REVIEW

AG-2019-157
doi.org/10.1590/S0004-2803.202000000-27

Pancreatic steatosis: a new diagnosis and therapeutic challenge in Gastroenterology

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Received: 21 October 2019
Accepted: 20 February 2020

ABSTRACT – Fat infiltration in the pancreas is called pancreatic steatosis and it has several synonyms such as pancreatic lipomatosis, non-alcoholic fatty pancreatic disease, lipomatous pseudohypertrophy, fatty replacement, fatty pancreas and fatty infiltration. Pancreatic steatosis describes a disease ranging from infiltration of fat in the pancreas to pancreatic inflammation, and development of pancreatic fibrosis. There are multiple aetiologies of this condition, such as metabolic syndrome, alcohol intake, viral infections, toxins, congenital syndromes, etc. Pancreatic steatosis is usually diagnosed by trans-abdominal ultrasound, computed tomography scan and magnetic resonance imaging. Fatty infiltration in pancreas may lead to pancreatitis, diabetes mellitus and may be a predisposing cause of pancreatic cancer. Now a day, pancreatic steatosis is a common incidental finding during abdominal ultrasonography for other reasons and is a new challenge in Gastroenterology. But there is no guideline for pancreatic steatosis till now. In this review article, we are trying to give an overall idea (aetiologies, diagnosis, management, clinical significances) on pancreatic steatosis.

HEADINGS – Pancreas. Pancreatic diseases. Lipomatosis. Magnetic resonance imaging. Endosonography. Ultrasonography. Review.

INTRODUCTION

Pancreatic steatosis (PS) is the most common benign pathologic condition of the pancreas in adult[1] and commonly related to obesity and associated insulin resistance[2]. PS (used for all forms of pancreatic fat accumulation) has several synonyms such as: pancreatic fatty infiltration (pancreatic fatty infiltration due to obesity, reversed by weight reduction and medications), pancreatic lipomatosis (used for all forms of fatty infiltration of pancreas), fatty replacement (irreversible damage of pancreatic acinar cells and replacement by adipocytes), non-alcoholic fatty pancreatic disease (obesity and metabolic syndrome causing pancreatic fat accumulation), lipomatous pseudohypertrophy (when pancreas is uniformly or focally enlarged and/or the pancreatic exocrine system is altered by fat accumulation, and not related to obesity), fatty pancreas (used for all types of pancreatic fat accumulation)[3,4]. Pancreatic fat accumulation increases with age and replacement of more than 25% of pancreas by fat is associated with severe generalized atherosclerosis and increased risk of development of diabetes mellitus type 2[5]. On abdominal computed tomography scan, pancreas becomes hypodense and on ultrasound (US) examination it shows typical hyperechogenicity. Pancreatic steatosis is the commonly identifying pancreatic pathology during radiological examination but there is no guideline for PS till now. This article is trying to describe pancreatic steatosis in details including aetiology, diagnosis, clinical significance and management.

Definition of pancreatic steatosis

Pancreatic steatosis (PS) is defined by fat accumulation in pancreas and when there is presence of obesity or metabolic syndrome; it is called "non-alcoholic fatty pancreas disease" (NAFPD) and usually associated with NAFLD (non-alcoholic fatty liver disease)[4]. In 1933, Ogilvie first described pancreatic steatosis in literature[4].

Aetiologies of pancreatic steatosis

There are several causes of pancreatic steatosis (FIGURE 1). Similar to NAFLD, advanced age, obesity, metabolic syndrome and insulin resistance are the common risk factors of pancreatic steatosis. Pancreatic fat content is significantly associated with greater body mass index (BMI) and advanced age[6]. Prevalence is extremely low in women with age less than 50 years, but increases

Metabolic causes	Drugs and Toxin	Infection	Others	Local causes
Diabetes	Steroids	Hepatitis B	Haemochromatosis	Chronic pancreatitis
Severe malnutrition	Antiretroviral	AIDS	Cystic fibrosis	Hereditary pancreatitis
Obesity	Rosiglitazone	Reovirus	Old age	Pancreatic ductal obstruction
Dyslipidemia	Gemcitabine		Cirrhosis	
Insulin resistance	Alcohol			
Metabolic syndrome	Octreotide			

