Fatty Pancreas: Clinical Implications

Jimil Shah¹, Anupam K Singh², Surinder Rana³

ABSTRACT

The fatty pancreas is a newly recognized entity with limited available literature on its risk factors, pathogenesis, diagnosis, and management. Obesity and metabolic syndrome both are emerging pandemic in recent times and the fatty pancreas is closely linked with both of them. Though obesity is one of the most important risk factors for the development of a fatty pancreas, it is not prerequisite for the development of same. Radiological investigations are the most commonly used modality for the diagnosis of the fatty pancreas; however, criteria to define fatty pancreas are still not present. Studies have shown that fatty pancreas is associated with metabolic syndrome, acute/chronic pancreatitis, pancreatic exocrine insufficiency, and the development of pancreatic carcinoma. However, none of the associations is proved to have a cause-effect relationship and it requires further exploration in future studies. Though the pathophysiological mechanism of the fatty pancreas is unclear, one can assume that similar to the nonalcoholic fatty liver disease the pathological changes of the fatty pancreas may be reversible. However, the effect of lifestyle modification, weight reduction, and medical therapy in reversing fatty pancreas and its sequelae still requires further exploration in future studies.

Keywords: Computed tomography, Endoscopic ultrasound, Magnetic resonance imaging, Metabolic syndrome, Obesity.

Journal of Postgraduate Medicine, Education and Research (2021): 10.5005/jp-journals-10028-1427

INTRODUCTION

Obesity is a complex, multifactorial, and largely preventable disease affecting more than 600 million adults worldwide. Obesity is considered as a modern pandemic with a projected state-level prevalence of obesity and severe obesity in the USA is 48.9 and 24.2% by 2030.¹ Due to change in lifestyle and dietary habits, obesity is a growing problem even in developing countries. In India, the estimated prevalence of obesity varies from 11.8 to 31.3% and it is growing even faster than the world's obesity growth rate.^{2,3} Obesity and especially central obesity is closely related to metabolic syndrome and various aspects of its components like hypertension, diabetes mellitus (DM), and hypertriglyceridemia. In recent years, it has been shown that obesity and metabolic syndrome are also a proinflammatory state with increased levels of IL-6 and TNF-alpha which is associated with multiple systemic effects like increased risk of cardiovascular diseases, nonalcoholic fatty liver diseases (NAFLD), gout, and increased risk of mortality compared to the general population.^{4,5} Apart from increased fat content in the liver, obesity, and central visceral fat is associated with increased fat content in other organs like the heart, muscles, and pancreas as well. Recent studies have shown a strong association between obesity and metabolic syndrome to the increased fat content in the pancreas.⁶ Fatty infiltration in the pancreas is a less well-defined entity and less explored compared to NAFLD may be due to a difficult location and absence of standard noninvasive tests to diagnose the condition. It is termed differently in various articles as the fatty pancreas, pancreatic steatosis, pancreatic lipomatosis, nonalcoholic fatty pancreas, or nonalcoholic steato-pancreatitis.^{7,8} In the absence of uniform terminology, definition, and defined cutoff, this entity still remains a diagnostic dilemma with uncertain clinical impact. In this review, we will discuss the etiopathogenesis, diagnosis, and clinical consequences of the fatty pancreas.

¹⁻³Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Corresponding Author: Jimil Shah, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, Phone: +91 8655376773, e-mail: shahjimil22@gmail.com

How to cite this article: Shah J, Singh AK, Rana S. Fatty Pancreas: Clinical Implications. *J Postgrad Med Edu Res* 2021;55(1):21–26.

Source of support: Nil

Conflict of interest: None

EPIDEMIOLOGY

Ogilvie first described autopsy series of findings of the pancreas in 19 obese individuals and compared it with 19 control patients. He noticed the presence of fat in the pancreas of 17% of obese individuals compared to only 7% in control patients.⁹ Later, Olsen showed a relationship of pancreatic lipomatosis with age and overweight.¹⁰ With the advent of various imaging technologies, fatty pancreas is found to be associated with type II DM, hypertension, obesity, and increased visceral fat.⁶ However, obesity is not always a prerequisite for fatty pancreas as it can be present in nonobese individuals as well as in presence of chronic alcoholism, in patients with cystic fibrosis or undergoing chemotherapy.^{8,11}

The true prevalence of this condition is not entirely known in absence of large-scale epidemiological studies. Lesmana et al. conducted a prospective single-center study in 2013 in Indonesia including 1,054 adults with an abdominal ultrasound. In their study, the prevalence of fatty pancreas was 35% and it was associated with age, blood pressure, body mass index (BMI), fasting glucose levels, and serum cholesterol levels.¹² Similarly, Zhou et al. also conducted a large prospective study on 1,190 individuals with trans-abdominal ultrasound. The prevalence of pancreatic steatosis was 30.7% in that study and it was associated with age, central obesity, diabetes,

hypertriglyceridemia, and hepatic steatosis.¹³ However, larger multicentric studies are required to know the true prevalence of fatty pancreas in various populations.

