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Review Article

Fatty Pancreas: Linking Pancreas Pathophysiology to Nonalcoholic Fatty Liver Disease

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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 epidemiology, diagnosis, risk factors, and metabolic consequences of fatty pancreas and discusses its pathophysiology links to NAFLD.

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Introduction

The prevalence of obesity is rapidly increasing worldwide because of sedentary lifestyles and the westernization of diets.[1] It is well known that obesity causes numerous metabolic derangements and accumulation of fat in specific visceral organs, including the liver and the pancreas.[2] 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.[3,4] 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first reported by Ogilvie in 1933, who called it pancreatic lipomatosis.[5] The term pancreatic lipomatosis has since been replaced by various terms, including fatty pancreas, pancreatic steatosis, pancreatic fat accumulation, fatty infiltration of the pancreas, lipomatous pseudohypertrophy,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.[6–8] 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.[9–11] The prevalence of fatty pancreas increased to 61.4% in individuals visiting an obesity clinic.[12] 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).[13]

To date, Wong and colleagues[14] 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-

Keywords: Fatty pancreas; Nonalcoholic fatty liver disease; β-cell function; Insulin resistance; Diabetes mellitus.

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; HR, hazard ratio; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk; STK25, serine/threonine-protein kinase 25; US, ultrasound; VAT, visceral adipose tissue.

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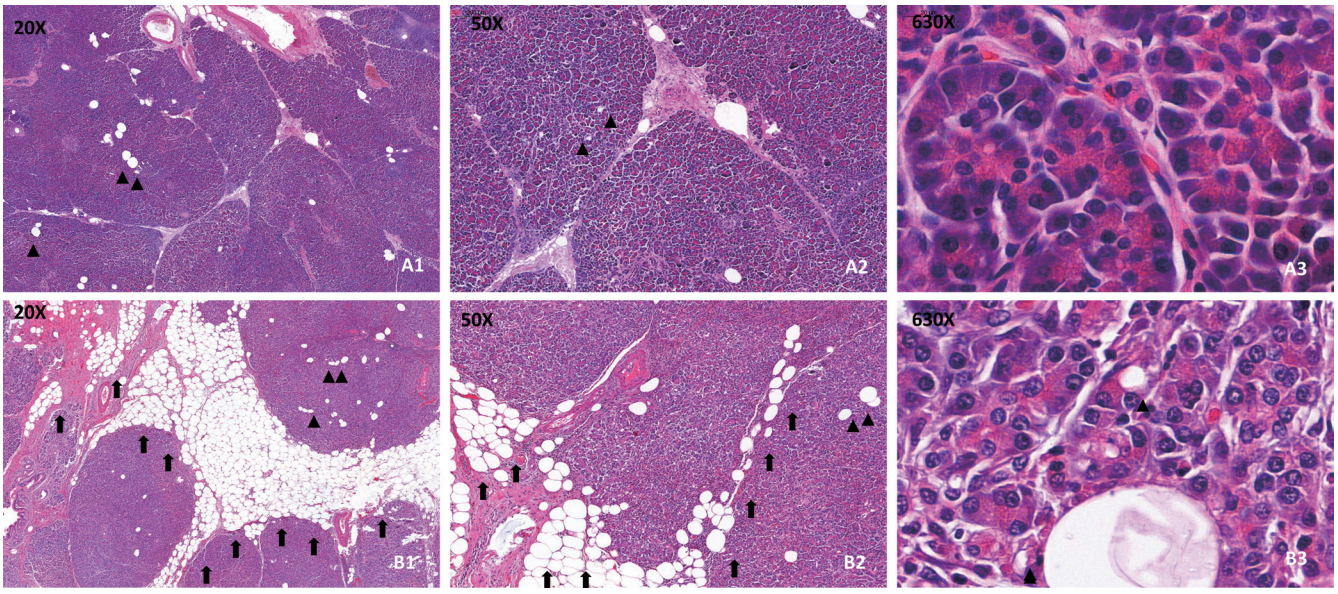

