**Fatty Pancreas: Linking Pancreas Pathophysiology to Nonalcoholic Fatty Liver Disease**

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Received: 17 February 2022 | Revised: 5 June 2022 | Accepted: 27 June 2022 | Published: 14 July 2022

**Abstract**

Currently, scientific interest has focused on fat accumulation outside of subcutaneous adipose tissue. As various imaging modalities are available to quantify fat accumulation in particular organs, fatty pancreas has become an important area of research over the last decade. The pancreas has an essential role in regulating glucose metabolism and insulin secretion by responding to changes in nutrients under various metabolic circumstances. Mounting evidence has revealed that fatty pancreas is linked to impaired β-cell function and affects insulin secretion with metabolic consequences of impaired glucose metabolism, type 2 diabetes, and metabolic syndrome. It has been shown that there is a connection between fatty pancreas and the presence and severity of nonalcoholic fatty liver disease (NAFLD), which has become the predominant cause of chronic liver disease worldwide. Therefore, it is necessary to better understand the pathogenic mechanisms of fat accumulation in the pancreas and its relationship with NAFLD. This review summarizes the current knowledge of the epidemiology, diagnosis, risk factors, and metabolic consequences of fatty pancreas and discusses its pathophysiology links to NAFLD.

**Citation of this article:** Rugivarodom M, Geeratragool T, Pausawasdi N, Charatcharoenwittaya P. Fatty Pancreas: Linking Pancreas Pathophysiology to Nonalcoholic Fatty Liver Disease. J Clin Transl Hepatol 2022;10(6):1229–1239. doi: 10.14218/JCTH.2022.00085.

**Introduction**

The prevalence of obesity is rapidly increasing worldwide because of sedentary lifestyles and the westernization of diets. It is well known that obesity causes numerous metabolic derangements and accumulation of fat in specific visceral organs, including the liver and the pancreas. In the liver, the accumulation of triglycerides in the absence of excessive alcohol intake and other chronic liver diseases has been defined as nonalcoholic fatty liver disease (NAFLD). NAFLD can progress from simple steatosis to the more active form of nonalcoholic steatohepatitis and eventually lead to cirrhosis, hepatocellular carcinoma, and a short life expectancy. Recently, fat accumulation in the pancreas has gained considerable attention. Excessive fat storage in pancreatic tissue was first reported by Ogilvie in 1933, who called it pancreatic lipomatosis. The term pancreatic lipomatosis has since been replaced by various terms, including fatty pancreas, pancreatic steatosis, pancreatic fat accumulation, fatty infiltration of the pancreas, lipomatous pseudohypertrophy, and nonalcoholic fatty pancreas. In this review, the general term “fatty pancreas” refers to all cases of fat accumulation in the pancreas. To date, growing evidence has shown associations between fat content in the pancreas and the liver, suggesting a potential relationship between fatty pancreas and NAFLD. The data also suggest that fatty pancreas has unfavorable effects on glucose metabolism and that it is involved in the pathogenesis of NAFLD. This review summarizes the current knowledge on the epidemiology, diagnostic modality, risk factors, and metabolic consequences of fatty pancreas and its pathophysiology links to NAFLD.

**Epidemiology**

The prevalence of fatty pancreas varies significantly population ethnicity and the diagnostic methods used. Health examinations utilizing transabdominal ultrasound (US) show a prevalence of fatty pancreas ranging from 11% to 35% in Asian populations. The prevalence of fatty pancreas increased to 61.4% in individuals visiting an obesity clinic. However, data on the epidemiology of fatty pancreas in Western populations is limited. The prevalence of fatty pancreas was 27.8% in 230 patients who were referred for various reasons to an academic medical center in the United States of America for endoscopic ultrasound (EUS). To date, Wong and colleagues reported the most comprehensive data on the prevalence of fatty pancreas in the general population. A group of 685 adults chosen randomly from the government census database in Hong Kong, un-
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derwent standardized chemical shift-encoded magnetic res-
onance imaging (MRI) of the pancreas. The upper limit of
normal was the ninety-fifth percentile of intrapancreatic fat
deposition in individuals who did not meet any of the criteria
for metabolic syndrome and had no history of alcohol abuse.
Fatty pancreas was found in 16.1% of the general popula-
tion [95% confidence interval (CI): 13.3–18.8%]. Data on
the prevalence of fatty pancreas in selected populations of
persons with various metabolic disorders were systemati-
cally reviewed by Singh and colleagues. 15 A meta-analysis
of 11 studies comprising 12,675 individuals estimated a
pooled prevalence of 33% (95% CI: 24–41%). It is note-
worthy that the included studies used a variety of imaging
modalities. Fatty pancreas was found to be associated with
a 67% increased risk of hypertension, a 108% increased
risk of diabetes mellitus, and a 137% increased risk of met-
abolic syndrome.15 Several studies have reported an asso-
ciation between fatty pancreas and NAFLD.9,10,16 According
to imaging studies, approximately 50–80% of patients with
nonalcoholic steatohepatitis have fatty pancreas.17,18 The
findings indicate that individuals with metabolic syndrome
and NAFLD should be tested for fatty pancreas; however,
further research is needed to better define the epidemiology
of fatty pancreas.