NOMENCLATURE

Researchers have used different terminology for “pancreatic fat accumulation” in the literature including fatty pancreas, pancreatic steatosis, pancreatic lipomatosis, fatty replacement, fatty infiltration, nonalcoholic fatty pancreatic disease (NAFPD), or nonalcoholic fatty steato-pancreatitis.^{7,14–17} Smits and van Geenen have tried to give uniform nomenclature in their recent article, though it has not been validated prospectively in trials⁸ (Table 1).

RISK FACTORS AND PATHOGENESIS

Age

Increasing age is one of the important risk factors for the development of the fatty pancreas. The aging process is associated with changes in pancreatic parenchyma including pancreatic atrophy, fibrosis, and fatty infiltration. Studies have shown that age >60 years is associated with a higher prevalence of fatty pancreas compared to younger individuals.^{18–20}

Metabolic Syndrome

Obesity is closely associated with metabolic syndrome which includes hypertension, impaired fasting glucose levels, low plasma HDL cholesterol levels, hypertriglyceridemia, and abdominal obesity. The association of obesity and metabolic syndrome with NAFLD appears to be bidirectional. Patients with obesity and metabolic syndrome are at a higher risk of developing NAFLD and patients with NAFLD appear to be at a higher risk of development of metabolic syndrome, insulin resistance, and cardiovascular morbidity.^{21,22} Studies have shown 60–97% of patients with fatty liver have associated fatty pancreas as well.^{22–24} A recent meta-analysis has shown that presence of NAFLD is also associated with increased risk of NAFLD (RR = 2.49; 95% CI, 2.06–3.02; $p < 0.00001$), metabolic syndrome (RR = 2.25, 95% CI, 2.00–2.53; $p < 0.00001$), DM (RR = 1.99, 95% CI, 1.18–3.35; $p = 0.01$), and hypertension (RR = 1.43,

95% CI, 1.08–1.90; $p = 0.013$).⁶ Pancreatic β -cell dysfunction and insulin resistance both are considered to be important pathogenic events in the development of NAFLD. Studies have shown that pancreatic fat accumulation is present in pre-diabetics which increases before the development of type II DM.^{25,26} Lipotoxicity and glucotoxicity associated with increased pancreatic fat content have been postulated for the development of β -cell dysfunction in these patients. In a study by Tushuizen et al. also, they found a negative correlation between NAFLD and β -cell function in nondiabetic individuals.²⁷ However, at present times, there is still limited evidence to define a causal relationship between NAFLD and type II DM.⁸

Congenital Syndromes

The pancreatic fat replacement has been associated with certain congenital syndromes with or without associated pancreatic exocrine insufficiency. Cystic fibrosis is associated with increased viscosity of pancreatic secretion and mucous plug resulting in pancreatic duct blockage and exocrine pancreatic insufficiency with fatty infiltration.¹¹ Johanson–Blizzard syndrome is associated with developmental anomalies with pancreatic necrosis–fibrosis followed by pancreatic fatty replacement.²⁸ Shwachman–Diamond syndrome is also associated with pancreatic fatty infiltration and pancreatic exocrine insufficiency along with musculoskeletal abnormality and bone marrow failure.²⁹ Mutation in carboxyl-ester-lipase is also associated with fatty pancreas with DM.³⁰

Iron Overload

Hemochromatosis is associated with iron overloading in the cells of the reticuloendothelial system and visceral organs like the liver, pancreas, skin, and heart. In primary and secondary iron overload, both the pancreatic parenchyma gets replaced by adipose tissue. Moreover, it is associated with damage to pancreatic parenchyma resulting in endocrine and exocrine insufficiency.³¹

Toxic Agents or Medications

Few drugs like rosiglitazone, corticosteroids, octreotide, and gemcitabine are associated with development of fatty pancreas.^{32,33}

Other Factors

Certain viral infections like reovirus or human immunodeficiency virus, malnutrition especially kwashiorkor, hepatitis B, and liver cirrhosis are also associated with development of fatty pancreas.^{34–36}

DIAGNOSIS

Currently, no definite criteria exist for the diagnosis of the fatty pancreas and different authors have used an arbitrary scoring system to quantitatively assess the degree of pancreatic fat infiltration.^{37,38} Despite the use of these scores in different studies, none have been validated for use in clinical practice. In clinical practice, a diagnosis of a fatty pancreas is usually made by various radiological investigations.

