertriglycerideremia.[26,27] The possible mechanism in adipocytes is TG accumulation, which facilitated or followed by adipocyte hypertrophy and proliferation, adipocyte hypertrophy leads to many changes in adipocyte function and production of anti-and pro-inflammatory cytokines. Because of

**Table 2. Logistic regression analysis for risk factors of nonalcoholic fatty pancreas disease**

| Risk factor                          | OR   | 95% CI        | P    |
|-------------------------------------|------|---------------|------|
| BMI (kg/m²)                         | 1.36 | 0.84–2.99     | 0.156|
| NAFLD (%)                           | 16.76| 2.33–120.76   | 0.005|
| T2DM (%)                            | 3.31 | 0.04–287.11   | 0.599|
| Triglycerides (mg/dL)               | 4.65 | 1.36–15.90    | 0.014|
| ApoA1 (g/L)                         | 0.002| 0.00–0.50     | 0.0127|

BMI: Body mass index; NAFLD: Nonalcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; ApoA-1: Apolipoprotein A-1; CI: Confidence interval; OR: Odds ratio

Inpatients who underwent pancreas examination by EUS between September 1, 2012 and August 31, 2020 (N = 4,704)

| Solid pancreatic mass (N = 2925) |
|----------------------------------|
| Chronic pancreatitis (N = 479)   |
| Pancreatic pseudocyst (N = 386)  |
| Biliary abnormalities (N = 273)   |
| Pancreatic-cystic lesions (N = 254) |
| Other findings (N = 221)         |

| NAFPD group (N = 57) |
|----------------------|
| Excluded:            |
| Acute pancreatitis (N = 10) |
| Suspicious pancreatic lesions (N = 3) |
| History of alcohol abuse (N = 2) |
| lipid-lowering agents (N = 1) |
| No follow-up (N = 1)    |

| NP group (N = 109) |
|--------------------|
| Excluded:          |
| Acute or chronic inflammation (N = 15) |
| History of malignant disease (N = 9) |
| History of alcohol abuse (N = 4) |
| History of surgery (N = 3) |
| No follow-up (N = 9) |

| Patients of NAFPD for analysis (N = 40) |
|----------------------------------------|

| Patients of NP for analysis (N = 69) |
|-------------------------------------|

Excluded: Acute or chronic inflammation (N = 15) History of malignant disease (N = 9) History of alcohol abuse (N = 4) History of surgery (N = 3) No follow-up (N = 9)

Figure 2. Study flow chart. NAFLD: Nonalcoholic fatty liver disease; NP: Normal pancreas
these, visceral obesity that is a better correlate of metabolic abnormalities than BMI and the amount of subcutaneous fat has now been established as being part of a complex phenotype including ectopic fat and dysfunctional adipose tissue in several sites including the liver, muscle, and pancreas.\textsuperscript{[25,28]} Therefore, as the most easily found ectopic fat, NAFLD can be usually considered an early predictor of metabolic disorders, even in the normal-weight population.\textsuperscript{[29]}

Significant amounts of TG in hepatocytes of NAFLD can progress to hepatic steatosis which may lead to steatohepatitis, fibrosis, and cirrhosis.\textsuperscript{[30]} In contrast to NAFLD, the pathophysiological mechanisms and clinical relevance of NAFPD remain unclear. NAFPD is histologically characterized by an increased number of adipocytes.\textsuperscript{[22,31]} The long-term impact of heavy infiltration of the pancreas by TG can potentially lead to both pancreatitis and exocrine dysfunction of the pancreas.\textsuperscript{[32]} Several previous studies have shown an augmented pro-inflammatory response secreted from adipocytes and mediated by pro-inflammatory cytokines such as leptin, interleukin 6, interleukin 1-beta, and tumor necrosis factor \(\alpha\) which render the pancreas vulnerable to pancreatitis.\textsuperscript{[32,33]} In addition, a longer duration of high-fat diet feeding increased TG content in the pancreas but not the liver, suggesting that the pancreas is particularly susceptible to ectopic fat deposition.\textsuperscript{[34]} We speculate that NAFPD, like NAFLD, is the pancreatic manifestation of MetS. In our study, NAFLD was seen in 29.4\% of 109 participants. There was a 48.4\% observed increase in the prevalence of NAFLD in NAFPD cases compared with controls. Despite this, it cannot be ruled out that NAFPD and NAFLD influence each other regarding disease onset and progression. It was suggested that fatty liver-derived fetuin-A may stimulate pancreatic fat cells, which would lead to the expression of cytotoxic proinflammatory cytokines and B-cell impairment.\textsuperscript{[35]} On multivariate analysis, NAFLD was the strongest predictor with an OR of approximately 17-fold.