Detection of pancreatic fat
Fat accumulation in the pancreas can be either intralobular
or interlobular. Intralobular fat comprises lipid droplets in
endocrine cells, lipid droplets in acinar cells, and the re-
placement of acinar or other apoptotic cells with adipocytes.
In contrast, interlobular fat constitutes interlobular adipocy-
tes and a small lipid droplet in stellate cells and is exclu-
sively observed in a quiescent state.19 Intrapancreatic fat
is usually located within the interstitial septa and spares
the acini and islets of Langerhans,20 as shown in Figure 1.
Of note, fat accumulation may be unequally distributed
throughout the pancreas.21 Different cut-off values of fat accumulation in the pan-
creas for determining fatty pancreas have been used. An
initial study reported that 60% of healthy subjects had a
pancreatic fat content of more than 5%.14 Several studies
found that a normal pancreas had a maximum fat content of
10.4%.14,22 A meta-analysis reported that the highest limit
of normal pancreatic fat in healthy persons participating in
MRI studies was 6.2%.15 This threshold is recommended for
use in future research.
There is no standard grading system for the severity of
fatty pancreas. In a cross-sectional study of 367 patients
who underwent pancreatoduodenectomy for pancreatic
ductal adenocarcinoma, the histology of pancreatic fat accu-
cumulation was classified into three grades, mild (fat infiltra-
tion of less than 10% of total pancreatic tissue), moderate
(fat infiltration of 10–20% of total pancreatic tissue), and
severe (fat infiltration of more than 20% of total pancreatic
tissue).23 Therefore, to determine the presence and severity
of fatty pancreas in routine patient care, standardized ex-
amination approaches with a clinically meaningful threshold
for fatty pancreas must be developed.
Pathophysiology of pancreatic fat accumulation
The two main mechanisms for pancreatic fat accumulation
are fatty replacement and fatty infiltration.6,8,24,25 Fatty
replacement, which is often believed to be irreversible,
occur because of pancreatic acinar cell death. This theo-
retical pathogenic pathway was derived from animal and
observational studies. In animal studies, pancreatic duct
ligation resulted in an increased pancreas volume in mice
because of interstitial edema in the first 2 days, followed
by a rapid decrease in pancreas volume because of acinar
cell apoptosis. After 2 weeks, the pancreas gradually be-
came more prominent because of fatty replacement, reach-
ing a volume comparable to a normal pancreas within 8
weeks.25 Several human observational studies showed that
pancreatic insults causing necrosis of acinar cells resulted
in fatty replacement. Recurrent acute pancreatitis may re-
duce the parenchymal mass and substitute it with adipo-
cytes. Medications, such as corticosteroids and gemcitabine, can induce pancreatic necrosis and fatty tissue replacement. Certain congenital syndromes, including cystic fibrosis, hemochromatosis, Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, and carboxyl-ester-lipase gene mutations, were found to be associated with pancreatic fatty replacement. In cystic fibrosis, mucous plugs obstruct the pancreatic ductules, causing pancreatic parenchyma damage and death, and the resulting empty spaces are occupied by adipocytes. In hemochromatosis, iron overload causes fatal damage to the pancreatic parenchyma, which is subsequently replaced by adipose tissue. The pathophysiology of fatty pancreas in specific congenital syndromes is not yet known.

On the other hand, fatty infiltration of the pancreas by adipocytes that typically occurs in obesity is potentially reversible. Circulating free fatty acids, dietary fat intake, and de novo lipogenesis are all potential sources of fatty infiltration. In an animal study, Zucker diabetic fatty rats fed a high-fat diet developed fat accumulation in pancreatic acinar cells. Animal and in vitro studies led to the description of a potential mechanism of fatty infiltration. In the presence of oxidative stress, an increase in free fatty acid transport to the pancreas by very-low-density lipoprotein and changes in various adipokines such as adiponectin, lipocalin-2, and hepatokine fetuin-A via the serine/threonine-protein kinase 25 (STK-25) pathway may contribute to this type of pancreatic fat accumulation.

**Risk factors for fatty pancreas**

Age, sex, and ethnicity have been shown to be associated with fatty pancreas. In addition to genetic predisposition, metabolic and environmental risk factors, notably cigarette smoking and alcohol consumption, have been linked to fatty pancreas. Fat accumulation in the pancreas increases until the sixth decade, whereas parenchymal pancreatic volume increases until the third decade and then declines. That leads to an increase in the fat/parenchyma ratio in the elderly. According to a study that used fat-water MRI and proton-magnetic resonance spectroscopy (MRS) to measure pancreatic fat in healthy Chinese subjects, the overall risks of developing fatty pancreas were 4.95 (95% CI: 2.07–11.8) in elderly and 3.20 (95% CI: 1.56–6.19) in younger adults.

The prevalence of fatty pancreas also varies with sex. Obese men have higher visceral adipose tissue (VAT) and ectopic fat deposition in the liver and pancreas than obese women, regardless of body mass index (BMI). Fatty pancreas is more common in men between 40 and 49 years of age. In women, the prevalence of fatty pancreas is highest in the past 5 years. This finding is supported by data showing that menopause changes adipose tissue toward a more android phenotype.

The occurrence of fatty pancreas also differs with ethnicity. Fatty pancreas defined by MRI is more prevalent in Hispanics and Caucasians than in African Americans. A study that used computed tomography (CT) as a diagnostic modality found that Asians were more likely than Caucasians to have fatty pancreas. Insulin resistance has been associated with fatty pancreas in African Americans but not in Hispanics.

The impact of lifestyle factors, such as tobacco smoking and alcohol consumption, on the development of fatty pancreas has been evaluated. Alcohol intake, even moderate alcohol consumption, was associated with increased fat deposition in the pancreas. In a study using MRI to measure intrapancreatic fat deposition, the amount of tobacco used but not the duration of smoking contributed to a higher variation in intrapancreatic fat deposition in patients after an attack of acute pancreatitis. This finding provides insight into the interplay between these risk factors and pancreatic fat deposition, particularly after pancreatitis.