Histopathological Examination

Histopathological examination of a biopsy specimen is the gold standard test to assess the pancreatic fat content.^{26,39} However, a pancreatic biopsy is an invasive investigation that can be associated with severe complications and hence not a clinically valid and justified approach to diagnose the fatty pancreas. Based

Table 1: Proposed nomenclature for fatty pancreas⁸

Nomenclature	Proposed definition
Pancreatic steatosis	General term for pancreatic fat accumulation
Fatty pancreas	Fat accumulation in pancreatic adipocytes; islet or acinar cells or fatty replacement of exocrine cells
Pancreatic lipomatosis	
Fatty replacement	Death of acinar cells with subsequent replacement with adipocytes
Nonalcoholic fatty pancreatic disease	Pancreatic fat accumulation in association with obesity and metabolic syndrome
Nonalcoholic fatty steato-pancreatitis	Pancreatitis owing to pancreatic fat accumulation
Lipomatous pseudohypertrophy	Extreme variant of pancreatic fat accumulation

on the distribution of fat among the pancreas, the fatty pancreas is classified into four categories with prevalence noted as: type IA (35%, involvement of pancreatic head without involving the uncinate and peribiliary region), type IB (35%, involves head, neck, and body of pancreas without involving the uncinate and peribiliary region), type IIA (12%, involves head and uncinate process without peribiliary region), and type IIB (18%, affects head, neck, body and uncinate process of the pancreas without peribiliary region).⁴⁰

Radiological Examinations

Though a wide range of imaging modalities are available for diagnosing fatty pancreas, the diagnostic accuracy of each modality is different and at present, there is no consensus on which modality should be the first line.

Ultrasonography

Transcutaneous abdominal ultrasonography (USG) is routine imaging to visualize the pancreas. It compares the pancreatic echogenicity to the adjacent solid abdominal organs like the liver, spleen, and kidney, and a relatively hyperechogenic pancreas is labeled as a fatty pancreas. The transcutaneous abdominal USG is an easily available, cheaper, and risk-free modality for diagnosis of the fatty pancreas. However, it holds the disadvantage that the pancreas cannot always be visualized in all the patients, due to body habitus, overlying small bowel, and stomach. Also, the diagnostic accuracy is highly operator dependent. However, due to its noninvasive character and ease of availability, it is usually one of the first-line investigations in the diagnosis of the fatty pancreas.

Computed Tomography

Computed tomography (CT) abdomen is one of the most commonly performed imaging modalities to see the abdominal organs. Adipose tissue shows negative (−150 to −30 HU) attenuation on noncontrast CT and the fatty pancreas appears hypodense compared to the spleen (Fig. 1). A noncontrast CT is ideal while evaluating for pancreatic fat content only, as variable contrast uptake in normal pancreatic tissue in-between fatty infiltration can sometimes lead to misdiagnosis for solid lesion appearing as mixed hypo-hyperdense or hyperdense.⁴¹ However, no specific cutoff points have been suggested to identify fatty pancreas. Saisho et al. found comparable results for fat/parenchyma ratio compared to

histological diagnosis and a reasonable correlation exists between CT and histological quantification of fat ($r = 0.67$).⁴²

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) abdomen has superior soft-tissue resolution compared to CT and is the preferred imaging modality for diagnosing the fatty pancreas because of its high sensitivity and safety profile (Fig. 2). The use of the difference in resonance frequency to discriminate the fat and water, first described by Dixon in 1984,⁴³ remains the basis of the most widely used method for MRI quantification of pancreatic fat. Studies in healthy subjects have identified the fat content in the pancreas ranging from 2.7 to 10.4%.^{44–46} Though, reference cutoff values to identify the fatty pancreas are not available, studies have shown similar diagnostic performance for diagnosing fatty pancreas when compared MRI with histologic assessment.⁴⁷