Fig. 1. Histology of normal and fatty pancreas. Histological examination with hematoxylin and eosin stain reveals interlobular adipocytes (arrowhead, A1) predominately with only a few intralobular lipid droplets (arrowhead, A2), accounting for 3% of the total, indicating a normal pancreas (A3). Histological examination shows many peripancreatic (arrowhead, B1) and interlobular adipocytes (arrow, B2) with an increase in intralobular intracellular lipid droplets (B3), accounting for 23% of the total, indicating fatty pancreas.

derwent standardized chemical shift-encoded magnetic resonance 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 population [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 systematically 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%).[15] It is noteworthy 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 metabolic syndrome.[15] Several studies have reported an association 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 replacement of acinar or other apoptotic cells with adipocytes. In contrast, interlobular fat constitutes interlobular adipocytes and a small lipid droplet in stellate cells and is exclusively 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 pancreas 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 accumulation was classified into three grades, mild (fat infiltration 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 examination 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, occurs because of pancreatic acinar cell death. This theoretical 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 became more prominent because of fatty replacement, reaching a volume comparable. to a normal pancreas within 8 weeks.[26] Several human observational studies showed that pancreatic insults causing necrosis of acinar cells resulted in fatty replacement. Recurrent acute pancreatitis may reduce the parenchymal mass and substitute it with adipo-

cytes.[27,28] Medications, such as corticosteroids and gemcitabine, can induce pancreatic necrosis and fatty tissue replacement.[29–32] 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.[6,25] In cystic fibrosis, mucous plugs obstruct the pancreatic ductules, causing pancreatic parenchyma damage and death, and the resulting empty spaces are occupied by adipocytes.[33] In hemochromatosis, iron overload causes fatal damage to the pancreatic parenchyma, which is subsequently replaced by adipose tissue.[6] 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.[6] Circulating free fatty acids, dietary fat intake, and *de novo* lipogenesis are all potential sources of fatty infiltration.[34] In an animal study, Zucker diabetic fatty rats fed a high-fat diet developed fat accumulation in pancreatic acinar cells.[35] 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,[36] lipocalin-2,[37] and hepatokine fetuin-A[38] via the serine/threonine-protein kinase 25 (STK-25) pathway may contribute to this type of pancreatic fat accumulation.[39]

Risk factors for fatty pancreas

Age, sex, and ethnicity have been shown to be associated with fatty pancreas.[9,10,16,40] In addition to genetic predisposition, metabolic and environmental risk factors, notably cigarette smoking and alcohol consumption, have been linked to fatty pancreas.[41,42] 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/parenchymal ratio in the elderly.[43] 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: 1.44–7.15) in middle-aged, compared with young adults.[14]

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).[44] Fatty pancreas is more common in men between 40 and 49 years of age. In women, the prevalence of fatty pancreas is highest after the sixth decade.[14] This finding is supported by data showing that menopause changes adipose tissue toward a more android phenotype.[45]

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.[46,47] A study that used computed tomography (CT) as a diagnostic modality found that Asians were more likely than Caucasians to have fatty pancreas.[48] Insulin resistance has been associated with fatty pancreas in African Americans but not in Hispanics.[49]

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.[17] 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.[42] 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.[9,13,50,51] Metabolic features, including increased BMI and obesity, have been linked to pancreatic fat accumulation.[44,52,53] 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.[9,10,13,16,40]

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.[54] 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.[55] Moreover, the presence of precancerous or cancerous lesions significantly increased the risk of fatty pancreas [relative risk (RR) 2.78, 95% CI: 1.56–4.94].

