Extended Review and Updates of Nonalcoholic Fatty Pancreas Disease

Elmukhtar Habas[1,2], Kalifa Farfar[3], Eshrak Habas[4], Amnna Rayani[5], Abdul-Naser Elzouki[1,2]

[1]Department of Medicine, Hamad Medical Corporation, [2]Department of Medicine, College of Medicine, Qatar University, Doha, [3]Department of Medicine, Alwakra General Hospital, Alwakra, Qatar, [4]Department of Medicine, Tripoli Central Hospital, [5]Tripoli Children Hospital, Medical College, Tripoli University, Tripoli, Libya

Abstract

Non-alcoholic fatty pancreatic disease (NAFPD), also known as pancreatic steatosis, is a benign condition characterized by deposition of lipids in the pancreas and is associated with insulin resistance, malnutrition, obesity, metabolic syndrome, aging, and absence of heavy alcohol intake or infection. Similar to nonalcoholic fatty liver disease, NAFPD is a phenotypic entity that includes fat buildup in the pancreas, pancreatic inflammation, and subsequent fibrosis. The extent to which pancreatic fat infiltration is clinically important remains unclear. Despite these clinical associations, most of the clinical effects of NAFPD are not known. NAFPD may be identified by transabdominal and elastography ultrasound, computed tomography scan, or magnetic resonance imaging modalities, but a confirmatory diagnosis can only be made through tissue histology. In addition to complications such as acute and chronic pancreatitis, NAFPD may progress to pancreatic ductal adenocarcinoma. However, further research is required to fully understand the associations, pathophysiology, and effects of NAFPD. This review provides a narrative synthesis of the current literature on the epidemiology, pathophysiology, complications, diagnostic and imaging tools, and management of NAFPD.

Keywords: Diagnosis, metabolic syndrome, nonalcoholic fatty pancreatic disease, obesity, pancreatic steatosis, pathophysiology

INTRODUCTION

Nonalcoholic fatty pancreatic disease (NAFPD) is characterized by the deposition of lipids in the pancreas and is associated with obesity and absence of heavy alcohol intake.[1] Pancreatic fat content surges with age, and >25% of pancreatic fat replacement is linked with generalized atherosclerosis and increased risk of diabetes mellitus type 2 (DM2).[2]

Obesity, defined as having a body mass index (BMI) ≥30, is a chronic condition affecting all ages. According to the World Health Organization, in 2022, about 890 million adults worldwide were obese.[3] Obesity rates among adult women and men increased from 6.6% and 3% in 1975 to 18.5% and 14% in 2022, respectively.[4] The WHO estimates that in 2019, about 5 million deaths attributed to noncommunicable diseases were due to higher-than-optimal BMI.[3] Obesity, particularly abdominal obesity, is linked with insulin resistance, increasing the risk of DM2. Obesity also causes fat infiltration in organs such as the heart, kidneys, liver, and pancreas.[4] The

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hyperinsulinemia status might also cause dyslipidemia and atherosclerotic cardiovascular disease, as reported in human studies and animal models.[5,6]

It is documented that pancreatic size is tightly correlated with the total body weight.[7] NAFPD, also referred to as pancreatic steatosis, has long been known to be associated with increased accumulation of fat in the pancreas. NAFPD has been found to depend on age and ethnicity[8] and on conditions such as DM2 and severe widespread atherosclerosis.[2] Furthermore, Van Geenen *et al*.[9] proposed that pancreatic adipocyte infiltration, which results in pancreatic steatosis, is significantly influenced by obesity and related insulin resistance. In addition, peripheral lipolysis brought on by insulin resistance increases the flow of fatty acids in the liver, resulting in nonalcoholic fatty liver disease (NAFLD), which may indicate that the same occurs in NAFPD.[9] However, the epidemiology of NAFPD is not fully established, likely due to the absence of defined diagnostic criteria, difficulties in diagnosis, and lack of awareness among healthcare professionals.

This narrative review synthesizes the current literature regarding the epidemiology, pathophysiology, complications, diagnostic and imaging tools, and management of NAFPD.

NONALCOHOLIC FATTY PANCREATIC DISEASE ALTERNATIVE TERMS AND NOMENCLATURE

Fatty replacement, pancreatic steatosis, fatty pancreas infiltration, and pancreatic lipomatosis are used to describe increased pancreatic fat content. However, these terms describe increased pancreatic fat content, and there is a lack of standardization in the usage of terms across studies. While NAFPD has recently become more widely acceptable, replacement of injured pancreatic acinar cells with adipocytes rather than fat materials has been reported.