Magnetic Resonance Proton Density Fat-fraction

Among the currently available imaging modalities, magnetic resonance proton density fat-fraction (MR-PDFF) is a novel and most accurate method for estimating the fat content in the tissues.⁴⁸ PDFF-based assessment significantly improves the accuracy of fat quantification by correcting for confounders such as T1 and T2 stage biases.⁴⁹ However, most of the available studies have measured the accuracy of fat estimation in other organs like the liver with good correlation and only a few studies have used the MR-PDFF imaging for pancreatic fat quantification.⁵⁰

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) has been used in various studies to quantify the liver fat content with limited studies evaluating its role in the diagnosis of the fatty pancreas. Hu et al. found in their study that, though MRS is an accurate tool for the identification of hepatic fat content, use of Iterative Decomposition with Echo Asymmetry and Least-squares estimation (IDEAL) technique creates a more accurate representation of the fat signal and better identifies the fat content in hepatic steatosis and more accurately determines the pancreatic fat content.⁵¹ Iterative Decomposition with Echo Asymmetry and Least-squares estimation has a higher spatial resolution, requires a shorter image acquisition time, and overall seems to be better suited for clinical use.

Fig. 1: CT abdomen shows diffusely hypodense pancreas suggestive of fatty pancreas

Fig. 2: T2-weighted fat saturated MR shows fatty replacement of the pancreas

Fig. 3: Radial endoscopic ultrasound image showing hyperechoic pancreatic body

Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) identifies the fatty pancreas as a hyperechoic structure compared to the adjacent solid structure (Fig. 3).⁵² Endoscopic ultrasonography has also been used for grading of the fatty pancreas, however, no consensus exists for the diagnosis of the fatty pancreas, and the possibility of poor interobserver agreement exists. Sepe et al. used clarity of pancreatic parenchyma and duct margins along with comparative echogenicity to grade the fatty pancreas from grade I to grade IV.⁵³ Endoscopic ultrasonography overcomes the limitation of abdominal USG of nonvisualization of the pancreas in obese patients and it provides the potential advantage of obtaining fine needle aspiration/biopsy, however, it is a more invasive procedure compared to all the other imaging modalities.

CLINICAL CONSEQUENCES

Metabolic Syndrome and Diabetes Mellitus

Obesity, metabolic syndrome, NAFLD, and insulin resistance are closely related to NAFLD as described above.

Exocrine Dysfunction

Pancreatic exocrine insufficiency develops when the majority of the pancreatic parenchyma gets destroyed. The literature on pancreatic exocrine insufficiency with pancreatic steatosis is very scarce and limited to mainly in childhood congenital causes.^{54,55} Recently, Tahtacı et al. evaluated 31 patients with pancreatic steatosis diagnosed based on MRI abdomen. In that cohort, 35.5% of patients were having fecal elastase levels <200 mg/g compared to 12% of controls ($n = 25$) without pancreatic steatosis ($p = 0.042$). However, the authors did not explore the clinical correlation of low elastase levels in this study. So, the clinical implication of this study still remains uncertain.⁵⁶ Moreover, whether increasing adipose tissue in the pancreas has negative paracrine effects on acinar cells or directly causes the death of acinar cells leading to exocrine insufficiency is still not clear.^{54,57}

Pancreatic Cancer

Obesity is associated with multiple cancers including breast, endometrial, and colonic carcinoma. Pancreatic steatosis is closely associated with obesity and its association with pancreatic carcinoma is also increasing. Adipocytes and fibrosis both are found in increasing amounts in pancreatic tumors of obese mice than in lean mice.⁵⁸ However, whether adipocytes are responsible for inflammation and fibrosis leading to adenocarcinoma or fibrosis is a sequela of pancreatic carcinoma is not known. Recently,

Lesmana et al. conducted a retrospective single-center study in Indonesia evaluating the relationship between pancreatic adenocarcinoma and fatty pancreas (diagnosed based on EUS). In that study, the fatty pancreas was more common in patients with pancreatic carcinoma and it was the only risk factor associated with the development of pancreatic carcinoma.⁵⁹ Larger, properly designed prospective studies are required before implicating a causal relationship between these two conditions.