Several investigations have discovered an association between metabolic syndrome and an increased risk of fatty pancreas in individuals with different ethnic backgrounds. Metabolic features, including increased BMI and obesity, have been linked to pancreatic fat accumulation. The association is likely attributed to visceral obesity, as VAT is related to fatty pancreas. Other components of the metabolic syndrome, such as hypertension, diabetes, and hypertriglyceridemia, have also been reported to be independent factors associated with fatty pancreas.

Local inflammation of the pancreas has been shown to be associated with pancreatic fatty replacement. A study evaluating clinical and radiological characteristics of patients with chronic pancreatitis showed that more severe chronic pancreatitis was significantly correlated with higher intrapancreatic fat content measured by MRI. A systematic review of 13 studies, including 2178 patients, reported a prevalence of fatty pancreas of up to 52% in patients with pancreatic cancer or other premalignant lesions. Moreover, the presence of precancerous or cancerous lesions significantly increased the risk of fatty pancreas. Diagnostic accuracy of this method is hampered by operator dependency, body habitus interference, and difficulty in visualizing endoscopic fine “salt and pepper” dots in the pancreatic parenchyma and the visibility of the pancreatic duct margin (Fig. 2). The severity of fatty pancreas was reported as grade I (hyperchoic or isochoic parenchyma with a clear appearance of salt and pepper dots in the pancreatic parenchyma and a clear delineation of the main pancreatic duct), grade II (hyperechoic parenchyma with a clear appearance of salt and pepper dots in the pancreatic parenchyma and a clear delineation of the main pancreatic duct), grade III (moderate hyperechoic parenchyma with moderate obscuration of salt and pepper dots in the pancreatic parenchyma and the pancreatic duct margin), or grade IV (severely hyperechoic parenchyma with severe obscuration of salt and pepper dots in the pancreatic parenchyma and the pancreatic duct margin).

**Diagnosis of fatty pancreas**

Tissue sampling of the pancreas is not feasible for determining fatty pancreas in daily practice because of its anatomic position. Imaging modalities allow for the noninvasive detection and quantification of fat accumulation in the pancreas. Transabdominal US has been used to visualize pancreatic tissue and detect fat accumulation within the organ. Fatty pancreas is diagnosed by comparing the echogenicity of the pancreas with that of the kidney or liver (Fig. 2). The diagnostic accuracy of this method is hampered by operator dependency, body habitus interference, and difficulty in visualizing endoscopic fine “salt and pepper” dots in the pancreatic parenchyma and the visibility of the pancreatic duct margin (Fig. 2). The severity of fatty pancreas was reported as grade I (hyperechoic or isochoic parenchyma with a clear appearance of salt and pepper dots in the pancreatic parenchyma and a clear delineation of the main pancreatic duct), grade II (hyperechoic parenchyma with a clear appearance of salt and pepper dots in the pancreatic parenchyma and a clear delineation of the main pancreatic duct), grade III (moderate hyperechoic parenchyma with moderate obscuration of salt and pepper dots in the pancreatic parenchyma and the pancreatic duct margin), or grade IV (severely hyperechoic parenchyma with severe obscuration of salt and pepper dots in the pancreatic parenchyma and the pancreatic duct margin).
Fig. 2. Imaging of fatty pancreas. (A) Transabdominal ultrasonography shows iso-echogenicity of normal pancreatic parenchyma (arrowhead) compared with the liver. (B) A sonographic image of fatty pancreas reveals increased parenchymal echogenicity of the pancreas (arrowhead) compared with the liver. (C) Computed tomography of the normal pancreas shows iso-attenuation of the pancreas compared with the spleen. (D) Computed tomography of histologically proven fatty pancreas reveals lower pancreatic parenchyma attenuation compared to the spleen. (E) Endoscopic ultrasound shows iso-echogenicity of normal pancreatic parenchyma with a distinctive salt and pepper appearance and a delineated main pancreatic duct. (F) An endosonographic image of fatty pancreas reveals increased parenchymal echogenicity, obscuring the characteristic salt and pepper appearance and the main pancreatic duct margin. (G) Magnetic resonance imaging with the Dixon technique of a subject with normal pancreatic fat content. (H) Magnetic resonance imaging of the pancreatic fat fraction with the Dixon technique in a subject with fatty pancreas.
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Fig. 3. Organ crosstalk in the pathophysiology of fatty pancreas and nonalcoholic fatty liver disease (NAFLD). Excessive calorie consumption and specific dietary components increase the risk of insulin resistance, metabolic disorders, and fat accumulation in the liver, pancreas, and visceral adipose tissue (VAT). In insulin resistance, hepatic steatosis with an increased hepatic very-low-density lipoprotein (VLDL) can accelerate fat accumulation in the pancreas, causing islet cell death. Alterations in adipocytokines, such as increased lipocalin-2 and serine/threonine-protein kinase 25 (STK-25) and decreased adiponectin from VAT and pancreatic fat, directly cause β-cell death. Fetuin-A, a hepatokine generated by the fatty liver, activates adipocytes and macrophages in the pancreatic islets and accelerates β-cell dysfunction, leading to insulin resistance and ectopic fat deposition in other tissues. Hepatic fat accumulation further promotes insulin resistance, resulting in a self-perpetuating loop in which insulin stimulates the synthesis of free fatty acids (FFA) spilling into the pancreas. This vicious cycle interaction between the liver and pancreas is the twin cycle hypothesis. Moreover, fatty pancreas and insulin resistance promote fat accumulation in the liver and accelerate the progression of NAFLD.