Pancreatic steatosis characterizes fatty accumulation in the pancreas as a reversible process.[10] Pancreatic steatosis, pancreatic lipomatosis, and fatty pancreas are general terms used to describe excessive fat accumulation in the pancreas. Fatty replacement describes irreversible replacement of adipocytes with dyed acinar cells, while fatty infiltration describes reversible pancreatic tissue infiltration by adipocytes in obese individuals. NAFPD is a monoculture that describes fat accretion in the pancreas in metabolic syndrome (MeTS) and obesity, while non-alcoholic steatopancreatitis describes pancreatitis due to excessive fat deposition.[1,11-13]

NAFPD refers to the pancreatic steatosis phenotype linked to malnutrition, obesity, insulin resistance, MeTS, or aging rather than being brought on by alcohol intake,

congenital metabolic diseases, viral infections, or toxins. The spectrum of pancreatic fat deposition ranges from minimal fat accumulation to less frequent nonalcoholic steatopancreatitis, which causes chronic pancreatitis that possibly leads to pancreatic adenocarcinoma.[14]

Pancreatic lipomatosis is a general term that cannot be used for all types of pancreatic fat accumulation. Pancreatic steatosis and fatty pancreas are the alternative nomenclatures used. Fatty pancreas disease is not solely determined by a high BMI; it can arise from factors such as excess fat deposition in the acinar-to-adipocyte transdifferentiation, interlobular stroma, acinar cells, islets of Langerhans, or replacement of apoptotic acinar cells, and thus can result in various disorders such as DM2, acute and chronic pancreatitis, pancreatic cancer, and exocrine pancreas diabetes.[13] Fatty pancreases are considered to be reversible, with weight loss-induced decreases in intrapancreatic fat being closely linked DM2 remission and its redeposition with disease recurrence.[13] Lipomatous pseudohypertrophy (a variant of pancreatic lipid deposition that causes complete or focal pancreatic enlargement) and fatty replacement have been used to describe NAFPD. Finally, non-alcoholic fatty steatopancreatitis is characterized by pancreatitis due to pancreatic fat deposition without a clear cause, especially alcohol intake.[1]

EPIDEMIOLOGY

Owing to the absence of universally accepted noninvasive diagnostic tests and the difficulties and complication risks of pancreatic biopsy, the epidemiology of NAFPD remains uncertain. Notably, the prevalence of NAFPD has increased as the obesity epidemic has become a major public health concern, affecting people of all ages. The rate of adult obesity in the United States is at a record high of 39.8%, and the prevalence of NAFLD (30%) is higher than all other liver diseases.[15,16] Similarly, fatty pancreas affect 16%–35% of adults, about 27% of the population.[17,18] According to epidemiological studies, men have a higher risk of developing NAFPD than women.[19,20] However, NAFLD is associated with advanced fibrosis (10.3% of patients), an independent factor that increases mortality. NAFPD is not commonly associated with advanced fibrosis or chronic pancreatitis.[1,16,18] However, many researchers have studied the connections, pathophysiology, interplay, and impact of these two related diseases because of the close embryological and anatomical relationship between the liver and pancreas. Despite the significant improvement in fat accumulation detected by ultrasonography (US), elastography, computed tomography (CT), and magnetic

resonance imaging (MRI), the epidemiology of NAFPD is not well documented, mostly because they are not confirmatory investigations.

PATHOPHYSIOLOGY OF NONALCOHOLIC FATTY PANCREATIC DISEASE

The pathophysiology of NAFPD encompasses a spectrum from pancreatic lipid accumulation to inflammation and fibrosis and is closely linked to obesity.[1,11,21,22] Studies on animal models demonstrate that the offspring of obese mothers with an obesogenic diet exhibit more severe dysmetabolic and NAFPD phenotypes.[23] Gender and age are human factors that influence the development of NAFPD,[19,20] although infants are also at risk.[24] Pancreatic fat content, insulin resistance, and MeTS are directly related to BMI, with fatty pancreas and DM2 being mutually exclusive but linked.[25] Obesity is a significant contributor to NAFPD,[10] promoting fat deposition in the pancreas.[1] Maternal obesogenic diets during pregnancy and lactation can lead to NAFPD in mice.[23,26] NAFLD is a substantial risk factor for NAFPD, with a high co-occurrence rate.[27] The link between NAFPD and nonalcoholic steatohepatitis has been explored,[28] and NAFPD is associated with progressive fibrosis. The negative predictive value of NAFPD for advanced fibrosis is 93%, suggesting that it is a reliable and affordable index to rule out the condition.[24]

Lifestyle factors such as sedentary behavior, smoking, and high meat consumption may affect NAFPD, increase serum ferritin, and decrease serum lipase activity.[25,28-33] Pancreatic fatty infiltration can affect endocrine and exocrine pancreatic functions, potentially leading to diabetes. However, fatty replacement of injured tissue may add to exocrine pancreatic fat after establishing diabetes. As an alternative, hyperglycemia-induced elevated levels of malonyl coenzyme A may block carnitine palmitoyltransferase-1, impairing mitochondrial oxidation and further promoting intracellular triglyceride formation,[25] which increases stress damage to pancreatic cells.