Pancreatic Fistula

Various studies have shown that pancreatic steatosis is associated with an increased risk of the development of a pancreatic fistula.^{60,61} In a study by Lee et al., patients with postoperative pancreatic fistula had soft pancreatic texture, small pancreatic duct, and total fat and relative signal intensity decrease (RSID) on MRI was higher compared to patients without postoperative fistula. Patients with soft pancreas had higher interlobular and intralobular fat on histology and pancreatic fat content was positively correlated with RSID. The authors concluded that pancreatic steatosis is a risk factor for the development of pancreatic fistula (as shown by other researchers as well) and preoperative MRI can predict the postoperative pancreatic fistula.⁶²

Acute Pancreatitis

Obesity is associated with increased severity of acute pancreatitis including increased risk of developing organ failure, local complications, a longer hospital stay, and even increased mortality.⁶³ Presence of increased pancreatic adipocytes may be associated with increased secretion of adipokines, chemokines, and cytokines causing a greater inflammatory response and associated systemic complications. In mice models, levels of IL-1 β and TNF- α have been found to be increased in obese mice.⁶⁴ Moreover, initial data also suggest a correlation between pancreatic steatosis and CT severity index in patients with acute pancreatitis.⁸ Moreover, a fatty pancreas is also shown to be a risk factor for the development of chronic pancreatitis in a recent study.⁶⁵

TREATMENT

Lifestyle modification including weight reduction, exercise, and dietary restriction can improve the fatty infiltration of the pancreas when associated with metabolic syndrome. In a study by Honka et al.,⁶⁶ morbidly obese patients who underwent bariatric surgery showed that insulin resistance in association with fatty pancreas was reduced after weight loss and there was a notable decrease in pancreatic fat volume ($p < 0.01$), fatty acid uptake ($p < 0.05$), and blood flow ($p < 0.05$) postbariatric surgery, whereas no change was seen in pancreatic fat-free volume.⁶⁶ Furthermore, animal models have shown promising efficacy of medical treatment with the use of a combination of sitagliptin and telmisartan, troglitazone, and berberine (traditional Japanese medication in combination with cinnamic acid).^{67–69} However, in the absence of any robust evidence and absence of human studies, no medical therapy can be advocated for the treatment of fatty pancreas and requires more investigational studies to find an effective treatment.

To conclude, the fatty pancreas is still an evolving entity with many unanswered questions. Uniform definition and nomenclature are required in future trials for a better understanding of this entity. Moreover, specific cutoff points are needed to be identified on radiological investigations to define “clinically significant” pancreatic steatosis. Such patients can be followed up to identify

and manage its sequelae like acute/chronic pancreatitis, pancreatic cancer, or pancreatic fistula development. Moreover, the effect of weight reduction or bariatric surgery and medical management also needs to be explored to identify its role in reducing the pancreatic fat content and whether it can prevent the above-mentioned long-term complications or not.