Diagnosis of fatty pancreas

Tissue sampling of the pancreas is not feasible for determining fatty pancreas in daily practice because of its anatomical 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[16] or liver[10] (Fig. 2). The diagnostic accuracy of this method is hampered by operator dependency, body habitus interference, and changes in parenchymal echogenicity caused by pancreatic fibrosis.[7] EUS has been used to estimate pancreatic fat content. The presence of fatty pancreas was determined by comparing the echogenicity of the pancreas to that of the spleen.[56] The grading system for EUS was proposed based on the pancreatic parenchymal echogenicity with the identifiable characteristic fine "salt and pepper" dots in the pancreatic parenchyma and the visibility of the pancreatic duct margin (Fig. 2).[13] The severity of fatty pancreas was reported as grade I (hypoechoic or isoechoic 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 (moderately 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).[13] However, the system has not been validated by histologic examination or pancreatic fat estimation using CT or MRI. Although EUS enables clear visualization because of the short distances between the measurement instrument and the area of interest, it still has limitations similar to transabdominal US, such as operator dependence. Notably, the need for an endoscopic examination makes EUS relatively more invasive than other imaging modalities. CT is a commonly used imaging technology for quantifying pancre-

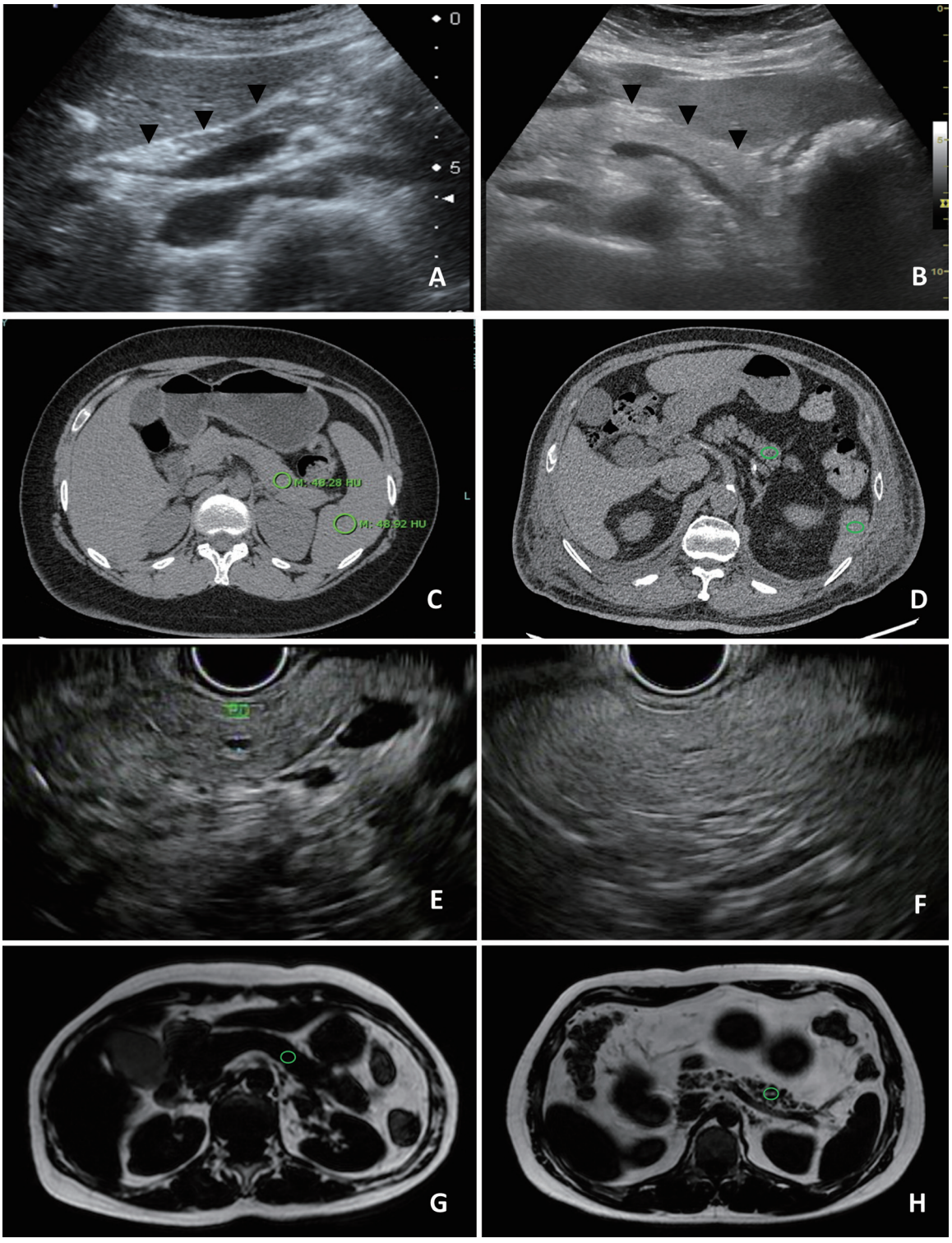

Fig. 2. Imaging of fatty pancreas. (A) Transabdominal ultrasonography shows iso-echogenicity of normal pancreatic parenchyma (arrowhead) compared with the liver. (B) A sonographic image of fatty pancreas reveals increased parenchymal echogenicity of the pancreas (arrowhead) compared with the liver. (C) 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.

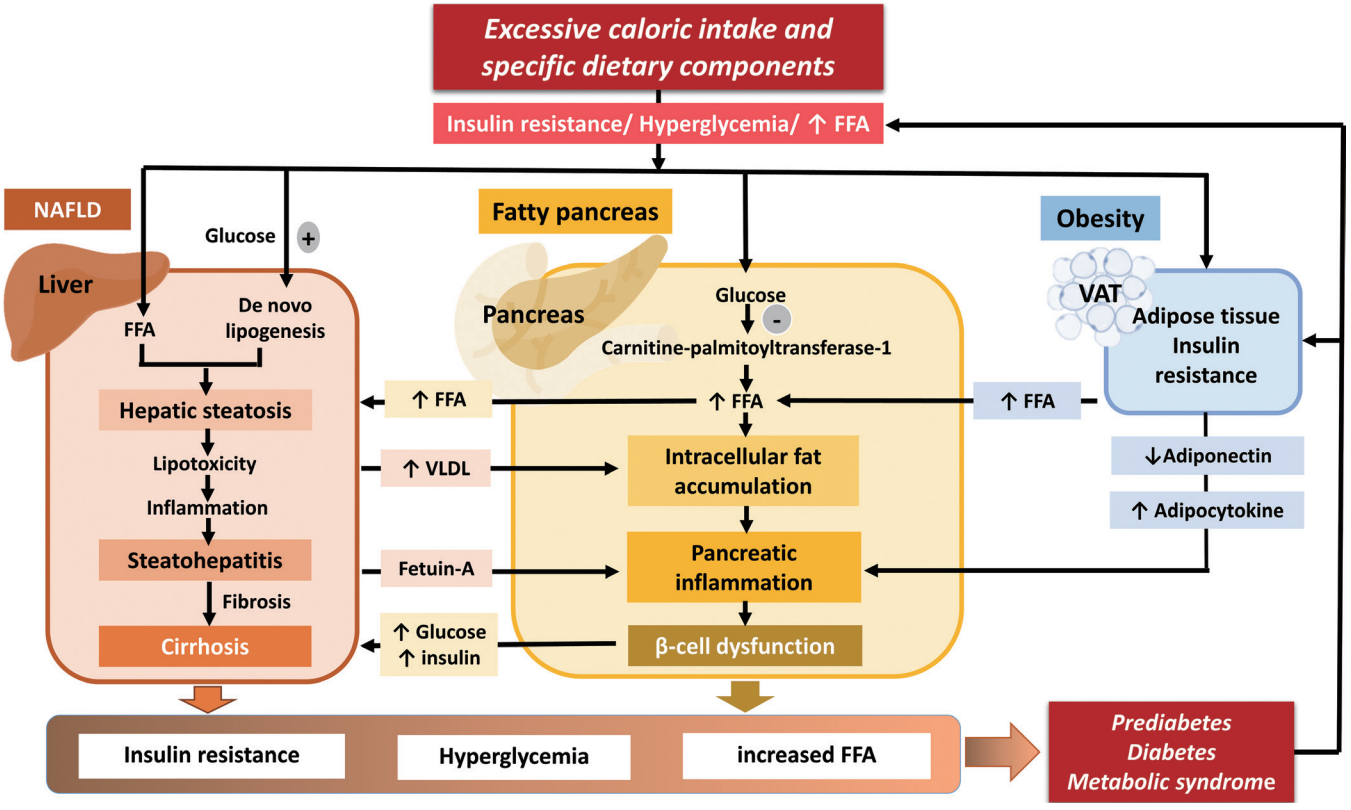

Fig. 3. Organ crosstalk in the pathophysiology of fatty pancreas and nonalcoholic fatty liver disease (NAFLD). Excessive calorie consumption and specific dietary components increase the risk of insulin resistance, metabolic disorders, and fat accumulation in the liver, pancreas, and visceral adipose 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.