Other factors implicated in NAFPD include alcohol use, medications, genetic factors, and hyperlipidemia. Inflammation plays a role in the pathophysiology of NAFPD,[21] with oxidative stress, free fatty acid metabolism, and inflammatory pathways contributing to acinar cell death, malignancy, and acute pancreatitis.[34] Adipocyte inflammatory factors may also influence NAFPD. Fatty acid composition affects inflammation by inducing adipocyte to deposit fat in the pancreas intracellularly, exacerbated by increased saturated fatty acids.[22,35] However, further research on the genetic and molecular pathways is required. Ko *et al*.[36] reported that in a study of 50 individuals experiencing their first incidence of non-necrotizing acute pancreatitis and 100 healthy controls, there was a 1% increase in intrapancreatic fat deposition (IPFD), which was significantly associated with a 30% higher risk of an initial acute pancreatitis attack ($P = 0.004$). Moreover, in individuals with normal serum triglyceride levels, a 1% increase in IPFD correlated with up to a 27% higher risk of a first acute pancreatitis attack in both the unadjusted and adjusted models. These findings indicate that an increased IPFD may elevate the risk of acute pancreatitis, suggesting potential primary prevention measures to mitigate the disease burden.[36]

The link between NAFPD and bowel bacterial infection and other infections (*Clostridioides difficile* colonization, *Helicobacter pylori*, and coronavirus disease 2019) is unclear, but there is an association between intestinal microbiota and MeTS,[21,37] which is also associated with NAFPD, possibly due to reduction of interleukins activity and their plasma level.[38] The association of NAFPD with various clinical conditions, including cardiovascular disease risk, recurrent pancreatitis, fibrosis, and pancreatic cancer, has been established.[25,27,31,39] However, the relationship between NAFPD and these conditions and their causality requires further investigation.

NAFPD may progress to steatopancreatitis, potentially predisposing individuals to pancreatitis.[22] Furthermore, NAFPD and obesity have been linked to organ failure,[40] local complications,[41] extended hospital stays,[42] and a higher mortality rate.[43] Potential mechanisms include decreased pancreatic microcirculation, inflammation, hepatic dysfunction, and inflammation.

Mechanistic hypotheses regarding the cause–effect relationship between acute pancreatitis and obesity have been presented. One hypothesis is that patients with NAFPD have decreased pancreatic microcirculation, resulting in decreased local oxygen content and ischemic injury. The second is that local inflammation brought on by NAFPD is often found in pancreatic fat, and hepatic dysfunction brought on by obesity may intensify systemic inflammation.[44] A chemokine and cytokine imbalance may develop an inflammatory status in adipocytes.[45] A pro-inflammatory environment that results in acinar cell damage and increases the acute pancreatitis severity is brought on by the cytokines (IL-1 and TNF) released by adipocytes in conjunction with free radicals formed from fatty acids.[46]

NONALCOHOLIC FATTY PANCREATIC DISEASE COMPLICATIONS

Pancreatic dysfunction

NAFPD affects the exocrine portion of the pancreas,[21] mostly due to recurrent acute pancreatitis or chronic pancreatitis, causing pancreatic enzyme deficiency. Several studies have shown that NAFPD is the second leading cause of juvenile pancreatic insufficiency. It commonly coexists with exocrine dysfunction, a feature of children disorders such as Johanson–Blizzard syndrome[47] and Shwachman–Diamond syndrome.[48] However, there is limited literature regarding exocrine dysfunction and NAFPD.[49,50] Fecal elastase-1, a commonly used marker of pancreatic exocrine function, was significantly lower in patients with NAFPD than those without NAFPD in a recent study.[51] Patients with exocrine dysfunction exhibit symptoms of malabsorption, such as steatorrhea, bloating, stomach discomfort, and weight loss. Ductal stones and chronic pancreatitis have also been linked to NAFPD.[52] Exocrine dysfunction may occur due to oxidative damage caused by NAFPD. In addition, adipocytes likely have a paracrine impact that reduces pancreatic exocrine function.[35] However, these processes have only been examined *in vitro*, and thus there is need for *in vivo* studies to corroborate these findings.