**Metabolic consequence of fatty pancreas**

Experimental and clinical studies provide evidence that fatty pancreas is associated with the development of prediabetes, type 2 diabetes mellitus (T2DM), and metabolic syndrome through the main mechanisms of β-cell dysfunction and insulin resistance (Fig. 3).  

**Fatty pancreas and β-cell dysfunction**

Animal and preclinical studies have shown that fatty pancreas induces local inflammation that causes β-cell destruction. In mice fed a high-fat diet, the overexpression of STK-25 from ectopic adipose tissue aggravates fat infiltration of the pancreas, resulting from increased pancreatic inflamma-
Glucolipotoxicity is the conceptual hypothesis that explains the pathogenesis of fatty pancreas for β-cell dysfunction. Hyperglycemia causes an increase in malonyl coenzyme A via the tricarboxylic acid cycle. Increased malonyl coenzyme A inhibits carnitine palmitoyltransferase-1 and reduces mitochondrial β-oxidation while promoting intracellular triglyceride accumulation in β-cells. The lipolysis from VAT increases circulating free fatty acids and then promotes intracellular triglyceride accumulation in β-cells. Chronic intracellular triglyceride accumulation blunts insulin gene expression, and glucose-stimulated insulin secretion results in β-cell dysfunction. In addition, alterations of adipocytokines, such as increased lipocalin-2 and STK-25 and decreased adiponectin, mediate this process. The lipolysis from VAT increases mitochondrial β-oxidation while promoting intracellular triglyceride accumulation in β-cells. Therefore, adiponectin inhibits carnitine palmitoyltransferase-1 and reduces mitochondrial β-oxidation.

**Fatty pancreas and insulin resistance**

Preclinical studies revealed that C57BL/6 mice fed a high-fat diet developed NAFLD and fatty pancreas that resulted in insulin resistance determined by the intraperitoneal insulin tolerance test and the OGTT. However, the association between fatty pancreas and insulin resistance remains controversial in human studies. Insulin resistance confirmed by homeostasis model assessment of insulin resistance (HOMA-IR), circulating levels of tumor necrosis factor-α, and interleukin-1β, was higher in obese children with NAFLD complicated by fatty pancreas than in children without fatty pancreas. Although a large cohort of Chinese adults did not show an association between fatty pancreas and HOMA-IR, adults with both fatty pancreas and NAFLD had a higher HOMA-IR than those with either condition alone. Furthermore, even after adjusting for hepatic fat content and BMI, pancreatic fat content was still associated with an increased hepatic very-low-density lipoprotein (VLDL) and triglyceride production in the pancreas at baseline. Based on the existing evidence, it is now established that there is a vicious cycle of NAFLD complications with an increased hepatic very-low-density lipoprotein (VLDL) and triglyceride production in the pancreas at baseline.
### Table 1. Clinical studies of the relationships of fatty pancreas, metabolic dysfunction, and NAFLD

| Author             | Year | Study Design | No. of Patients | Diagnostic Modality | Fatty Pancreas in Relation to Metabolic Dysfunction and NAFLD |
|--------------------|------|--------------|----------------|---------------------|-------------------------------------------------------------|
| **Metabolic dysfunction** | | | | | |
| Ou *et al.* | 2013 | Retrospective | 7464 | Transabdominal US | Increase the risk of prediabetes (OR 1.22, 95% CI: 1.002–1.491). Increase the risk of diabetes (OR 1.38, 95% CI: 1.05–1.82). |
| Wang *et al.* | 2014 | Cross-sectional | 8097 | Transabdominal US | Association with age (OR 2.211, 95% CI: 1.895–2.602), obesity (OR 1.908, 95% CI: 1.641–2.219), and diabetes (OR 1.465, 95% CI: 1.194–1.797). |
| Lesmana *et al.* | 2015 | Cross-sectional | 1054 | Transabdominal US | Association with diabetes (OR 1.95, 95% CI: 1.16–3.28), male sex (OR 1.82, 95% CI: 1.35–2.45), age >35 years (OR 4.01, 95% CI: 2.82–5.70), hypertension (OR 2.18, 95% CI: 1.58–2.99), central obesity (OR 4.13, 95% CI: 3.09–5.52), hypertriglyceridemia (OR 1.92, 95% CI: 1.41–2.62), and hypercholesterolemia (OR 1.88, 95% CI: 1.42–2.49). |
| Singh *et al.* | 2016 | Systematic review | 1209 | MRI | Increase the risk of diabetes (RR 2.08, 95% CI: 1.44–3.0). Increase risk of metabolic syndrome (RR 2.37, 95% CI: 2.07–2.71) |
| Zhou *et al.* | 2016 | Cross-sectional | 1190 | Transabdominal US | Association with age <40 years (OR 0.41, 95% CI: 0.27–0.64), central obesity (OR 5.76, 95% CI: 3.75–8.84), diabetes (OR 1.52 95% CI: 1.08–2.14), and hypertriglyceridemia (OR 1.35, 95% CI: 1.01–1.80). |
| Bi *et al.* | 2019 | Meta-analysis | 49,329 | Transabdominal US, EUS, MRI | Increase the risk of diabetes (RR 1.99, 95% CI: 1.67–2.19). Increase risk of metabolic syndrome (RR 2.2.5, 95% CI: 2.00–2.53). |
| Yamazaki *et al.* | 2018 | Prospective | 320 | CT scan | Increase risk of metabolic syndrome (RR 2.04, 95% CI: 1.14–3.64). |
| Wang *et al.* | 2018 | Cross-sectional | 2093 | Transabdominal US | Association with central obesity (OR 5.36, 95% CI: 1.89–15.2), NAFLD (OR 2.67, 95% CI: 1.33–5.34), and age (OR 1.03, 95% CI: 1.01–1.06). |
| Weng *et al.* | 2018 | Cross-sectional | 4419 | Transabdominal US | The severity of fatty pancreas was correlated with central obesity (OR 0.06, 95% CI: 0.02–0.15), and triglyceride level (0.67, 95% CI: 0.50–0.92). |
| Yamazaki *et al.* | 2020 | Prospective | 1478 | CT scan | Increases risk of diabetes (OR 1.32, 95% CI: 1.06–1.63). |
| Chan *et al.* | 2021 | Prospective | 631 | MRI | Increases risk of diabetes (HR 1.81, 95% CI: 1.1–3.0). |
| **NAFLD** | | | | | |
| Schwener *et al.* | 2008 | Cross-sectional | 17 | MRI | No correlation with hepatic fat content. |
| van Greenen *et al.* | 2010 | Cross-sectional | 80 | Autopsy pathology | No association with NAFLD when adjusting for BMI. |
| Targher *et al.* | 2012 | Cross-sectional | 42 | MRI | No correlation with liver fat when adjusted for age, sex, and visceral fat content. |
| Wang *et al.* | 2014 | Cross-sectional | 8097 | Transabdominal US | Association with NAFLD (OR 2.28, 95% CI: 1.96–2.65). |
| Uygun *et al.* | 2015 | Cross-sectional | 119 | Transabdominal US | The prevalence of fatty pancreas in NASH patients was higher than that of the healthy controls (51.2% vs. 14%, p=0.001). The combined prevalence of diabetes and prediabetes was higher in patients with NASH and fatty pancreas than patients with only NASH (74.4% vs. 41.4%, p=0.004). |