FIGURE 1. Aetiologies of pancreatic steatosis.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
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progressively after 50 years of age[7]. Some medications are also responsible for pancreatic steatosis such as steroid hormones[6], antiretroviral therapy[8], rosiglitazone[9], gemcitabine chemotherapy[10] and octreotide[11]. The presence of one or more component of metabolic syndrome, such as diabetes, BMI ≥30, hypertension or hyperlipidemia is associated with 37% increased prevalence of pancreatic steatosis[12]. Chronic alcohol abuse increases pancreatic cholesteryl ester accumulation and induces pancreatic steatosis[13] and usually is seen when person consuming more than 30 gram/day of ethanol[14]. Several infections such as acquired immunodeficiency syndrome (AIDS)[15], chronic hepatitis B[16] and reovirus infection[17] can produce fatty pancreas. Haemochromatosis[4] and malnutrition state such as kwashiorkor[18] can also be responsible NAFPD.

Diagnosis of pancreatic steatosis

Pancreatic steatosis (PS) is most commonly diagnosed by using different imaging techniques[1,3,7] (FIGURE 1). When using any imaging technique to identify pancreatic steatosis, we should know that there is up to 6.2% fatty infiltration of the pancreas in normal individuals. But specificity and sensitivity of different imaging modalities has not been clearly mentioned in several articles on PS.

Ultrasonography in diagnosis of pancreatic steatosis

Ultrasonography (USG) is widely available to detect PS but obesity and bowel gas may cause invisibility of pancreas. To diagnose pancreatic steatosis, pancreas echogenicity is traditionally compared with kidney echogenicity. Hyperechogenic pancreas can be seen in both pancreatic fibrosis and in fatty pancreas. Pancreatic steatosis can be classified into four grades by identifying patterns of pancreas echogenicity in abdominal USG (FIGURE 2); grade 0: when pancreas and renal echogenicity are similar; grade 1: when pancreas echogenicity is increased and is slightly higher than in the kidney; grade 2: when substantial increase in pancreas echogenicity than renal echogenicity but the retroperitoneal fat echogenicity is more than pancreatic echogenicity; and grade 3: the pancreas echogenicity is ≥ retroperitoneal fat echogenicity[19,20].

Computed tomography (CT) in diagnosis of pancreatic steatosis

Focal pancreatic steatosis can be presented as a hypo attenuating mass lesion on CT scan[21]. Non contrast computed tomography (CT) can be used to diagnose PS. Disadvantages of CT scan are exposure to radiation, high cost and can miss focal fatty replacement of pancreas. Fatty pancreas can be classified by CT scan into five grades depending on site of pancreatic involvement (FIGURE 2); Grade 0– normal appearance without fatty replacement, Grade 1– fatty infiltration involving less than 25% of given pancreatic region, Grade 2– fatty replacement that involved 25%–50% of a given pancreatic region, Grade3– fatty replacement involving 50%–75% of a given pancreatic regions; and Grade 4 corresponded to fatty infiltration which involves more than 75% of a given pancreatic region[22]. Fat concentration in pancreas is positively correlated with attenuation indexes in CT scan; this finding suggests that unenhanced CT is useful non-invasive assessment of pancreatic fat[23].

Endoscopic ultrasonography in diagnosis of pancreatic steatosis

Diagnostic accuracy of pancreatic steatosis by endoscopic ultrasound (EUS) is superior to CT scan and magnetic resonance imaging (MRI). The disadvantages are invasive procedure, risk of complications and needs of sedation. EUS is still the most sensitive investigation for pancreas screening but till now pancreatic biopsy is the best method to measure pancreatic fat concentration[24]. However, it is unethical to use EUS as a screening tool[25]. EUS grading system adapted from radiology incorporating the echotexture of the pancreas relative to the spleen as well as the ability to visualize the main pancreatic duct and "salt and pepper" dots in the parenchyma has been suggested to assess fatty pancreas[12].

