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Fatty Pancreas:

Should We Be Concerned?

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Abstract

The metabolic consequences of visceral fat deposition are well known, and the presence of intrapancreatic fat (IPF) has been recognized for decades. However, our knowledge about the distribution of fat in the pancreas and its clinical implications is in a nascent stage. Various terms have been proposed to describe IPF; for the purpose of this narrative review, we chose the general term fatty pancreas. Herein, we describe the radiologic, endoscopic, and histopathologic aspects of diagnosing fatty pancreas and provide an overview of the diseases associated with this condition. Our purpose is to highlight diagnostic challenges and identify specific clinical questions that would benefit from further study. As evident in this review, IPF is associated with various metabolic diseases, pancreatitis, pancreatic cancer, and precancer—yet establishing causality needs careful, further study.

Keywords

diabetes mellitus; fatty pancreas; obesity; pancreatitis; steatosis

Obesity results in visceral fat deposition that in some cases has profound metabolic consequences, directly contributing to the risk of cardiovascular disease and insulin resistance and to increased risk of malignancy. Nearly 70% of the US adult population is either obese or overweight.¹ Obese persons are at increased risk of fatty liver disease, which can lead to steatohepatitis and, subsequently, advanced liver fibrosis. Similarly, an increased likelihood of fat deposition in the pancreas, also called fatty pancreas (FP), has been described in obese persons, but our knowledge about the health consequences of pancreatic fat deposition is at a rudimentary stage.

Debate continues on whether FP is clinically relevant or innocuous. Increased pancreatic fat is not infrequently reported on abdominal imaging studies. However, no consensus currently exists on terminology, prevalence, normal thresholds, and diagnostic criteria of this

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condition. This lack of consensus has led to speculation on whether FP represents normal peripancreatic fat interdigitating with the pancreatic lobules or true fat deposition in adipocytes within the pancreas, or a combination of both. In addition, various terms have been used to describe intrapancreatic fat (IPF), including *pancreatic steatosis*, *nonalcoholic fatty pancreas disease*, *lipomatous atrophy of the pancreas*, *pancreatic lipomatosis*, *pancreatic adiposity*, *fatty replacement of pancreas*, and *fatty infiltration of pancreas*.^{2–6} In this review, we use the general term fatty pancreas to describe accumulation of IPF and summarize key studies that have described clinical associations of this condition with the aim to highlight areas where the need for further study is critical.

MATERIALS AND METHODS

We searched the MEDLINE database through the Ovid interface using the aforementioned terms. We limited the search to English-language articles indexed from database inception to December 2015. Our literature search retrieved a total of 87 abstracts that were carefully reviewed by 2 investigators (N.A.P. and S.M.) for clinical relevance. Case reports and narrative reviews were excluded. For inclusion in this review, 61 full-text articles were selected, and the bibliographies of these articles were manually searched to identify additional studies of relevance to the topic.

RESULTS

Diagnosis of FP

Before the availability of medical imaging, FP was studied at necropsy or at the time of pancreatic surgery.^{7–9} The clinical approach to diagnosing FP was modeled on approaches for quantifying hepatic fat. The retroperitoneal location of the pancreas makes it difficult to visualize on transabdominal ultrasonography (TUS), and obtaining pancreatic tissue for histologic assessment can be technically challenging. Only recently have studies started correlating imaging and histologic findings of IPF.¹⁰ Pancreatic resection specimens are mostly procured in the context of a pathologic state and do not allow for accurate assessment of the “normal” amount of IPF. Not surprising, studies correlating imaging and histology of FP are scarce, and no criterion standard is available for FP diagnosis.

Imaging

A wide range of techniques have been described for imaging IPF, including magnetic resonance imaging (MRI), computed tomography (CT), TUS, and endoscopic ultrasonography (EUS).

Transabdominal Ultrasonography—Traditionally, pancreatic echogenicity has been compared with the liver, kidney, and spleen,^{11–14} and a comparatively hyperechoic pancreas has been labeled as FP. Transabdominal ultrasonography is an inaccurate tool for the assessment of IPF. It is subjective; the highly operator-dependent results are influenced by imaging presets (gain and frequency), as well as the patient’s body habitus. Moreover, another inherent limitation to this approach is that hepatic echogenicity is altered by steatosis. Because TUS is widely available, some of the largest studies of FP have used data

from TUS evaluations. A large Chinese study reported the presence of FP in 1297 persons (16%) of 8097 healthy volunteers.¹⁵ These results have yet to be validated by subsequent studies.

Endoscopic Ultrasonography—Endoscopic ultrasonography has been used to diagnose and grade FP.^{13,16,17} A hyperechoic pancreas is considered synonymous with FP (Fig. 1). Sepe et al¹⁶ used clarity of pancreatic parenchyma and duct margins, in addition to comparative echogenicity, and proposed an EUS grading system (Grades I–IV). However, this observational study did not incorporate tissue sampling or pancreatic fat estimation with CT or MRI. Interobserver agreement is poor for all EUS features of chronic pancreatitis, and the same is likely true for FP.¹⁸ Clearly defined and well-validated EUS criteria with histologic correlation may allow for a more definitive diagnosis of FP.