(continued)
### Table 1. Fatty Pancreas in Relation to Metabolic Dysfunction and NAFLD

| Author          | Year   | Study Design   | No. of Patients | No. of Patients | Diagnostic Modality     | Findings                                                                 |
|-----------------|--------|----------------|-----------------|-----------------|-------------------------|--------------------------------------------------------------------------|
| Pacifico et al. | 2015   | Cross-sectional | 158             | 1054            | Transabdominal US       | No association with hepatic fat content when adjusted for age, gender, Tanner stage, BMI standard deviation score, and visceral adipose tissue. |
| Lesmana et al.  | 2015   | Cross-sectional | 1054            | Transabdominal US | Association with NAFLD (OR 2.52, 95% CI: 1.83–3.48) | Association with NAFLD (OR 5.20, 95% CI: 3.84–7.03). |
| Wang et al.     | 2016   | Cross-sectional | 1190            | Transabdominal US | Association with NAFLD (OR 0.27, 95% CI: 0.13–0.54) | Increase the risk of advanced liver fibrosis (OR 0.55, p = 0.001). |
| Weng et al.     | 2018   | Cross-sectional | 4419            | Transabdominal US | Association with NAFLD (OR 0.27, 95% CI: 0.13–0.54) | Increase the risk of NASH (OR 5.37, p < 0.001). |
| Rosenblatt et al.| 2019   | Retrospective   | 104             | Transabdominal US | Association with NAFLD (OR 2.67, 95% CI: 1.33–5.34) | Increase the risk of NASH (OR 2.49, 95% CI: 2.06–3.02). |
| Bi et al.       | 2019   | Meta-analysis   | 49,329          | Transabdominal US, EUS, MRI | Association with NAFLD (OR 2.52, 95% CI: 1.83–3.48) | Increase the risk of NAFLD (RR 2.49, 95% CI: 2.06–3.02). |

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; CT, computed tomography; EUS, endoscopic ultrasound; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; OR, odds ratio; RR, relative risk; TG, triglyceride; US, ultrasonography.

### Evidence from clinical studies

Several cross-sectional human studies showed that NAFLD is an independent factor associated with fatty pancreas (Table 1).9–11,16,18,40,52,77,88–91 Likewise, NAFLD was associated with more severe fat accumulation in the pancreas.1 On the other hand, a recent meta-analysis including 49,329 individuals revealed that fatty pancreas was independently associated with NAFLD (RR 2.49, 95% CI: 2.06–3.02).77 Fatty pancreas is prevalent among patients with nonalcoholic steatohepatitis and increases the rate of prediabetes and diabetes.18 Further, fatty pancreas was also related to subclinical atherosclerosis in NAFLD patients.82 Cumulative evidence has shown that fatty pancreas is significantly associated with more severe histologic features of NAFLD. The histological evaluation of NAFLD children showed a higher liver fibrosis stage, hepatocyte ballooning grading, and NAFLD activity score among NAFLD patients coexisting with fatty pancreas.47 A postmortem pathology study found that intralobular pancreatic fat was associated with nonalcoholic steatohepatitis.39 An analysis of 104 adults with biopsy-proven NAFLD demonstrated that ultrasonographic fatty pancreas was significantly associated with the histologic feature of nonalcoholic steatohepatitis (OR 5.37).91 As fatty pancreas is independently associated with nonalcoholic steatohepatitis and fibrosis stage, fatty pancreas is a potential driver of NAFLD progression.91 Therefore, the existence of fatty pancreas in the NAFLD population warrants meticulous attention.