Another NAFPD complication is MeTS, characterized by abdominal obesity, hypertension, insulin resistance, low plasma levels of HDL cholesterol, and hypertriglyceridemia.[12] The incidence of MeTS is rising due to unhealthy food and lifestyle choices. Abdominal obesity alters the metabolism of fatty acids, increasing the risks of cardiovascular and gastrointestinal complications, including pancreatic diseases.[53,54] People with MeTS are at a significant risk of developing DM2 and cardiovascular diseases, which are intimately associated with NAFLD. Various reported studies have recently found a link between NAFPD and MeTS, leading experts to conclude that NAFLD and NAFPD must be included in the definition of MeTS.[55,56] However, further research is required to determine whether the link between NAFPD and MeTS is directly causative or results from obesity.

Pancreatic cancer

Obesity has been described as a risk for pancreatic cancer.[57-59] While NAFLD and obesity are both substantially related, it is alleged that NAFPD may accelerate the rate of pancreatic cancer via nonalcoholic steatopancreatitis or fibrosis.[60] Some studies have supported this hypothesis, although the data are scarce.[61] Endoscopic ultrasound (EUS), a sensitive investigation of NAFPD, has shown the predominance of NAFPD in individuals with pancreatic cancer. In fact, in the regression analysis, NAFPD was found to be the only significant risk factor for pancreatic cancer.[62] Histopathology studies have shown a clear correlation between steatopancreatitis and the prevalence of intraepithelial neoplasia and pancreatic ductal adenocarcinoma.[63,64] NAFPD is now independently linked to an increased pancreatic cancer risk.[64] NAFPD also dramatically raises the risk of surgical complications,[65] death[66] and the spread of pancreatic cancer.[67] MetS may influence pancreatic cancer, oxidative stress, adipocytokine imbalance, and inflammation.[68] Adipocytokine imbalance caused by abnormally elevated adipocytes in NAFPD increases the incidence of recurrent pancreatitis, leading to chronic pancreatitis that may predispose patients to pancreatic cancer. More basic mechanistic investigations and prospective cohort studies with long-term follow-up are required to fully understand the mechanism underlying the relationship between pancreatic cancer and NAFPD.

It is also conceivable that obesity may cause pancreatic cancer via pancreatic steatosis, like the association of hepatic cell carcinoma (HCC) with NAFPD, because the liver and pancreas have the same embryological origins.[11] However, Carter *et al*.[23] reported that fetal and neonatal exposure to maternal obesogenic environment may resultantly lead to NFAPD; however, no studies have substantiated these findings. In contrast, Smits and van Geenen state that NAFPD alone predisposes people to pancreatic cancer.[1] The link between pancreatic cancer and NAFPD may result from lipogenic inflammation similar to that reported in NAFLD and HCC;[61] however, the exact mechanism remains unknown and requires to be studied further.

DIAGNOSTIC TOOLS

Pancreatic fat infiltration is usually detected during imaging studies, and thus NAFPD remains a secondary diagnosis until we fully understand its function in pancreatic disease. CT and MRI are used for the diagnosis of NAFPD. To our knowledge, there has been no laboratory investigation of the blood or fluid to diagnose NAFPD.

Assessment of pancreatic fatty infiltration

In animal models, the amount of fat deposited in the pancreas is frequently assessed using histological examination. Autopsies, surgical specimens, and even fine-needle aspiration cytology are viable options for collecting human specimens, although they are difficult and not free of complication. In contrast to hepatic steatosis, in which fat accumulates in hepatocytes, pancreatic fatty infiltration preferentially accumulates within the pancreatic interstitial septa for unknown reasons. The histopathologic

appearance correlates well with the appearance of lobules of acini surrounded by macroscopic fat density on CT.[69]

Rarely, ectopic fat deposition may be uneven, occurring mostly in the pancreatic head.[70] This is likely due to the different embryological genes in the dorsal and ventral pancreatic buds. The irregular fat distribution, its hazy margins, and retroperitoneal positioning of the pancreas cause difficulty in accurately assessing the amount of fat deposition.[71] A recent meta-analysis established a normal mean pancreatic fat content value of 4.5% ± 0.9% by collating data from several different MRI techniques and imaging modalities.[72]

IMAGING MODALITIES

CT and MRI are superior to US imaging but have disadvantages, including cost, intravenous contrast contraindications for patients with renal illness, and radiation exposure, especially if repeated investigations are required.