Magnetic resonance imaging for diagnosis of PS

Magnetic resonance imaging (MRI) can estimate fat concentration in pancreas with high accuracy. MRI may be the test of choice for detection of intrapancreatic fat but available data is little to correlate pancreatic steatosis on MRI or EUS with histology. During MRI, commonly three methods are used to measure the fat in the pancreas. Advanced chemical shift-based gradient echo magnetic resonance imaging technique that measures the proton-density-fat-fraction (PDFF) has been shown to accurately quantify liver fat fraction when compared with the magnetic resonance spectroscopy (MRS) technique[26] and reliably measures pancreatic fat content when compared with other MRI imaging techniques[27].

Pathological classification

Pathologically pancreatic steatosis is classified into homogenous pancreatic lipomatosis and non homogenous pancreatic lipomatosis. Again non homogenous lipomatosis is classified into four types; type 1a: head is usually replaced by fat, type 1b: head, neck and body are replaced by fat, type 2a: head and uncinate process replaced by fat, type 2b: most of the pancreas except the peribiliary region is replaced by fat[28]. However, histological examination is not recommended for only diagnosis of pancreatic steatosis.

Clinical significances

Development of diabetes mellitus: Wang et al. (2014) in their study found that the patients with fatty pancreas has an higher risk of development of diabetes than patients without fatty pancreas[29]

Grading of Pancreatic steatosis	USG Findings	CT findings
Grade 0	When pancreas and renal echogenicity are similar	Normal appearance without fatty replacement
Grade 1	When pancreas echogenicity was slightly higher than in the kidney	Fatty infiltration involving less than 25% of given pancreatic region
Grade 2	When substantial increase in pancreas echogenicity than renal echogenicity but lower than the retroperitoneal fat echogenicity	Fatty replacement that involved 25%–50% of a given pancreatic region
Grade 3	The pancreas echogenicity is similar to or higher than the retroperitoneal fat	Fatty replacement involving 50%–70% of a given pancreatic regions
Grade 4		Fatty infiltration which involves more than 75% of a given pancreatic region

FIGURE 2. Pancreatic steatosis grading by trans abdominal ultrasonography (UGS) and abdominal computed tomography (CT).

and newly diagnosed patients with type 2 diabetes mellitus (DM2) have significantly greater pancreatic fat content[30]. Pancreatic islets cell fat infiltration leads to a reduced insulin secretion and increases development of DM2[31]. Presence of >25% pancreatic fatty infiltration is associated with significantly increased risk of development of type 2 diabetes mellitus and generalized atherosclerosis[32].

Post operative pancreatic fistula: developing a pancreatic fistula is significantly increased after pancreatic surgery in patients with pancreatic steatosis[33,34], and have a ten times higher risk of incidence of fistula formation in pancreas than those with fibrotic pancreas[35].

Carotid atherosclerosis: pancreatic steatosis is an independent risk factor for the development of carotid atherosclerosis in non-obese subjects with type 2 diabetes mellitus. So, it could be a marker of higher risk of cardiovascular disease, especially in non-obese individuals[36].

Pancreatitis: risk factors of pancreatic steatosis such as obesity and components of metabolic syndrome are known risk factors for acute pancreatitis. When acute pancreatitis due to any aetiology affects fatty pancreas, it is usually severe in intensity[37] and also is a significant risk factor for developing subclinical chronic pancreatitis[38].

Pancreatic carcinoma: fatty pancreas is independently associated with an increased risk of development of pancreatic carcinoma[3,39]. PS promotes dissemination and lethality of pancreatic carcinoma by alteration of tumour microenvironment, enhanced tumour spread[40]. Patients with increased pancreatic fat have a poor outcome than those who develop cancer in a pancreas without steatosis. Chronic inflammation with excessive fat accumulation might be the cause of cell injury and development of pancreatic carcinoma[41]. But another study found that there is no association between fatty pancreas and chronic pancreatitis or carcinoma of pancreas[12]. Non alcoholic fatty liver disease (NAFLD) is positively correlated with pancreatic cancer in these patients and NAFLD patients with pancreatic cancer have poorer outcome than patients without NAFLD[42]. Pathophysiology of development of pancreatic cancer in NAFPD is similar to how NAFLD causes liver cancer [4].