Computed Tomography—Adipose tissue shows negative (–150 to –30 HU) attenuation on non–contrast-medium CT¹⁹ (Fig. 2). Attenuation of the pancreas is expected to decrease with fatty infiltration. For glands that appear diffusely hypoattenuating, mean attenuation from regions of interest across different areas of the gland is used. A reasonable correlation seems to exist between CT and histologic quantification of IPF ($r = 0.67$).¹⁰ The difference between pancreatic and splenic attenuation on CT has also been used to quantify IPF. In a cohort of 62 patients, Kim et al²⁰ demonstrated reasonable correlation between histologic characteristics and CT attenuation indices. A population-based study of 1721 healthy volunteers that used volumetric histography showed a mean (standard deviation [SD]) pancreatic fat volume of 27.9 (15.7) cm³ and a mean (SD) fat to parenchyma ratio of 0.69 (0.44).²¹ This approach is probably the most accurate CT method for quantifying IPF because it evaluates individual pixel values. However, the fat to parenchyma ratio in that study seems to be abnormally high, most likely due to exclusion of pancreatic tissue with intermediate attenuation.

Although non–contrast-medium CT is widely available and relatively inexpensive, it has limitations when used to assess FP. A hypoattenuating mass or cyst can occasionally mimic focal fatty change (Fig. 3). In addition, the attenuation range for fat is based on adipose tissue measurement, which is exclusively adipocytes, and the same threshold is unlikely to be accurate for measuring IPF where adipocytes and pancreatic tissue are interspersed.^{7,8,22}

Magnetic Resonance Imaging—Magnetic resonance imaging has superior soft tissue resolution compared with CT and identifies IPF without relying solely on attenuation. Use of the difference in resonance frequency to discriminate between fat and water protons was first described by Dixon²³ in 1984. Although this technique has been subsequently modified, it continues to be the basic principle for the most widely used method for MRI quantification of pancreatic fat (Fig. 2). Wong et al²⁴ studied 202 healthy volunteers and found 90% of this population to have a pancreatic fat content ranging from 1.8% to 10.4%. In another MRI study of 1241 volunteers, mean IPF was 4.5%.²⁵ In a smaller study of 36 healthy volunteers, median total pancreatic fat was 2.7% (interquartile range, 1.0%–6.5%).²⁶ Magnetic resonance imaging–measured IPF needs to be studied and validated in large healthy cohorts to define an accurate diagnostic cutoff value for the reference IPF level.

Magnetic resonance imaging–estimated proton density fat fraction (MR-PDFF) is a novel technique that has been used for quantification of hepatic fat. Results from initial studies suggest good correlation with liver histologic characteristics.^{27–29} A recent study demonstrated the feasibility of using MR-PDFF to estimate IPF.³⁰ Magnetic resonance spectroscopy (MRS) is another technique that can accurately quantify triglyceride content of the liver, as well as skeletal and cardiac muscle,^{31–33} with high sensitivity.^{26,33} In a study of Zucker diabetic fatty rats, MRS-estimated pancreatic triglyceride content had good correlation with biochemically determined tissue triglyceride content, and the investigators demonstrated technical reproducibility with human volunteers.³⁴ Interest is considerable in a 3-dimensional reconstruction algorithm termed iterative decomposition with echo asymmetry and least squares estimation (IDEAL).^{35,36} Studies comparing IDEAL with MRS have shown variable correlation between the 2 techniques.^{37,38} However, IDEAL has higher spatial resolution, requires a shorter image acquisition time, and overall seems to be better suited for clinical use.

Histology

Currently, no validated objective scoring system is available for histologic assessment of FP. Early studies used a subjective grading score from 1 to 4, where 1 represented few scattered adipocytes in the exocrine pancreas and 4 represented partial or complete replacement by fat.³ More recently, studies have used morphometric analysis and software-aided calculation of percentage pixel area of adipocytes to gain a more objective assessment.^{10,21}

In contrast to the liver, where intrahepatocyte fat accumulation has been described, IPF is located within adipocytes. Human autopsy studies have not shown intra-acinar staining for the adipocyte marker perilipin-1 (Fig. 4).¹⁰ Interestingly, cytoplasmic vacuoles in the exocrine pancreas of mice fed a high-fat diet have been noted to stain positively for adipose differentiation–related protein but were negative for perilipin.³⁹ The mechanistic pathways involved in possible infiltration of adipocytes or transformation of human exocrine pancreas are being investigated.

Associations and Clinical Consequences of FP

Various conditions have been associated with FP (Table 1). Fatty pancreas can be an end result of a disease process affecting the pancreas (eg, cystic fibrosis [CF]), parallel fat infiltration elsewhere (eg, obesity), or a determinant of clinical outcome (eg, acute pancreatitis). In this section, we summarize the available evidence on the conditions associated with FP.