Interestingly, a study exploring pancreatic and hepatic fat after bariatric surgery showed that bariatric surgery reduced hepatic and pancreatic fat. Nevertheless, there was no correlation between hepatic and pancreatic fat content reduction, suggesting the tissue-specific mobilization of these ectopic fat stores.93 From this finding, it seems that the association between fatty pancreas and NAFLD is mediated by obesity.

### Therapeutic approaches for fatty pancreas

Weight reduction is currently the most effective treatment for NAFLD. Weight loss, whether accomplished by diet and lifestyle modifications, bariatric surgery, or pharmacotherapy, has been shown to improve NAFLD biomarkers, prevent progression, and reverses fibrosis in some cases. Given the importance of providing effective weight loss treatment to patients suffering from obesity-related disorders, much clinical research has examined the effect of weight loss interventions in patients with fatty pancreas.44 Evidence from a randomized controlled trial showed that exercise significantly reduced fat accumulation in the pancreas as measured by MRS, and it improved insulin sensitivity.44 A post-hoc analysis of the data from a randomized controlled trial...
for assessing weight management intervention for T2DM demonstrated that intrapancreatic fat content quantified by MRI significantly declined in T2DM patients with weight loss-induced diabetes remission. Glucagon-like peptide 1 receptor agonists are the only pharmacotherapy shown to reduce pancreatic fat content. The literature is limited, but a few reports have shown that 6 months of exenatide, liraglutide, and dulaglutide, treatment improved liver fat content in patients with T2DM but did not significantly change pancreatic fat content measured by MRI techniques. However, because these drugs induce mild weight reduction in such patients, they may not be effective in causing a decrease in pancreatic fat content.

Several studies investigated the effects of bariatric surgery and subsequent significant weight loss on the fat content of the pancreas. Discovering the molecular pathways of β-cell function in response to loss of pancreatic fat after surgery, the change was independent of a reduction in liver fat content. The results also showed improvement in β-cell function in response to loss of pancreatic fat after bariatric surgery. Discovering the molecular pathways that mediate the metabolic consequences of fatty pancreas would enable clinicians to target the pancreas therapeutically in the management of patients with NAFLD and fatty pancreas.

**Conclusion**

The understanding of fatty pancreas has evolved since the discovery of its relationship with obesity. Age, sex, ethnicity, unhealthy lifestyle, and metabolic disorders are all risk factors. Several imaging modalities have been developed to diagnose fatty pancreas, with MRI being the most accurate method for quantifying pancreatic fat content in clinical studies. Advancements in imaging technology have helped to comprehend pathophysiological relationships between fatty pancreas and other obesity-related disorders, including NAFLD. It is evident that fat accumulation in the pancreas is harmful and subsequently induces mechanisms that impair endocrine function. Moreover, recognizing the strong relationship between fatty pancreas and metabolic disorders has intensified considerable interest in the putative impact of fatty pancreas on the development and progression of NAFLD. Growing evidence has uncovered potential linkages and therapeutic possibilities for fatty pancreas and NAFLD. Moreover, several questions have been raised. How can we better stratify individuals with fatty pancreas who are at high risk of developing metabolic syndrome and NAFLD? Are there any noninvasive biomarkers that can accurately detect fatty pancreas? Are there different types of fatty pancreas, and how do they affect the natural course of NAFLD? What are the best therapeutic approaches for patients with fatty pancreas and NAFLD? Further studies focusing on the pathophysiologic mechanisms may provide novel therapeutics for individuals with NAFLD and fatty pancreas.

**Funding**

This study was supported by a grant from the Siriraj Research Development Fund.

**Conflict of interest**

PC has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

**Author contributions**

Drafted the first version of the manuscript (MR, TG, NP), edited and revised the manuscript, and contributed to the conceptual development of the study (PC).

**References**

[1] Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15(5):288-298. doi:10.1038/s41574-019-0176-6, PMID:30816666.

[2] Neerland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, Shai I, et al. visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Diabetes Endocrinol 2019;7(9):715-725. doi:10.1016/s2213-8587(19)30084-1, PMID:31301983.

[3] Estes C, Chan HLY, Chen RN, Chuang WL, Fung J, Goh GB, et al. Modelling long-term outcomes of patients with non-alcoholic fatty pancreas disease: a prospective evaluation of fatty pancreas by using EUS. Gastrointest Endosc 2011;73(5):987-993. doi:10.1016/j.gie.2011.01.015, PMID:21521567.

[4] Wong VW, Wong GL, Yeung DK, Abrigo JM, Kong AP, Chan RS, et al. Prevalence and incidence of nonalcoholic fatty pancreas disease and its severity in a Chinese population. J Am Heart Assoc 2014;3(1):e000297. doi:10.1161/JAHA.113.000297, PMID:24572250.

[5] Wang CY, Ou HY, Chen MF, Chang TC, Chang CJ. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. J Am Heart Assoc 2014;3(1):e000297. doi:10.1161/JAHA.113.000297, PMID:24572250.

[6] Al-Haddad M, Khishaba M, Zyromski N, Pungnapong S, Wallace MB, Scalpi J, et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. Pancreas 2009;38(6):672-675. doi:10.1097/TPA.0b013e31819406e4, PMID:19505631.