REFERENCES

- Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-level prevalence of adult obesity and severe obesity. *N Engl J Med* 2019;381(25):2440–2450. DOI: 10.1056/NEJMsa1909301.
- Luhar S, Timæus IM, Jones R, et al. Forecasting the prevalence of overweight and obesity in India to 2040. *PLoS ONE* 2020;15(2):e0229438. DOI: 10.1371/journal.pone.0229438.
- Ahirwar R, Mondal PR. Prevalence of obesity in India: a systematic review. *Diabetes Metab Syndr* 2019;13(1):318–321. DOI: 10.1016/j.dsx.2018.08.032.
- Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract* 2014;2014:943162. DOI: 10.1155/2014/943162.
- Lee L, Sanders RA. Metabolic syndrome. *Pediatr Rev* 2012;33(10):459–468. DOI: 10.1542/pir.33-10-459.
- Bi Y, Wang J-L, Li M-L, et al. The association between pancreas steatosis and metabolic syndrome: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2019;35(5):e3142. DOI: 10.1002/dmrr.3142.
- Dite P, Blahos M, Bojkova M, et al. Nonalcoholic fatty pancreas disease: clinical consequences. *Dig Dis* 2020;38(Suppl. 2):143–149. DOI: 10.1159/000505366.
- Smits MM, van Geenen EJM. The clinical significance of pancreatic steatosis. *Nat Rev Gastroenterol Hepatol* 2011;8(3):169–177. DOI: 10.1038/nrgastro.2011.4.
- Ogilvie RF. The islands of langerhans in 19 cases of obesity. *J Pathol Bacteriol* 1933;37(3):473–481. DOI: 10.1002/path.1700370314.
- Olsen TS. Lipomatosis of the pancreas in autopsy material and its relation to age and overweight. *Acta Pathol Microbiol Scand [A]* 1978;86A(1-6):367–373. DOI: 10.1111/j.1699-0463.1978.tb02058.x.
- Feigelson J, Pécau 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(2):145–151. DOI: 10.1097/00005176-200002000-00010.
- Lesmana CRA, Pakasi LS, Inggriani S, et al. 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(1):174. DOI: 10.1186/s12876-015-0404-1.
- Zhou J, Li M-L, Zhang D-D, et al. The correlation between pancreatic steatosis and metabolic syndrome in a Chinese population. *Pancreatol* 2016;16(4):578–583. DOI: 10.1016/j.pan.2016.03.008.
- Wilson JS, Somer JB, Pirola RC. Chronic ethanol feeding causes accumulation of serum cholesterol in rat pancreas. *Exp Mol Pathol* 1984;41(3):289–297. DOI: 10.1016/0014-4800(84)90016-9.
- Altinel D, Basturk O, Sarmiento JM, et al. Lipomatous pseudohypertrophy of the pancreas. *Pancreas* 2010;39:392–397.
- Patel S, Bellon EM, Haaga J, et al. Fat replacement of the exocrine pancreas. *AJR Am J Roentgenol* 1980;135(4):843–845. DOI: 10.2214/ajr.135.4.843.
- Mathur A, Zyromski NJ, Pitt HA, et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. *J Am Coll Surg* 2009;208(5):989–994. DOI: 10.1016/j.jamcollsurg.2008.12.026; discussion 994–996.
- Kölbel G, Majer MC, Hess CF, et al. The internal echo pattern of the normal pancreas. An assessment of the aging process and body weight dependence by sonographic gray-scale analysis. *ROFO Fortschr Geb Röntgenstr Nuklearmed* 1987;146(04):415–419. DOI: 10.1055/s-2008-1048513.
- Marks WM, Filly RA, Callen PW. Ultrasonic evaluation of normal pancreatic echogenicity and its relationship to fat deposition. *Radiology* 1980;137(2):475–479. DOI: 10.1148/radiology.137.2.7433680.
- Glaser J, Stienecker K. Pancreas and aging: a study using ultrasonography. *Gerontology* 2000;46(2):93–96. DOI: 10.1159/000022141.