FP and Age

Pancreatic fat content increases with age and seems to be highest in the third and fourth decades.²¹ Pancreatic parenchymal volume declines beyond the sixth decade and, as a result, the fat to parenchyma ratio increases in that age group, although total pancreatic fat volume remains stable.²¹ In a recent study of 126 healthy male volunteers, the MRI-estimated IPF was noted to be greater in men aged 50 to 70 years than in younger men (mean [SD], 6.32% [1.18%] vs 2.8% [0.66%], $P < 0.01$).⁴⁰

FP and Genetic Syndromes

Complete fatty replacement is the most common pancreatic imaging finding in adult patients with CF.⁴¹ The degree of fatty change differs with allelic variation and disease duration.⁴² Fat replacement of the pancreatic parenchyma in CF is a response to acinar injury resulting from ductal obstruction by inspissated secretions. It is unclear whether fat deposition in CF pancreas precedes the development of exocrine and endocrine insufficiency.

Other rare genetic syndromes associated with FP include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, and heterozygous carboxyl ester lipase (CEL) mutations.^{43–46} In a small case-control study, pancreatic fat deposition was found to precede the onset of pancreatic endocrine insufficiency in carriers of heterozygous CEL mutations.⁴⁶

FP and Obesity

Compared with lean persons, obese persons have more IPF.²¹ This association is independent of age and glycemic status. In a cohort of age- and sex-matched healthy volunteers (lean, n = 460; overweight, n = 460; and obese, n = 230), Saisho et al²¹ demonstrated a linear incremental relationship between body mass index and IPF in both diabetic and nondiabetic participants (no diabetes, $r = 0.4$, $P < 0.0001$; type 2 diabetes mellitus [DM], $r = 0.5$, $P < 0.0001$). Visceral adipose tissue area has also been noted to be an independent predictor of FP.¹⁷ Interestingly, a metabolomic analysis comparing the fat composition of pancreata in obese and lean mice showed a greater content of triglycerides and free fatty acids and less content of phospholipid and cholesterol in the obese animals.⁴⁷ This finding is consistent with the lipid content of adipocytes being predominantly triglyceride. In addition, evidence suggests that the release of nonesterified fatty acids from pancreatic adipocytes may potentiate local pancreatic injury during acute pancreatitis.¹⁰

The effect of weight loss on FP and its downstream metabolic consequences has been an area of interest in recent years. In a study of 23 patients who underwent bariatric surgery (Roux-en-Y gastric bypass and sleeve gastrectomy), IPF decreased significantly after surgery (14% vs 20%, $P < 0.01$). Of note, changes were unrelated to change in body weight and intra-abdominal fat. Patients with DM who achieved normoglycemia postoperatively had a significantly greater decrease in PF percentage.⁴⁸ Another recent bariatric surgery study found similar improvement in glycemic outcomes associated with a decrease in IPF independent of postoperative change in body mass index.⁴⁹ Decreased insulin resistance alone or in combination with a change in IPF quantity and composition may be contributory. The association between bariatric procedures, quantity and composition of IPF, and beta cell function needs further study.

FP and Nonalcoholic Fatty Liver Disease

In a large cross-sectional study involving 8097 patients, the prevalence of nonalcoholic fatty liver disease (NAFLD) was higher in patients with FP than those without it (67.2% vs 35.1%).¹⁵ Study of a cohort of 60 patients reported a similar high prevalence (57%) of NAFLD.¹³ Increased prevalence of FP in patients with NAFLD has also been observed (Table 2).^{50,51} However, a recent study of 41 patients with histologically proven NAFLD did not show a significant correlation between MRI pancreatic fat fraction and the histologic

grade of hepatic steatosis ($r_s = 0.212$).³⁰ Although studies indicate a trend toward FP predicting a higher risk of NAFLD and vice versa, reaching a firm conclusion based on currently available evidence is difficult.

FP and DM

The amount of IPF is greater in persons with DM than those with prediabetes and increases with the duration of DM^{52–56} (Table 3). A recent study found less IPF in new-onset DM than in long-standing DM (mean % [SD], 4.3 [4.0] vs 9.3 [7.7]).⁵⁴ It is unclear whether this finding represents a cumulative increase in IPF or fat replacement of atrophic pancreatic parenchyma secondary to diabetic exocrine pancreatopathy.⁵⁷

In another large case-control study, patients with FP had a higher prevalence of DM than the non-FP controls (12.6% vs 5.2%), and DM was independently associated with FP in an adjusted logistic regression analysis.¹⁵ In addition, patients with nonalcoholic steatohepatitis (NASH) and FP have been shown to have a higher prevalence of DM and prediabetes than NASH patients without FP (74.4% vs 41.4%, $P = 0.004$).⁵⁰ In the cohort of 41 patients with biopsy-proven NASH, MR-PDFF patients with DM had more IPF than patients without diabetes (12.2% vs 4.8%, $P = 0.028$).³⁰

To date, the relationship between IPF and beta cell dysfunction is unclear. Magnetic resonance spectroscopy–estimated median pancreatic triglyceride content has been shown to be greater in patients with impaired fasting glucose, impaired glucose tolerance, or type 2 DM compared with healthy volunteers.³⁴ However, a more recent study found no significant difference in pancreatic triglyceride content among normoglycemic patients versus diabetic patients.⁵⁸ Although animal studies have demonstrated the direct toxic effect of triglycerides on beta cell function and some human studies have reported a negative association between FP and beta cell function, the evidence is not convincing that IPF contributes to the pathogenesis of DM.^{56,59,60} Glycemic and cardiovascular risks associated with the combination of DM and FP are poorly understood. It is unclear whether FP is a harbinger of DM in normoglycemic persons.