[7] Uygur A, Kadayifci A, Demirci H, Saglam M, Saim K, Ozturk K, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis. Hepatol Res. 2015;10(6):589-597. doi:10.1111/1751-0088.12368, PMID:26034872.

[8] Shah N, Rocha JP, Bhutiani N, Endashaw O. Nonalcoholic Fatty Pancreas Disease. Nutr Clin Pract 2019;34(Suppl 1):S49-S56. doi:10.1002/ncc.13573. PMID:31537357.

[9] Tsai YJ, Chen Y, Liu HJ, Kao YF, Yeh CH, et al. Fatty pancreas and NAFLD: the clinical significance of pancreatic steatosis. Hepatology 2011;53(5):1367-1377. doi:10.1002/hep.24379, PMID:21616264.

[10] Majumder S, Philip NA, Takahashi N, Levy MJ, Singh VP, Chari ST. Fatty pancreas. Pancreas 2017;46(10):1251-1258. doi:10.1097/MPA.0000000000000941, PMID:28940184.

[11] Weng S, Zhou J, Chen X, Sun Y, Mao Z, Chai K. Prevalence and factors associated with nonalcoholic fatty pancreas disease and its severity in China. Medicine (Baltimore) 2018;97(26):e12193. doi:10.1097/MD.0000000000011293, PMID:29953011.

[12] Lee JS, Kim SH, Jun DW, Han JH, Jang EC, Park JY, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome in a Chinese population. Pancreatology 2016;16(4):578-583. doi:10.1016/j.pan.2016.03.008, PMID:27050733.

[13] Lesmana CR, Pakasli LS, Supriatna M, Aidawati ML, Lesmana LA. Prevalence of Non-Alcoholic Fatty Pancreas Disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. BMC Gastroenterol 2015;15:174. doi:10.1186/s12876-015-0404-1, PMID:26521757.

[14] Wong VW, Wong GL, Yeung DK, Abrigo JM, Kong AP, Chan RS, et al. Fatty pancreas, insulin resistance, and β-cell function: a population study using fat-water magnetic resonance imaging. Am J Gastroenterol 2014;109(4):589-597. doi:10.1038/ajg.2014.1, PMID:24492753.

[15] Singh RG, Yoon HD, Wu LM, Lu J, Plank LD, Petrov MS. Ectopic fat accumulation in the pancreas and its clinical relevance: A systematic review, meta-analysis, and meta-regression. Metabolism 2017;69:1-13. doi:10.1016/j.metabol.2016.12.012, PMID:28285630.

[16] Wang CY, Ou HY, Chen MF, Chang TC, Chang CJ. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. J Am Heart Assoc 2014;3(1):e000297. doi:10.1161/JAHA.113.000297, PMID:24572250.

[17] Al-Haddad M, Khishaba M, Zyromski N, Pungnapong S, Wallace MB, Scalpi J, et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. Pancreas 2009;38(6):672-675. doi:10.1097/TPA.0b013e31819406e4, PMID:19505631.

[18] Uygur A, Kadayifci A, Demirci H, Saglam M, Saim K, Ozturk K, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis. Hepatol Res. 2015;10(6):589-597. doi:10.1111/1751-0088.12368, PMID:26034872.

[19] Petrov MS, Taylor R. Intra-pancreatic fat deposition: bringing hidden fat to the fore. Nat Rev Gastroenterol Hepatol 2021;18(3):153-168. doi:10.1038/s41575-021-00551-0, PMID:34480411.

[20] Shah N, Rocha JP, Bhutiani N, Endashaw O. Nonalcoholic Fatty Pancreas Disease. Nutr Clin Pract 2019;34(Suppl 1):S49-S56. doi:10.1002/ncc.13573. PMID:31537357.

[21] Matsumoto S, Mori H, Miyake H, Takaki H, Maeda T, Yamada Y, et al. Un-even fatty replacement of the pancreas: evaluation with CT. Radiology 1995;194(2):453-458. doi:10.1148/radiology.194.2.7824726, PMID:7824726.

[22] Chan TT, Tse YK, Lui RN, Wong GL, Chim AM, Kong AP, et al. Fatty Pancreas
Is Independently Associated With Subsequent Diabetes Mellitus Development: A 10-Year Prospective Cohort Study. Clin Gastroenterol Hepatol 2021;10:1016/j.cgh.2021.09.027. PMID:34571257.

[51] Mori H, Takahashi N, Yamashita M, Ishigami R, et al. Association of pancreatic fatty infiltration with pancreatic ductal adenocarcinoma. Clin Transl Gastroenterol 2014;5:s13. doi:10.1038/ctg.2014.5, PMID:24622649.

[52] Wagner R, Eckstein SS, Yamazaki H, Gerst F, Machann J, Jaghurzati BA, et al. Non-alcoholic pancreatic steatosis: quantitative assessment with preoperative multi-parametric MR Imaging. Radiology 2016;279(1):140–150. doi:10.1148/radiol.2015142284. PMID:26556228.

[53] Al-Marhabe A, Hollingsworth KS, Stevens T, Trinkaus D, Taylor R. Quantification of pancreatic steatosis in type 2 diabetes mellitus: a prospective study. J Gastroenterol Hepatol 2018;34(12):2451–2455. doi:10.1111/jgh.14266, PMID:29697157.

[54] Reeder SB, Hu BH, Sirlin CB. Proton density fat fraction: a standardized MR-based biomarker of tissue fat concentration. J Magn Reson Imaging 2011;34(2):361–367. doi:10.1002/jmri.22579, PMID:21460092.