- Kul S, Karadeniz A, Dursun İ, et al. Non-alcoholic fatty pancreas disease is associated with increased epicardial adipose tissue and aortic intima-media thickness. *Acta Cardiol Sin* 2019;35:118–125.
- 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(15):1869–1875. DOI: 10.3748/wjg.15.1869.
- Catanzaro R, Cuffari B, Italia A, et al. Exploring the metabolic syndrome: nonalcoholic fatty pancreas disease. *World J Gastroenterol* 2016;22(34):7660–7675. DOI: 10.3748/wjg.v22.i34.7660.
- 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(6):1512–1519. DOI: 10.1007/s00261-015-0385-0.
- Lingvay I, Esser V, Legendre JL, et al. Noninvasive quantification of pancreatic fat in humans. *J Clin Endocrinol Metab* 2009;94(10):4070–4076. DOI: 10.1210/jc.2009-0584.
- Lee Y, Lingvay I, Szczepaniak LS, et al. Pancreatic steatosis: harbinger of type 2 diabetes in obese rodents. *Int J Obes* 2010;34(2):396–400. DOI: 10.1038/ijo.2009.245.
- 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(11):2916–2921. DOI: 10.2337/dc07-0326.
- Zenker M, Mayerle J, Reis A, et al. Genetic basis and pancreatic biology of Johanson-Blizzard syndrome. *Endocrinol Metab Clin North Am* 2006;35(2):243–253. DOI: 10.1016/j.ecl.2006.02.013, vii–viii.
- Myers KC, Bolyard AA, Otto B, et al. Variable clinical presentation of Shwachman-Diamond syndrome: update from the North American Shwachman-Diamond syndrome registry. *J Pediatr* 2014;164(4):866–870. DOI: 10.1016/j.jpeds.2013.11.039.
- Johansson BB, Torsvik J, Bjørkhaug L, et al. Diabetes and pancreatic exocrine dysfunction due to mutations in the carboxyl ester lipase gene-maturity onset diabetes of the young (CEL-MODY): a protein misfolding disease. *J Biol Chem* 2011;286(40):34593–34605. DOI: 10.1074/jbc.M111.222679.
- Papakonstantinou O, Ladis V, Kostaridou S, et al. The pancreas in beta-thalassemia major: MR imaging features and correlation with iron stores and glucose disturbances. *Eur Radiol* 2007;17(6):1535–1543. DOI: 10.1007/s00330-006-0507-8.
- Makay O, Kazimi M, Aydin U, et al. Fat replacement of the malignant pancreatic tissue after neoadjuvant therapy. *Int J Clin Oncol* 2010;15(1):88–92. DOI: 10.1007/s10147-009-0001-9.
- Fernandes-Santos C, Evangelista Carneiro R, de Souza Mendonça L, et al. Rosiglitazone aggravates nonalcoholic fatty pancreatic disease in C57BL/6 mice fed high-fat and high-sucrose diet. *Pancreas* 2009;38(3):e80–e86. DOI: 10.1097/MPA.0b013e3181987d9d.
- Sasaki M, Nakanuma Y, Ando H. Lipomatous pseudohypertrophy of the pancreas in a patient with cirrhosis due to chronic hepatitis B. *Pathol Int* 1998;48(7):566–568. DOI: 10.1111/j.1440-1827.1998.tb03951.x.
- Chehter EZ, Longo MA, Laudanna AA, et al. Involvement of the pancreas in AIDS: a prospective study of 109 post-mortems. *AIDS* 2000;14(13):1879–1886. DOI: 10.1097/00002030-200009080-00001.
- Walters MN-I, Leak PJ, Joske RA, et al. Murine infection with reovirus. *Br J Exp Pathol* 1965;46:200–212.
- 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(10):1845–1851. DOI: 10.1007/s11605-009-0974-8.
- 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 N Y N* 2007;20(8):933–942. DOI: 10.1002/ca.20543.