FP and Acute Pancreatitis

In patients in whom acute pancreatitis develops, obesity is an independent risk factor for its severity.⁶¹ Severe acute pancreatitis (SAP) is associated with a considerable mortality risk,⁶² and this risk seems to be potentiated by obesity irrespective of the cause of the pancreatitis. A human autopsy study of persons who died of SAP suggested an incremental association between IPF and more extensive pancreatic necrosis.¹⁰ In vitro studies have shown that unsaturated fatty acids generated from IPF are proinflammatory and cause pancreatic acinar cell necrosis through a mechanism that involves release of intracellular calcium and inhibition of mitochondrial complexes I and V.¹⁰ Animal studies have indicated possible presence of intra-acinar fat in obese mice.^{63,64} The presence and composition of fat in human pancreatic acinar cells need to be studied in greater detail to understand the role of IPF in this pathogenetic pathway. Therapy targeted at lowering the circulating levels of unsaturated fatty acid may have a future role in improving outcomes of SAP.

FP and Pancreatic Fistula

Pancreatic fistula is a frequent complication after pancreatoduodenectomy and has been reported in up to 25% of all patients.^{65,66} Several studies have found FP to be an independent predictor of postoperative pancreatic fistula.^{67–70} These studies used variable criteria for histologic assessments of IPF in the resected specimen. Lee et al⁷⁰ combined histologic assessment with preoperative MRI and demonstrated reasonable correlation between imaging and histologic characteristics for IPF assessment ($r^2 = 0.560$, $P = 0.013$). In their study, patients in the pancreatic fistula group ($n = 20$) had a greater amount of IPF than the healthy controls (mean [SD], 35.5 [14.7] vs 23.3 [10.6], $P = 0.006$). A more recent study using pancreatic attenuation on preoperative CT to assess FP did not show a risk association between FP and eventual development of pancreatic fistula. That study, however, did not incorporate histologic assessment of pancreatic fat.⁷¹

The role of FP as an independent risk factor for pancreatic fistula continues to be controversial. A study aimed at identifying the relative risk of pancreatic fistula in patients with both radiologic and histologic evidence of FP would be useful.

FP and Pancreatic Ductal Adenocarcinoma

Strong evidence from case-control and cohort studies suggests an association between obesity and the increased risk of pancreatic ductal adenocarcinoma (PDAC) and cancer death.^{72–74} The association of FP and PDAC has been assessed in only small case-control studies.^{75–78} Hori et al⁷⁵ quantified FP using image analysis software in carefully selected tumor-free areas of resected pancreas and reported a significantly greater median percentage of IPF in cases than in controls (26% vs 15%, $P < 0.001$). In another study that defined FP as higher than 5% fatty change in a resected section without malignant infiltration, PDAC cases had a greater proportion of IPF than controls without cancer (72% vs 44%).⁷⁶ Studies also have linked IPF to a higher risk of lymph node metastasis in patients with PDAC.⁷⁸ Evidence is not clear whether the increased IPF of patients with PDAC is a primary process or is secondary to acinar atrophy as a result of either underlying chronic pancreatitis or tumor-associated ductal obstruction. Rebours et al⁷⁹ recently demonstrated an association between IPF and pancreatic intraepithelial neoplasia lesions. Interestingly, the same study did not note incremental correlation between body mass index and the number of pancreatic intraepithelial neoplasia lesions, which is suggestive that IPF has a possible independent role in pancreatic tumorigenesis.

Some evidence suggests that the proinflammatory milieu induced by obesity contributes to pancreatic oncogenesis through the activation of K-ras signaling pathways.⁸⁰ The underlying mechanisms of adiposity-driven pancreatic tumorigenesis need to be carefully examined.

CONCLUSIONS

The existence of fat in the pancreas has been known for decades. The pathophysiologic mechanisms that lead to IPF deposition and the clinical and metabolic implications are beginning to be understood. The effect of excess IPF on pancreatic exocrine or endocrine function and fibrosis is unclear. Potential benefits and methods to reduce pancreatic fat

content need further exploration. It is safe to conclude on the basis of available evidence that IPF is not innocuous and may have a role in causing or aggravating metabolic, inflammatory, and neoplastic disease processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

CEL	carboxyl ester lipase
CF	cystic fibrosis
CT	computed tomography
DM	diabetes mellitus
EUS	endoscopic ultrasonography
FP	fatty pancreas
IDEAL	iterative decomposition with echo asymmetry and least squares estimation
IPF	intrapancreatic fat
MRI	magnetic resonance imaging
MR-PDFF	magnetic resonance–estimated proton density fat fraction
MRS	magnetic resonance spectroscopy
NAFPD	nonalcoholic fatty pancreas disease
NASH	nonalcoholic steatohepatitis
PDAC	pancreatic ductal adenocarcinoma
SAP	severe acute pancreatitis
TUS	transabdominal ultrasonography

