Fatty Pancreas: Clinical Implications

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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 perquisite 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.

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.

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 perquisite 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,
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hypertriglyceridemia, and hepatic steatosis. 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. Smits and van Geenen have tried to give uniform nomenclature in their recent article, though it has not been validated prospectively in trials (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.

**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 NAFPD appears to be bidirectional. Patients with obesity and metabolic syndrome are at a higher risk of developing NAFPD and patients with NAFPD appear to be at a higher risk of development of metabolic syndrome, insulin resistance, and cardiovascular morbidity. Studies have shown 60–97% of patients with fatty liver have associated fatty pancreas as well. A recent meta-analysis has shown that presence of NAFPD 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).

**Diabetes**

Pancreatic β-cell dysfunction and insulin resistance both are considered to be important pathogenic events in the development of NAFPD. Studies have shown that pancreatic fat accumulation is present in pre-diabetics which increases before the development of type II DM. 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 NAFPD and β-cell function in nondiabetic individuals. However, at present times, there is still limited evidence to define a causal relationship between NAFPD and type II DM.

**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. Johanson–Blizzard syndrome is associated with developmental anomalies with pancreatic necrosis-fibrosis followed by pancreatic fatty replacement. Shwachman–Diamond syndrome is also associated with pancreatic fatty infiltration and pancreatic exocrine insufficiency along with musculoskeletal abnormality and bone marrow failure. Mutation in carboxyl-ester-lipase is also associated with fatty pancreas with DM.

**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.

**Toxic Agents or Medications**

Few drugs like rosiglitazone, corticosteroids, octreotide, and gemcitabine are associated with development of fatty pancreas.

**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.

**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. 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. 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

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**Table 1: Proposed nomenclature for fatty pancreas**

| 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 | Death of acinar cells with subsequent replacement with adipocytes |
| Fatty replacement | 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 I A (35%, involvement of pancreatic head without involving the uncinate and peripancreatic region), type IB (35%, involves head, neck, and body of pancreas without involving the uncinate and peripancreatic region), type IIA (12%, involves head and uncinate process without peripancreatic region), and type IIB (18%, affects head, neck, body and uncinate process of the pancreas without peripancreatic 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.
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Endoscopic ultrasonography (EUS) identifies the fatty pancreas as a hyperechoic structure compared to the adjacent solid structure (Fig. 3). 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. 

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 NAFPD 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. 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. 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.

**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. 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. 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. 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.

**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. 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-1β and TNF-alpha have been found to be increased in obese mice. Moreover, initial data also suggest a correlation between pancreatic steatosis and CT severity index in patients with acute pancreatitis. Moreover, a fatty pancreas is also shown to be a risk factor for the development of chronic pancreatitis in a recent study.

**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., 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. 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). 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.

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