Pancreatic exocrine insufficiency: pancreatic steatosis can lead to exocrine pancreatic insufficiency (EPI) by (1) fat droplet accumulation in pancreatic acinar cells and consequent lipotoxicity, (2) destruction of acinar cells by both inflammation and fatty replacement, (3) by negative paracrine effect of adipocytes. Exocrine function in NAFPD patients has never been extensively investigated. In few case reports, patients with weight loss and massive steatorrhea were found to have severe pancreatic steatosis diagnosed by abdominal computed tomograms (CT scan) in whom the administration of pancreatic extracts improved symptoms[43,44].

Cardiovascular risk: risk factors of fatty pancreas are also risk factors of cardiovascular accident. The presence of NAFPD on ultrasonography is associated with increased aortic intima media thickness and epicardial adipose tissue[45]. Therefore, it could be a marker of a higher risk of cardiovascular disease.

Pancreatic enzymes level in PS: few study[46] showed that serum amylase value is significantly lower in patients with fatty pancreas compared to normal pancreas individuals but another study indicates that there is no association between fatty pancreas and serum amylase or lipase concentrations[12]. Benign pancreatic hyperenzymemia (BPH) or Gullo's syndrome is a diagnosis of exclusion and diagnosed by persistently elevated pancreatic enzymes without any clinical or pathological evidence of pancreatic disease. There is no relationship between NAFPD and Gullo's syndrome.

Correlation between non-alcoholic fatty liver and non-alcoholic fatty pancreas

Pancreatic steatosis is common in patients with NAFLD, and pancreatic fat content positively correlates with liver steatosis grading determined by histology[46,47]. Patients with histology-determined liver fibrosis have significantly less pancreatic fat infiltration than those without evidence of liver fibrosis[48]. Fatty infiltration in pancreas causes β-cell dysfunction, which may also lead to hepatic steatosis[49] and pancreatic fat also may play a role in the development of non alcoholic steatohepatitis (NASH)[37].

Differential diagnosis

Pancreatic steatosis of the dorsal caudal pancreas must be distinguished from dorsal pancreatic agenesis. Lipomatous pseudohypertrophy of the pancreas has probably been considered as a differential diagnosis of pancreatic steatosis[50,51].

Management of pancreatic steatosis (FIGURE 3)