REFERENCES

1. Ogden CL, Carroll MD, Fryar CD, et al. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS Data Brief. 2015;219: 1–8.
2. Smits MM, van Geenen EJ. The clinical significance of pancreatic steatosis. Nat Rev Gastroenterol Hepatol. 2011;8:169–177. [PubMed: 21304475]
3. Olsen TS. Lipomatosis of the pancreas in autopsy material and its relation to age and overweight. Acta Pathol Microbiol Scand A. 1978;86A: 367–373. [PubMed: 716899]
4. Altinel D, Basturk O, Sarmiento JM, et al. Lipomatous pseudohypertrophy of the pancreas: a clinicopathologically distinct entity. Pancreas. 2010;39: 392–397. [PubMed: 19904221]

5. Mathur A, Marine M, Lu D, et al. Nonalcoholic fatty pancreas disease. *HPB (Oxford)*. 2007;9:312–318. [PubMed: 18345311]
6. Patel S, Bellon EM, Haaga J, et al. Fat replacement of the exocrine pancreas. *AJR Am J Roentgenol*. 1980;135:843–845. [PubMed: 6778124]
7. Schmitz-Moormann P, Pittner PM, Heinze W. Lipomatosis of the pancreas: a morphometrical investigation. *Pathol Res Pract*. 1981;173: 45–53. [PubMed: 7335549]
8. Klöppel G, Dreyer T, Willemer S, et al. Human acute pancreatitis: its pathogenesis in the light of immunocytochemical and ultrastructural findings in acinar cells. *Virchows Arch A Pathol Anat Histopathol*. 1986; 409:791–803. [PubMed: 3094241]
9. Nordback I, Lauslahti K. Clinical pathology of acute necrotising pancreatitis. *J Clin Pathol*. 1986;39:68–74. [PubMed: 3950033]
10. Navina S, Acharya C, DeLany JP, et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci Transl Med*. 2011;3:107ra110.
11. Marks WM, Filly RA, Callen PW. Ultrasonic evaluation of normal pancreatic echogenicity and its relationship to fat deposition. *Radiology*. 1980;137:475–479. [PubMed: 7433680]
12. Worthen NJ, Beabeau D. Normal pancreatic echogenicity: relation to age and body fat. *AJR Am J Roentgenol*. 1982;139:1095–1098. [PubMed: 6983252]
13. Al-Haddad M, Khashab M, Zyromski N, et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. *Pancreas*. 2009;38:672–675. [PubMed: 19506531]
14. Lee JS, Kim SH, Jun DW, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. *World J Gastroenterol*. 2009;15:1869–1875. [PubMed: 19370785]
15. Wang CY, Ou HY, Chen MF, et al. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. *J Am Heart Assoc*. 2014;3:e000297. [PubMed: 24572250]
16. Sepe PS, Ohri A, Sanaka S, et al. A prospective evaluation of fatty pancreas by using EUS. *Gastrointest Endosc*. 2011;73:987–993. [PubMed: 21521567]
17. Choi CW, Kim GH, Kang DH, et al. Associated factors for a hyperechogenic pancreas on endoscopic ultrasound. *World J Gastroenterol*. 2010;16:4329–4334. [PubMed: 20818817]
18. Stevens T, Lopez R, Adler DG, et al. Multicenter comparison of the interobserver agreement of standard EUS scoring and Rosemont classification scoring for diagnosis of chronic pancreatitis. *Gastrointest Endosc*. 2010;71:519–526. [PubMed: 20189510]
19. Wegener OH. Whole-Body Computed Tomography. 2nd ed O'Neal Wandrey S, translator. Boston, MA: Blackwell Scientific Publications; 1993.
20. Kim SY, Kim H, Cho JY, et al. Quantitative assessment of pancreatic fat by using unenhanced CT: pathologic correlation and clinical implications. *Radiology*. 2014;271:104–112. [PubMed: 24475851]
21. Saisho Y, Butler AE, Meier JJ, et al. Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. *Clin Anat*. 2007;20:933–942. [PubMed: 17879305]
22. Acharya C, Cline RA, Jaligama D, et al. Fibrosis reduces severity of acute-on-chronic pancreatitis in humans. *Gastroenterology*. 2013;145: 466–475. [PubMed: 23684709]
23. Dixon WT. Simple proton spectroscopic imaging. *Radiology*. 1984;153: 189–194. [PubMed: 6089263]
24. Wong VW, Wong GL, Yeung DK, et al. Fatty pancreas, insulin resistance, and β -cell function: a population study using fat-water magnetic resonance imaging. *Am J Gastroenterol*. 2014;109:589–597. [PubMed: 24492753]
25. Kühn JP, Berthold F, Mayerle J, et al. Pancreatic steatosis demonstrated at MR imaging in the general population: clinical relevance. *Radiology*. 2015;276:129–136. [PubMed: 25658037]
26. Sijens PE, Edens MA, Bakker SJ, et al. MRI-determined fat content of human liver, pancreas and kidney. *World J Gastroenterol*. 2010;16: 1993–1998. [PubMed: 20419836]
27. Permutt Z, Le TA, Peterson MR, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease—MRI accurately