atic fat. As the radiodensity of different tissues and organic substances in CT images varies the acquisition and reconstruction parameters, pancreatic fat measurement is compared to an internal reference tissue with no lipid content, such as the spleen. With fatty pancreas, nonenhanced CT images depict decreased attenuation of the pancreas (Fig. 2).[57] Further, the difference between pancreatic and splenic attenuation can objectively estimate the severity of fatty pancreas.[51,58,59] The main strengths of this modality are the wide availability and relatively short imaging time; however, the risk of radiation exposure is a significant drawback.

MRI using the advanced multi-echo Dixon technique is a method of quantifying pancreatic fat accumulation. The technique provides a reliable and reproducible mapping of pancreatic proton density fat fraction, which has been shown to be correlated with histologically assessed fat content with a correlation coefficient of 0.71.[60] Nonetheless, the use of MRI is limited by low availability, high acquisition cost, and the time requirements of the examination procedure. MRI is also susceptible to observer-dependent bias because the inhomogeneous distribution of fat in the pancreas on an almost homogeneous background of retroperitoneal fat (Fig. 2). New MRI techniques, such as MRS, MR chemical shift imaging, and MR-opsy have improved diagnostic accuracy and have minimized interobserver variation.[61,62] MRI-proton density fat fraction (MRI-PDFF) is currently considered the most accurate method for quantifying visceral fat. It decreases T1 bias and T2* decay and lowers the signal-interference effect of protons in fat.[63] However, few studies have used MRI-PDFF to quantify pancreatic fat.[64,65] A study evaluating pancreatic fat with MRI-PDFF showed that histologic pancreatic fat content was significantly correlated with pancreatic fat quantified by MRI-PDFF (r=0.802).[65] In addition to its good correlation with histology, MRI-PDFF has gained popularity because it is more available and less technically difficult compared with other MRI-based methods.[66–68]

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-

tory cell infiltration, apoptosis, stellate cell activation, and fibrosis. The process ultimately causes a decrease in islet β/α-cell ratio and alteration of islet architecture.[69] Moreover, increased pancreatic free fatty acid and lipid peroxidation are associated with acinar cells and islet destruction.[70]

Glucolipotoxicity is the conceptual hypothesis that explains the role of fatty pancreas in 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 from VAT and pancreatic fat, directly cause β-cell death.[8,34]

Human studies have shown an association between fatty pancreas and β-cell dysfunction. The mean pancreatic fat content using MRI measurement was inversely associated with insulin secretion using the oral glucose tolerance test (OGTT) in patients with impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT).[53] A study in men found that pancreatic fat content measured by MRS was independently associated with various aspects of β-cell function.[71] However, the association was not found in men with diabetes. The findings highlight the importance of fatty pancreas in the deterioration of glucose homeostasis. Other factors superimposing the effect of fatty pancreas may contribute to a progressive decline in β-cell function once diabetes develops. On the contrary, some human studies have found no association between fatty pancreas and β-cell dysfunction. In a large cohort of adult Chinese subjects, fatty pancreas evaluated by MRI was not associated with β-cell function measured by homeostasis model assessment (HOMA-β) after adjusting for liver fat and BMI.[14] Another study using MRS to diagnose fatty pancreas did not find associations between total and intralobular pancreatic adipose tissue infiltration and insulin secretion or β-cell function in either normal populations or in patients with prediabetes or diabetes.[72]