[55] Hu HH, Kim HW, Nayak KS, Goran MI. Comparison of fat-water MRI and proton density fat fraction with quantitative CT: an MRI correlation analysis. Clin Radiol.2015;70(12):1512–1519. doi:10.1016/j.crad.2015.07.001, PMID:26393270.

[56] Idolman IS, Tuzun A, Savas B, Elhan AH, Celik A, Idilman R, et al. Pancreatic Steatosis Demonstrated at MR Imaging in the General Population: Clinical Relevance. Radiology 2015;276(1):129–136. doi:10.1148/radiol.13122883, PMID:24475851.

[57] Rugvaridom M, et al. Fatty pancreas and NAFLD
and fibrogenesis of pancreatic cells in rats. Diabetes 2008;57(3):e31–e38. doi:10.2337/db07-1331.

[71] Tushizui ME, Bunck MC, Pouwels PJ, Bontemps S, van Waesberghe JH, Schindhelm RK, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. Diabetes Care 2007;30(11):2916–2921. doi:10.2337/dc07-1331.

[72] Bregovatz P, Koliaki C, Weber K, Strasserburg K, Nouwotry B, Nouwotry P, et al. Pancreatic adipose tissue inflammation, parenchymal steatosis and beta cell function in humans. Diabetologia 2015;58(7):1646–1655. doi:10.1007/s00125-015-3545-5.

[73] Fraulob-JC, Ogg-Diamantino R, Fernandes-Santos C, Aguil MB, Mandram-Lacerda CA. A Mouse Model of Metabolic Syndrome: Insulin Resistance, Fatty Liver and Non-Alcoholic Fatty Pancreas Disease (NAFPD) in C57BL/6 Mice Fed a High Fat Diet. J Clin Biochem Nutr 2010;46(3):212–223. doi:10.3164/jbn.09-83. PMID:20490316.

[74] Della Corte C, Mosca A, Majo F, Lucidi V, Panera N, Giglioni E, et al. Non-alcoholic fatty pancreas disease and Non-alcoholic fatty liver disease: more than ectopic fat. Clin Endocrinol (Oxf) 2015;83(5):566–602. doi:10.1111/cen.12682. PMID:26201937.

[75] van der Zijl NJ, Goessens GH, Moors CC, van Raalte DH, Muskiet MH, Pouwels PJ, et al. Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on beta-cell function in individuals with impaired glucose metabolism. J Clin Endocrinol Metab 2011;96(2):459–467. doi:10.1210/jc.2010-1722. PMID:21084401.

[76] Ou HY, Wang CY, Yang YC, Chen MF, Chang CJ. The association between non-alcoholic fatty pancreas disease and diabetes. PLoS One 2013;8(5):e62561. doi:10.1371/journal.pone.0062561.

[77] Mantovani A, Byrne CD, Bonora E, Targar G. Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. Diabetes Care 2018;41(2):372–382. doi:10.2337/dct-17-0092. PMID:29385469.

[78] Ballestri S, Zona S, Targar G, Romagnoli D, Baldelli E, Nascimbieni F, et al. Non-alcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol 2016;31(8):1394–1404. doi:10.1111/jgh.13264. PMID:27076421.

[79] Harmon JS, Gleason CE, Tanaka Y, Poutot V, Robertson RP. Antecedent hyperglycemia, not hyperlipidemia, is associated with increased islet trafficking and decreased insulin gene mRNA level in Zucker diabetic fatty rats. Diabetes 2001;50(11):2481–2486. doi:10.2337/diabetes.50.11.2481.

[80] Zhao ZZ, Xin XL, Xia JH, Yang SL, Chen YX, Li K. Long-term High-fat High-sucrose Diet Promotes Enlarged Islets and β-Cell Damage by Oxidative Stress in Mice. Pancreas 2015;44(2):1798–1806. doi:10.1097/MPA.0000000000000349. PMID:25906446.

[81] van Raalte DH, van der Zijl NJ, Diamant M. Pancreatic steatosis in humans: cause or marker of lipotoxicity?Curr Opin Clin Nutr Metab Care 2010;13(4):478–485. doi:10.1097/MCO.0b013e328333a1ef. PMID:20986606.

[82] Miyake H, Sakagami J, Yosuda H, Sugami Y, Kato R, Suwa K, et al. Association of fatty pancreas with pancreatic endocrine and exocrine function. PLoS One 2018;13(12):e0209448. doi:10.1371/journal.pone.0209448. PMID:30597125.

[83] Wagnen R, Jaghutzi BA, Gerst F, Barroso Oquendo M, Machani J, Schick F, et al. Pancreatic Steatosis Associates With Impaired Insulin Secretion and Genetically Predisposed Individuals. J Clin Endocrinol Metab 2020;105(11):dgaa435. doi:10.1210/clinem/dgaa435. PMID:32725157.

[84] Lu T, Wang Y, Dou T, Xue B, Tan Y, Yang J. Pancreatic fat content is associated with beta-cell function and insulin resistance in Chinese type 2 diabetes subjects. Endocr J 2019;66(3):265–270. doi:10.1507/endocrj.E18-0436.

[85] Poutot V, Amiot J, Semache M, Zarrouki B, Hageman D, Fontes G. Glucolipotoxicity of the pancreatic beta cell. Biochim Biophys Acta 2010;1801(3):289–298. doi:10.1016/j.bbala.2009.08.006. PMID:19715772.

[86] Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. Diabetologia 2008;51(10):1781–1789. doi:10.1007/s00125-008-1116-7. PMID:18726585.