- quantifies hepatic steatosis in NAFLD. *Aliment Pharmacol Ther.* 2012;36:22–29. [PubMed: 22554256]
28. Tang A, Tan J, Sun M, et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. *Radiology.* 2013;267:422–431. [PubMed: 23382291]
 29. Idilman IS, Aniktar H, Idilman R, et al. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. *Radiology.* 2013;267:767–775. [PubMed: 23382293]
 30. Idilman IS, Tuzun A, Savas B, et al. Quantification of liver, pancreas, kidney, and vertebral body MRI-PDFF in non-alcoholic fatty liver disease. *Abdom Imaging.* 2015;40:1512–1519. [PubMed: 25715922]
 31. Szczepaniak LS, Babcock EE, Schick F, et al. Measurement of intracellular triglyceride stores by H spectroscopy: validation in vivo. *Am J Physiol.* 1999;276:E977–E989. [PubMed: 10329993]
 32. Szczepaniak LS, Dobbins RL, Metzger GJ, et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med.* 2003;49:417–423. [PubMed: 12594743]
 33. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab.* 2005;288:E462–E468. [PubMed: 15339742]
 34. Lingvay I, Esser V, Legendre JL, et al. Noninvasive quantification of pancreatic fat in humans. *J Clin Endocrinol Metab.* 2009;94: 4070–4076. [PubMed: 19773401]
 35. Reeder SB, Pineda AR, Wen Z, et al. Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL): application with fast spin-echo imaging. *Magn Reson Med.* 2005;54: 636–644. [PubMed: 16092103]
 36. Reeder SB, McKenzie CA, Pineda AR, et al. Water-fat separation with IDEAL gradient-echo imaging. *J Magn Reson Imaging.* 2007;25: 644–652. [PubMed: 17326087]
 37. Hu HH, Kim HW, Nayak KS, et al. Comparison of fat-water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. *Obesity (Silver Spring).* 2010;18:841–847. [PubMed: 19834463]
 38. Ma J, Song Z, Yan F. Detection of hepatic and pancreatic fat infiltration in type II diabetes mellitus patients with IDEAL-Quant using 3.0 T MR: comparison with single-voxel proton spectroscopy. *Chin Med J (Engl).* 2014;127:3548–3552. [PubMed: 25316227]
 39. Pinnick KE, Collins SC, Londos C, et al. Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. *Obesity (Silver Spring).* 2008;16:522–530. [PubMed: 18239594]
 40. Li J, Xie Y, Yuan F, et al. Noninvasive quantification of pancreatic fat in healthy male population using chemical shift magnetic resonance imaging: effect of aging on pancreatic fat content. *Pancreas.* 2011;40:295–299. [PubMed: 21178651]
 41. Robertson MB, Choe KA, Joseph PM. Review of the abdominal manifestations of cystic fibrosis in the adult patient. *Radiographics.* 2006; 26:679–690. [PubMed: 16702447]
 42. Feigelson J, Pecau Y, Poquet M, et al. Imaging changes in the pancreas in cystic fibrosis: a retrospective evaluation of 55 cases seen over a period of 9 years. *J Pediatr Gastroenterol Nutr.* 2000;30:145–151. [PubMed: 10697132]
 43. Ruggiero A, Molinari F, Coccia P, et al. MRI findings in Shwachman diamond syndrome. *Pediatr Blood Cancer.* 2008;50:352–354. [PubMed: 17183583]
 44. Kurdziel JC, Dondelinger R. Fatty infiltration of the pancreas in Shwachman's syndrome: computed tomography demonstration. *Eur J Radiol.* 1984;4:202–204. [PubMed: 6468413]
 45. Daentl DL, Frias JL, Gilbert EF, et al. The Johanson-Blizzard syndrome: case report and autopsy findings. *Am J Med Genet.* 1979;3: 129–135. [PubMed: 474625]
 46. Raeder H, Haldorsen IS, Ersland L, et al. Pancreatic lipomatosis is a structural marker in nondiabetic children with mutations in carboxyl-ester lipase. *Diabetes.* 2007;56:444–449. [PubMed: 17259390]
 47. Zyromski NJ, Mathur A, Gowda GA, et al. Nuclear magnetic resonance spectroscopy-based metabolomics of the fatty pancreas: implicating fat in pancreatic pathology. *Pancreatol.* 2009;9:410–419. [PubMed: 19451751]