In addition to NAFLD and hypertriglyceridemia, the decrease of serum ApoA-1 is also an independent predictor of NAFPD and can be used as a marker of ectopic fat infiltration in pancreas. ApoA-1 is the major apolipoprotein of HDL, it was down-regulated in fatty change liver cells. Hepatic metabolism disorder resulted in synthesis dysfunction of ApoA-1, which was main secreted in liver cells. ApoA-1 deficient mice do not form normal HDL granules and cannot effectively transport cholesterol into the liver tissue, and eventually develop cardiovascular diseases such as atherosclerosis.\textsuperscript{[36]} These serum lipoproteins also represent an integral part of innate immunity against organ injury in severe acute pancreatitis, with HDL binding the majority of endotoxin (60\%) \textit{in vitro}.\textsuperscript{[37]} In addition, ApoA-1 is inversely correlated to insulin resistance, the development of T2DM and obesity by regulating lipid and energy metabolism.\textsuperscript{[21,36,38]} In patients who develop acute pancreatitis, NAFPD is a risk factor for severe disease.\textsuperscript{[39,40]} The possible explanations include reduced synthesis of ApoA-1, elevated serum TG levels,\textsuperscript{[41]} and pro-inflammatory responses secreted by adipocytes and mediated by pro-inflammatory cytokines. Therefore, it may be of clinical significance to reduce the possibility of pancreatic fat infiltration. One study has shown a promising result in reducing severity of acute pancreatitis episodes in NAFPD state by administration of lipase inhibitor (Orlistat).\textsuperscript{[42]}

Taken together, liver and pancreas are all the involved organs of ectopic fat accumulation, dysfunctional adipose tissue resulting from positive energy balance, and increased storage of TG in adipocytes is associated with hypertriglyceridemia. NAFLD may not only impair the biosynthesis of APO A-1 but also facilitate pancreatic infiltration with adipocytes, rendering these patients even more susceptible to harmful consequences of pancreatic inflammation. Reducing the severity of NAFLD which is currently easier to evaluate by biopsy under abdominal ultrasonography or EUS compared to NAFPD,\textsuperscript{[14,19,43]} is likely to ameliorate pancreatic fatty infiltration and inflammation as well as disease progression. In particular, early detection of NAFLD provides opportunities for interventions to address the commonly associated ectopic fat deposition and abnormalities of lipid metabolism with the development of NAFPD, such as physical activity. Further investigations are warranted to verify this relationship and explore the potential role of EUS with diagnosis and treatment evaluation of NAFPD. CT and MRI fail to play a diagnostic role in our study, which to some extent reflects the lack of awareness or attention to NAFPD in the past.

There are several limitations to this study. First, the data from one single institution may limit the generalizability, the incidence proportion of NAFPD in this study was 1.2\%, which is not higher than that of previous Chinese population-based cohort study; second, it is a retrospective study with relatively small sample...
size of patients with NAFPD, some important data and potentially important variables (such as waist circumference, free fatty acids, HDL, inflammation factors, incidence of pancreatic cancer and acute pancreatitis, and so on) were not available, which may therefore impaired statistical analysis to demonstrate possible relations between NAFPD and some important elements; third, the diagnosis of NAFPD is not histologically confirmed because biopsy of the pancreatic tissue of these participants would be unethical. However, the inter-observer agreement of diagnosis of fat infiltration was excellent. Therefore, we believe that our method of assessing NAFPD and NAFLD was valid and reliable; fourth, it is unknown if intracellular or serum TG has a different clinical significance, but it is possible that pancreatic adipocytes influence the function of acinar and/or islet cells by a paracrine effect, while extracellular lipids may lead to lipotoxicity and therefore islet or acinar cells injury.[9]

CONCLUSIONS

NAFLD, hypertriglyceridemia, and decreased serum ApoA-1 are independent risk factors for NAFPD. They are all abnormal metabolic manifestations of ectopic fat accumulation. Further research for unraveling NAFPD’s pathophysiological mechanism and clinical consequences on the long term are warranted. We will conduct more prospective work in diagnosis and evaluation of NAFPD with a highly effective and useful modality of EUS.

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Conflicts of interest
Zhendong Jin is an Associate Editor of the journal. This article was subject to the journal’s standard procedures, with peer review handled independently of this editor and his research group.

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