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.[73] 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-1b, was higher in obese children with NAFLD complicated by fatty pancreas than in children without fatty pancreas.[74] Although a large cohort of Chinese adults did not show an association between fatty pancreas and HOMA-β, 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 HOMA-IR.[14] In patients with IFG or IGT, a positive correlation of insulin resistance determined by both HOMA-IR and a euglycemic clamp with the severity of fatty pancreas was observed.[12,75] However, after adjusting for VAT, the association between fatty pancreas and HOMA-IR disappeared, implying that VAT was more strongly associated or mediated the relationship between fatty pancreas and insulin resistance. Another study in obese subjects showed that insulin resistance using HOMA-IR was associated with NAFLD but not with fatty pancreas.[44] Based on the existing evidence, it is not clear whether fatty pancreas is associated with insulin resistance because it contributes to β-cell dysfunction or is a consequence of obesity.

Prediabetes, diabetes, and metabolic syndrome

Several clinical studies disclosed the relationship of fatty pancreas with prediabetes states, diabetes, and metabolic syndrome (Table 1).[9–11,15,16,22,40,51,59,76,77] A cross-sectional study of 7464 patients showed that fatty pancreas detected by transabdominal US was independently associated with prediabetes (OR 1.22, 95% CI: 1.00−1.49) and T2DM (OR 1.38, 95% CI: 1.05−1.82).[76] The findings were further supported by a prospective longitudinal study showing that prediabetes was associated with the development of fatty pancreas in patients who did not have fat accumulation in the pancreas at baseline.[58] To account for the potential confounding effect of baseline obesity, a prospective cohort of nonobese individuals were followed for a median of 6.19 years. The results confirmed that fatty pancreas diagnosed by CT was significantly associated with developing T2DM, with an OR of 1.32 (95% CI: 1.06−1.63).[59] Each increased percentage point of pancreatic fat increased the risk of incident diabetes by 7%.[22] Additionally, fatty pancreas was associated with the subsequent development of metabolic syndrome.[51] A meta-analysis of 11 studies including 12,675 individuals showed that fatty pancreas was significantly associated with T2DM (RR 2.08, 95% CI: 1.44−3.0), metabolic syndrome (RR 2.37, 95% CI: 2.07−2.71), and hypertension (RR 1.67, 95% CI: 1.32−2.10).[15] The results are in line with data from a recent meta-analysis of 13 studies investigating 49,329 patients displaying an association between fatty pancreas and significantly increased risks of T2DM (RR 1.99, 95% CI: 1.18−3.35), metabolic syndrome (RR 2.25, 95% CI: 2.00−2.53), arterial hypertension (RR 1.43, 95% CI: 1.08−1.90), and central obesity (RR 1.91, 95% CI: 1.67−2.19).[77] Large meta-analyses have explored the association between metabolic conditions and NAFLD,[78,79] and it is now established that there is a vicious cycle of NAFLD and metabolic dysfunction (Fig. 3). Taken together, existing evidence highlights the interplay between fatty pancreas, NAFLD, and components of metabolic syndrome.

Links between fatty pancreas and NAFLD

The pancreas and liver are derived from the same embryonic endoderm, which explains the relationship between fatty pancreas and NAFLD. Patients with fatty pancreas may be at increased risk of NAFLD development and progression because intrapancreatic fat affects glucose metabolism and insulin secretion. Available evidence from experimental models and human studies suggests a bidirectional relationship between fatty pancreas and NAFLD.[6,19,24,39]

Evidence from animal and translational studies

Early studies found that obesity was linked to increased fat accumulation in the pancreas by changes of metabolic mediators including adiponectin and lipocalin-2.[36,37] In the context of insulin resistance and hyperglycemia, hepatic steatosis with an increased hepatic very-low-density lipoprotein accelerates fat accumulation in the pancreas, causing islet cell death.[34,80] Fetuin-A, a hepatokine generated by a fatty liver, activates adipocytes and macrophages in the