48. Honka H, Koffert J, Hannukainen JC, et al. The effects of bariatric surgery on pancreatic lipid metabolism and blood flow. *J Clin Endocrinol Metab.* 2015;100:2015–2023. [PubMed: 25734253]
49. Gaborit B, Abdesselam I, Kober F, et al. Ectopic fat storage in the pancreas using 1H-MRS: importance of diabetic status and modulation with bariatric surgery-induced weight loss. *Int J Obes (Lond).* 2015;39: 480–487. [PubMed: 25042860]
50. Uygun A, Kadayifci A, Demirci H, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis. *Eur J Intern Med.* 2015;26:37–41. [PubMed: 25491010]
51. Della Corte C, Mosca A, Majo F, et al. Nonalcoholic fatty pancreas disease and nonalcoholic fatty liver disease: more than ectopic fat. *Clin Endocrinol (Oxf).* 2015;83:656–662. [PubMed: 26201937]
52. Begovatz P, Koliaki C, Weber K, et al. Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans. *Diabetologia.* 2015;58:1646–1655. [PubMed: 25740696]
53. Kim MK, Chun HJ, Park JH, et al. The association between ectopic fat in the pancreas and subclinical atherosclerosis in type 2 diabetes. *Diabetes Res Clin Pract.* 2014;106:590–596. [PubMed: 25444353]
54. Lim S, Bae JH, Chun EJ, et al. Differences in pancreatic volume, fat content, and fat density measured by multidetector-row computed tomography according to the duration of diabetes. *Acta Diabetol.* 2014;51: 739–748. [PubMed: 24671510]
55. Tushuizen ME, Bunck MC, Pouwels PJ, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. *Diabetes Care.* 2007;30:2916–2921. [PubMed: 17666465]
56. Heni M, Machann J, Staiger H, et al. Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: a nuclear magnetic resonance study. *Diabetes Metab Res Rev.* 2010;26:200–205. [PubMed: 20225188]
57. Mohapatra S, Majumder S, Smyrk TC, et al. Diabetes mellitus is associated with an exocrine pancreatopathy: conclusions from a review of literature. *Pancreas.* 2016;45:1104–1110. [PubMed: 26918874]
58. Wicklow BA, Griffith AT, Dumontet JN, et al. Pancreatic lipid content is not associated with beta cell dysfunction in youth-onset type 2 diabetes. *Can J Diabetes.* 2015;39:398–404. [PubMed: 26099932]
59. 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;13:478–485. [PubMed: 20489606]
60. Lee Y, Hirose H, Ohneda M, et al. Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci U S A.* 1994;91: 10878–10882. [PubMed: 7971976]
61. Whitcomb DC. Clinical practice. acute pancreatitis. *N Engl J Med.* 2006; 354:2142–2150. [PubMed: 16707751]
62. Vege SS, Gardner TB, Chari ST, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include “moderately severe acute pancreatitis.” *Am J Gastroenterol.* 2009;104: 710–715. [PubMed: 19262525]
63. Lee Y, Lingvay I, Szczepaniak LS, et al. Pancreatic steatosis: harbinger of type 2 diabetes in obese rodents. *Int J Obes (Lond).* 2010;34: 396–400. [PubMed: 20010902]
64. Matsuda A, Makino N, Tozawa T, et al. Pancreatic fat accumulation, fibrosis, and acinar cell injury in the Zucker diabetic fatty rat fed a chronic high-fat diet. *Pancreas.* 2014;43:735–743. [PubMed: 24717823]
65. Pratt WB, Callery MP, Vollmer CM Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg.* 2008;32:419–428. [PubMed: 18175170]
66. Kazanjian KK, Hines OJ, Eibl G, et al. Management of pancreatic fistulas after pancreaticoduodenectomy: results in 437 consecutive patients. *Arch Surg.* 2005;140:849–854; discussion 854–856. [PubMed: 16172293]
67. Mathur A, Pitt HA, Marine M, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg.* 2007;246:1058–1064. [PubMed: 18043111]

68. Rosso E, Casnedi S, Pessaux P, et al. The role of “fatty pancreas” and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. *J Gastrointest Surg.* 2009;13:1845–1851. [PubMed: 19639369]
69. Gaujoux S, Cortes A, Couvelard A, et al. Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy. *Surgery.* 2010;148:15–23. [PubMed: 20138325]
70. Lee SE, Jang JY, Lim CS, et al. Measurement of pancreatic fat by magnetic resonance imaging: predicting the occurrence of pancreatic fistula after pancreatoduodenectomy. *Ann Surg.* 2010;251: 932–936. [PubMed: 20395858]
71. Roberts KJ, Storey R, Hodson J, et al. Pre-operative prediction of pancreatic fistula: is it possible? *Pancreatology.* 2013;13:423–428. [PubMed: 23890142]
72. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst.* 1998;90:1710–1719. [PubMed: 9827525]
73. Arslan AA, Helzlsouer KJ, Kooperberg C, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch Intern Med.* 2010; 170:791–802. [PubMed: 20458087]
74. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. *Ann Oncol.* 2015;26: 2257–2266. [PubMed: 26347100]
75. Hori M, Takahashi M, Hiraoka N, et al. Association of pancreatic fatty infiltration with pancreatic ductal adenocarcinoma. *Clin Transl Gastroenterol.* 2014;5:e53. [PubMed: 24622469]
76. Tomita Y, Azuma K, Nonaka Y, et al. Pancreatic fatty degeneration and fibrosis as predisposing factors for the development of pancreatic ductal adenocarcinoma. *Pancreas.* 2014;43:1032–1041. [PubMed: 24991971]
77. Mathur A, Hernandez J, Shaheen F, et al. Preoperative computed tomography measurements of pancreatic steatosis and visceral fat: prognostic markers for dissemination and lethality of pancreatic adenocarcinoma. *HPB (Oxford).* 2011;13:404–410. [PubMed: 21609373]
78. Mathur A, Zyromski NJ, Pitt HA, et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. *J Am Coll Surg.* 2009;208: 989–994; discussion 994–996. [PubMed: 19476877]
79. Rebours V, Gaujoux S, d’Assignies G, et al. Obesity and fatty pancreatic infiltration are risk factors for pancreatic precancerous lesions (PanIN). *Clin Cancer Res.* 2015;21:3522–3528. [PubMed: 25700304]
80. Philip B, Roland CL, Daniluk J, et al. A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice. *Gastroenterology.* 2013;145: 1449–1458. [PubMed: 23958541]