39. Lopez JM, Bombi JA, Valderrama R, et al. Effects of prolonged ethanol intake and malnutrition on rat pancreas. *Gut* 1996;38(2):285–292. DOI: 10.1136/gut.38.2.285.
40. Khoury T, Asombang AW, Berzin TM, et al. The clinical implications of fatty pancreas: a concise review. *Dig Dis Sci* 2017;62(10):2658–2667. DOI: 10.1007/s10620-017-4700-1.
41. Kim HJ, Byun JH, Park SH, et al. Focal fatty replacement of the pancreas: usefulness of chemical shift MRI. *AJR Am J Roentgenol* 2007;188(2):429–432. DOI: 10.2214/AJR.05.1095.
42. Navina S, Acharya C, DeLany JP, et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci Transl Med* 2011;3(107):107ra110. DOI: 10.1126/scitranslmed.3002573.
43. Dixon WT. Simple proton spectroscopic imaging. *Radiology* 1984;153(1):189–194. DOI: 10.1148/radiology.153.1.6089263.
44. Sijens PE, Edens MA, Bakker SJL, et al. MRI-determined fat content of human liver, pancreas and kidney. *World J Gastroenterol* 2010;16(16):1993–1998. DOI: 10.3748/wjg.v16.i16.1993.
45. Kühn J-P, Berthold F, Mayerle J, et al. Pancreatic steatosis demonstrated at MR imaging in the general population: clinical relevance. *Radiology* 2015;276(1):129–136. DOI: 10.1148/radiol.15140446.
46. Wong VW-S, Wong GL-H, Yeung DK-W, 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.
47. Hannukainen JC, Borra R, Linderborg K, et al. Liver and pancreatic fat content and metabolism in healthy monozygotic twins with discordant physical activity. *J Hepatol* 2011;54(3):545–552. DOI: 10.1016/j.jhep.2010.07.029.
48. Yu H, Shimakawa A, McKenzie CA, et al. Multiecho water-fat separation and simultaneous R2* estimation with multifrequency fat spectrum modeling. *Magn Reson Med* 2008;60(5):1122–1134. DOI: 10.1002/mrm.21737.
49. Reeder SB, Hu HH, Sirlin CB. Proton density fat-fraction: a standardized MR-based biomarker of tissue fat concentration. *J Magn Reson Imaging JMRI* 2012;36(5):1011–1014. DOI: 10.1002/jmri.23741.
50. Kato S, Iwasaki A, Kurita Y, et al. Three-dimensional analysis of pancreatic fat by fat-water magnetic resonance imaging provides detailed characterization of pancreatic steatosis with improved reproducibility. *PLoS ONE* 2019;14(12):e0224921. DOI: 10.1371/journal.pone.0224921.
51. Hu HH, Kim H-W, Nayak KS, et al. Comparison of fat-water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. *Obes Silver Spring Md* 2010;18:841–847.
52. Al-Haddad M, Khashab M, Zyromski N, et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. *Pancreas* 2009;38(6):672–675. DOI: 10.1097/MPA.0b013e3181a9d5af.
53. Sepe PS, Ohri A, Sanaka S, et al. A prospective evaluation of fatty pancreas by using EUS. *Gastrointest Endosc* 2011;73(5):987–993. DOI: 10.1016/j.gie.2011.01.015.
54. Aubert A, Gornet J-M, Hammel P, et al. Diffuse primary fat replacement of the pancreas: an unusual cause of steatorrhea. *Gastroenterol Clin Biol* 2007;31(3):303–306. DOI: 10.1016/S0399-8320(07)89379-1.
55. Midiri M, Lo Casto A, Sparacia G, et al. MR imaging of pancreatic changes in patients with transfusion-dependent beta-thalassemia major. *Am J Roentgenol* 1999;173(1):187–192. DOI: 10.2214/ajr.173.1.10397124.
56. Tahtacı M, Algin O, Karakan T, et al. Can pancreatic steatosis affect exocrine functions of pancreas? *Turk J Gastroenterol* 2018;29(5):588–594. DOI: 10.5152/tjg.2018.17696.
57. Lozano M, Navarro S, Pérez-Ayuso R, et al. Lipomatosis of the pancreas: an unusual cause of massive steatorrhea. *Pancreas* 1988;3(5):580–582. DOI: 10.1097/00006676-198810000-00012.
58. Zyromski NJ, Mathur A, Pitt HA, et al. Obesity potentiates the growth and dissemination of pancreatic cancer. *Surgery* 2009;146(2):258–263. DOI: 10.1016/j.surg.2009.02.024.
59. Lesmana CRA, Gani RA, Lesmana LA. Non-alcoholic fatty pancreas disease as a risk factor for pancreatic cancer based on endoscopic ultrasound examination among pancreatic cancer patients: a single-center experience. *JGH Open* 2018;2(1):4–7. DOI: 10.1002/jgh3.12032.
60. Rungsakulkij N, Mingphruehdi S, Tangtawee P, et al. Risk factors for pancreatic fistula following pancreaticoduodenectomy: a retrospective study in a Thai tertiary center. *World J Gastrointest Surg* 2017;9(12):270–280. DOI: 10.4240/wjgs.v9.i12.270.
61. Mathur A, Pitt HA, Marine M, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg* 2007;246(6):1058–1064. DOI: 10.1097/SLA.0b013e31814a6906.
62. Lee SE, Jang J-Y, Lim C-S, et al. Measurement of pancreatic fat by magnetic resonance imaging: predicting the occurrence of pancreatic fistula after pancreatoduodenectomy. *Ann Surg* 2010;251(5):932–936. DOI: 10.1097/SLA.0b013e3181d65483.
63. Martínez J, Johnson CD, Sánchez-Payá J, et al. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatol* 2006;6(3):206–209. DOI: 10.1159/000092104.
64. Zyromski NJ, Mathur A, Pitt HA, et al. A murine model of obesity implicates the adipokine milieu in the pathogenesis of severe acute pancreatitis. *Am J Physiol-Gastrointest Liver Physiol* 2008;295(3):G552–G558. DOI: 10.1152/ajpgi.90278.2008.
65. Fujii M, Ohno Y, Yamada M, et al. Impact of fatty pancreas and lifestyle on the development of subclinical chronic pancreatitis in healthy people undergoing a medical checkup. *Environ Health Prev Med* 2019;24(1):10. DOI: 10.1186/s12199-019-0763-2.
66. 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(5):2015–2023. DOI: 10.1210/jc.2014-4236.
67. Zhao L, Jiang S, Lu F, et al. Effects of berberine and cinnamic acid on palmitic acid-induced intracellular triglyceride accumulation in NIT-1 pancreatic β cells. *Chin J Integr Med* 2016;22(7):496–502. DOI: 10.1007/s11655-014-1986-0.
68. Souza-Mello V, Gregório BM, Relvas-Lucas B, et al. Pancreatic ultrastructural enhancement due to telmisartan plus sitagliptin treatment in diet-induced obese C57BL/6 mice. *Pancreas* 2011;40(5):715–722. DOI: 10.1097/MPA.0b013e31812153922.
69. Jia DM, Fukumitsu KI, Tabaru A, et al. Troglitazone stimulates pancreatic growth in congenitally CCK-A receptor-deficient OLETF rats. *Am J Physiol Regul Integr Comp Physiol* 2001;280(5):R1332–R1340. DOI: 10.1152/ajpregu.2001.280.5.R1332.