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*.[76]	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*.[16]	2014	Cross-sectional	8097	Transabdominal US	Association with age (OR 2.221, 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*.[10]	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*.[15]	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*.[9]	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).
Yamazaki *et al*.[51]	2018	Prospective	320	CT scan	Increase risk of metabolic syndrome (RR 2.04, 95% CI: 1.14–3.64).
Wang *et al*.[40]	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*.[11]	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).
Bi *et al*.[77]	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*.[59]	2020	Prospective	1478	CT scan	Increases risk of diabetes (OR 1.32, 95% CI: 1.06–1.63).
Chan *et al*.[22]	2021	Prospective	631	MRI	Increases risk of diabetes (HR 1.81, 95% CI: 1.1–3.0).
NAFLD					
Schwenzer *et al*.[89]	2008	Cross-sectional	17	MRI	No correlation with hepatic fat content.
van Greenen *et al*.[90]	2010	Cross-sectional	80	Autopsy pathology	No association with NAFLD when adjusting for BMI.
Targher *et al*.[52]	2012	Cross-sectional	42	MRI	No correlation with liver fat when adjusted for age, sex, and visceral fat content.
Wang *et al*.[16]	2014	Cross-sectional	8097	Transabdominal US	Association with NAFLD (OR 2.28, 95% CI: 1.96–2.65).
Uygun *et al*.[18]	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. *(continued)*

Author	Year	Study Design	No. of Patients	Diagnostic Modality	Fatty Pancreas in Relation to Metabolic Dysfunction and NAFLD
Pacifico *et al.*[88]	2015	Cross-sectional	158	MRI	No association with hepatic fat content when adjusted for age, gender, Tanner stage, BMI standard deviation score, and visceral adipose tissue.
Lesmana *et al.*[10]	2015	Cross-sectional	1054	Transabdominal US	Association with NAFLD (OR 5.20, 95 % CI: 3.84–7.03).
Zhou *et al.*[9]	2016	Cross-sectional	1190	Transabdominal US	Association with NAFLD (OR 2.52, 95% CI: 1.83–3.48).
Wang *et al.*[40]	2018	Cross-sectional	2093	Transabdominal US	Association with NAFLD (OR 2.67, 95% CI: 1.33–5.34).
Weng *et al.*[11]	2018	Cross-sectional	4419	Transabdominal US	The severity of fatty pancreas was correlated with NAFLD (OR 0.27, 95% CI: 0.13–0.54).
Rosenblatt *et al.*[91]	2019	Retrospective	104	Transabdominal US	Increase the risk of advanced liver fibrosis (OR 10.52, $p<0.001$). Extensive pancreatic fat accumulation increases the risk of NASH (OR 5.37, $p<0.001$).
Bi *et al.*[77]	2019	Meta-analysis	49,329	Transabdominal US, EUS, MRI	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, NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; MRI, magnetic resonance imaging; OR, odds ratio; RR, relative risk; TG, triglyceride; US, ultrasonography.

pancreatic islets of Langerhans, which are responsible for producing and releasing hormones regulating glucose homeostasis. Increased chemoattractant expression promotes macrophage or monocyte infiltration and the expression of cytotoxic proinflammatory cytokines.[38] Pancreatic inflammation induced by triggering a proinflammatory response in pancreatic fat cells and islet macrophages/monocytes accelerate β-cell failure, leading to insulin resistance and ectopic fat deposition in other tissues, including the liver.[12,81–85] Hepatic fat accumulation further promotes insulin resistance, resulting in a self-perpetuating loop in which insulin stimulates the synthesis of free fatty acids spilling into the pancreas.[86] The cyclic interaction between the liver and pancreas is known as the twin cycle hypothesis (Fig. 3).[87]

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.[11] 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.[92]

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.[74] A postmortem pathology study found that intralobular pancreatic fat was associated with nonalcoholic steatohepatitis.[90] 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.[81]

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.[24] 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.[94] 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.[95]

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,[96] liraglutide,[97] and dulaglutide,[98] 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.[93,99–102] Although all of the studies showed a significant decrease in pancreatic fat content after surgery, the change was independent of a reduction in liver fat content. The results also showed improvement of β-cell function in response to loss of pancreatic fat after bariatric surgery.[93,100] 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 stimulated 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.

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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).

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