FIGURE 1.

Computed tomography and MRI of normal and FP. A, Normal attenuation of pancreas (arrow) on non-contrast-medium CT. B and C, No signal change (arrows) between opposed-phase (B) and in-phase (C) images in the pancreas. Of note, the signal of liver drops (asterisks) in opposed-phase image (B) because of diffuse hepatic steatosis. D, Low CT attenuation in the pancreatic body with marbling pattern (arrow) suggestive of FP. E and F, Signal of pancreas drops (arrows) in the opposed-phase (E) compared with in-phase (F) images correlate with CT finding of pancreatic parenchymal fat deposition.

FIGURE 2.

Focal pancreatic fat mimicking mass lesion. A, Contrast medium–enhanced CT showing hypoenhancing area in the pancreatic head (arrow). B, MRI scan (opposed phase) showing the suspected mass lesion in the pancreatic head (arrow). C, MRI (in phase) scan of the same region showing signal drop (arrow) suggestive of focal fat deposit.

FIGURE 3.
Endoscopic ultrasonography image of the pancreas showing a hyperechoic gland, suggestive of FP.

FIGURE 4.

Immunohistochemistry of human pancreatic section showing the adipocyte staining with perilipin-1. The perilipin-1 is stained brown. Inset, the vacuoles in adjacent pancreatic acinar cells (black arrows) and islets (red dash-outlined structure) do not show staining. Scale bar represents 50 μm.

TABLE 1.**Conditions Associated With FP**

Physiologic
Advanced age
Genetic syndromes
CF
Shwachman-Diamond syndrome
Johanson-Blizzard syndrome
CEL gene mutation
Metabolic
Obesity
Diabetes mellitus
NASH
Metabolic syndrome
Inflammatory
Acute pancreatitis
Chronic pancreatitis
Malignant
Pancreatic intraepithelial neoplasia
PDAC
Medication use
Gemcitabine
Rosiglitazone
Miscellaneous
Postoperative pancreatic fistula
HIV infection
Cushing syndrome

HIV indicates human immunodeficiency virus.

TABLE 2.

Reported Prevalence of FP in Patients With NAFLD

First Author	Year of Publication	Country of Origin	Patients With NAFLD, No.		Patients With FP, No.		Modality for Diagnosis of NAFLD	Modality for Diagnosis of FP	Reported Prevalence, %
			Male	Female	Male	Female			
Uygun et al ⁵⁰	2015	Turkey	64	20	31	12	Histology	USG	51.2
Della Corte et al ⁵¹ *	2015	Italy	73	48	33	25	USG, histology	USG	47.9

* Contained children and adolescents.
USG indicates ultrasonography.

TABLE 3.
Pancreatic Fat Percentage in Patients With DM and Prediabetes Compared With Normoglycemic Controls

First Author	Publication Year	Country of Origin	Cases (DM/Prediabetes [*]), No.	Controls, No.	Matching Criteria	Modality for Diagnosing FP	Pancreatic Fat Cases vs Controls
Tushuizen et al ⁵⁵	2007	Netherlands	12/0	24	Age, BMI	MRS	20.4% vs 9.7% [†] ($P=0.03$)
Saisho et al ^{21,‡}	2007	United States	165/0	660	Age, BMI	CT, histology	30.3 (15.2) cm ³ vs 31.6 (16.6) cm ³ [§]
Heni et al ⁵⁶	2010	Germany	0/23	28	Age, sex	MRI	8.3% vs 7.4% [§] ($P=0.40$)
Lim et al ^{54,}	2014	Korea	52/0	50	Age, BMI	CT	9.3% vs 2.9% [§] ($P<0.01$)
Begovatz et al ⁵²	2015	Germany	14/14	28	NA	MRI, MRS	DM, 8.35% vs 1.95% [†] ($P<0.05$); prediabetes, 4.79% vs 1.95% [†] (NS)
Idilman et al ³⁰	2015	Turkey	5/0	41	NA	MRI	12.2% vs 4.8% [§] ($P=0.03$)

^{*} Prediabetes includes impaired fasting glucose and impaired glucose tolerance.

[†] Median.

[‡] Included adults and children.

[§] Mean (SD).

^{||} Patients with long-standing DM (>5 years).

BMI indicates body mass index; NA, not applicable; NS, not significant.