There is no specific treatment for fatty pancreas. Until now

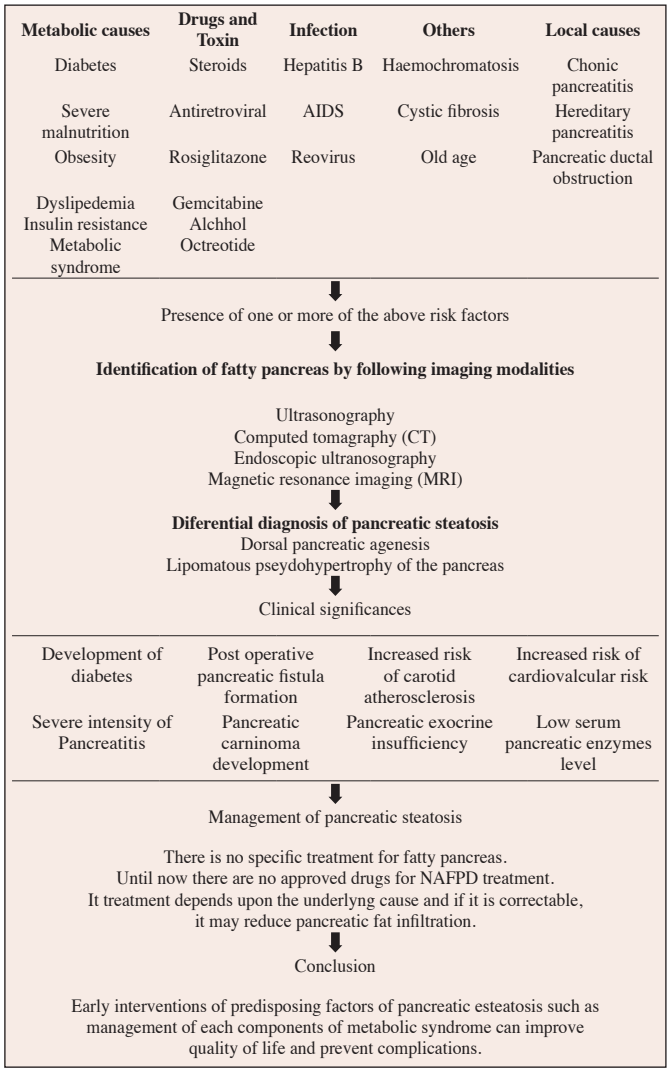

FIGURE 3. Flow chart of a practical approach of pancreatic steatosis (aetiology, diagnosis, clinical significance and management).

there are no approved drugs for NAFPD treatment. Treatment of PS depends on the underlying cause and if it is correctable, it may reduce pancreatic fat infiltration. If patient is having metabolic syndrome then tight diabetes control, diet restriction, physical exercise and weight reduction may improve condition. Pancreatic steatosis can be treated with a healthy diet, exercise, less meat consumption, and smoking cessation[52].

CONCLUSION

In majority cases, pancreatic steatosis is an incidental finding during trans-abdominal ultrasonography. It is commonly associated with metabolic syndrome, alcohol abuse and patients with non alcoholic fatty liver disease. NAFPD is usually diagnosed by radiological investigations such as abdominal USG, abdominal CT scan or abdominal MRI. Fatty pancreas has an increased risk of development of diabetes, pancreatic fistula after pancreatic surgery, development of carotid atherosclerosis in non-obese individuals, risk of development of pancreatic carcinoma, developing subclinical chronic pancreatitis and exocrine pancreatic insufficiency. Therefore early diagnosis and interventions for predisposing factors of pancreatic steatosis such as each component of metabolic syndrome can improve quality of life and prevent complications. But Until now there are no approved specific drugs for NAFPD treatment.

Authors' contribution

Paul J: conceptualization, methodology, supervision, writing-original draft, writing-review & editing. Shihaz AVH: conceptualization, writing-review & editing.

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Paul J, Shihaz AVH. Esteatose pancreática: um novo diagnóstico e desafio terapêutico na Gastroenterologia. Arq Gastroenterol. 2020;57(2):216-20.

RESUMO – A infiltração de gordura no pâncreas é chamada de esteatose pancreática ou lipomatose pancreática e tem vários sinônimos tais como: doença pancreática gordurosa não alcoólica, pseudo hipertrofia lipomatosa, reposição gordurosa, pâncreas gorduroso e infiltração gordurosa. A esteatose pancreática descreve uma doença que vai desde a infiltração de gordura no pâncreas até a inflamação pancreática com o desenvolvimento de fibrose pancreática. Existem múltiplas causas dessa condição, como síndrome metabólica, ingestão de álcool, infecções virais, toxinas, síndromes congênitas, etc. A esteatose pancreática é geralmente diagnosticada por ultrassom trans-abdominal, tomografia computadorizada ou ressonância magnética. A infiltração gordurosa no pâncreas pode levar à pancreatite e pode ser uma causa predisponente ao câncer de pâncreas. Hoje em dia, a fibrose pancreática é um achado incidental comum durante a ultrassonografia abdominal realizada por outras razões e é um novo desafio na Gastroenterologia. Mas não há diretriz para esteatose pancreática até agora. Neste artigo de revisão, objetivamos dar uma ideia geral sobre esteatose pancreática.

DESCRITORES – Pâncreas. Pancreatopatias. Lipomatose. Imagem por ressonância magnética. Endossonografia. Ultrassonografia. Revisão.

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