Transabdominal, endoscopic, and elastography ultrasound imaging modalities

Transabdominal ultrasonography (TUS) and EUS are useful for evaluating fatty pancreas. Owing to overlaying intestinal gas, TUS can often only partly image the pancreas, although this varies depending on the experience of the US operator. Due to the proximity and magnification advantages of EUS, the pancreas may be seen in more detail. Pancreatic steatosis is indicated when the echogenicity of the pancreas is greater than that of the liver, spleen, or kidneys. The detection of highly fatty pancreas was highest when the pancreatic echogenicity is similar to that of retroperitoneal fat.[27] In overweight patients, proper assessment of pancreas by US could be difficult, and pancreatic fibrosis may seem hyperechoic in the US scan.[33] Among US modalities, only EUS should be used for diagnosing other diffuse hyperechoic pancreas; however, other imaging modalities such as CT or MRI are better for diagnosis. However, further studies are needed to assess the therapeutic impact of EUS in NAFPD patients.

Tissue stiffness is an indicator of diseased tissues. Tissues with stiffness react to acoustic energy, and US elastography can quantify the mechanical characteristics of the tissue. Depending on the criteria related to the patient, pathology, and operator, the results of elastography US can be affected. Furthermore, the position of the pancreas prevents the use of transient elastography.[73] However, the acoustic radiation force impulse may be used to administer localized stress under the typical B-mode US imaging guidance. Progressive NAFPD is associated with decreased pancreatic stiffness,

although findings are inconsistent, limiting its use to compare the pancreas with the liver.[74]

Computed tomography and magnetic resonance

CT imaging offers several benefits owing to its extensive clinical use and rapid acquisition time. Although CT may detect fatty infiltration of the pancreas in the context of increasing interlobular fat, consensus criteria for diagnosing NAFPD using CT needs to be established. However, ectopic pancreatic fat is often unequally distributed throughout the organ.[71] The Hounsfield unit method is utilized to assess the extent of pancreatic fat deposition, which has low-density images compared with the spleen due to the high-fat content of the pancreas.[21] The ability of the pancreas to absorb the contrast is useful in contrast-based studies for confirmation and better assessing the severity of lipid deposition.[75]

MRI can be used to measure pancreatic fat in several ways. MRI signals originate from protons in distinct chemical environments (e.g., water and fat molecules in the body), resulting in minute changes in their resonance frequencies, and thus enabling measurement. MRI integrates spatial, anatomical, and quantitative data; hence, it is regarded as the best imaging modality for assessing NAFPD. Several MRI techniques have been utilized to measure pancreatic fat pancreas,[76] including the methods discussed below.

Magnetic resonance spectroscopy (MRS) is regarded as the gold standard non-invasive diagnostic tool for quantifying pancreatic fat. The user must manually select a voxel to include as much pancreatic tissue as feasible during MRS testing by avoiding the main pancreatic duct and vessels.[77] Saisho *et al.* reported that a CT scan evaluating the fat/parenchyma ratio was comparable to the histology results. Furthermore, the same article reported that normally, pancreatic fat content increases with age, but not in DM2 patients.[78] MRI is obtained using point-resolved spectroscopy or stimulated echo acquisition mode sequences to construct proton signal spectra.

Chemical-shift MRI (CSI) collects signals to assess the chemical shift between the water peaks and the original fat. To estimate fat content, "in-phase" and "out-of-phase" pictures may be removed.[79] Inhomogeneities in the background magnetic field and difficulty in measuring extremely high/low-fat fraction readings may impede the assessment of tissue fat content.[77] Fortunately, this method compares fat deposition in the pancreas with neighboring organs. Qualitative fat evaluation is also possible using CSI. MRI proton density fat fraction (PDFF) can quantify

the fat deposited in pancreatic parenchyma with high accuracy.[80]

Finally, the PDFF mapping radiology technique solves the constraints of the multipoint Dixon quantification, which is most pertinent to pancreatic imaging. In chronic pancreatic inflammation, T1 weighting is changed and may enhance the relative fat signal.[81] Pancreatic MRI segmentation is an alternative way to identify pancreatic fat.[82] The enhanced segmentation approach is a special tool for assessing the distribution of pancreatic fat through intralobular, interlobular, and extralobular compartments. While segmenting an entire organ is challenging, developing automated systems for segmenting an entire organ and multiple organs using an automatic machine is a promising technique.[83]

MANAGEMENT OF NONALCOHOLIC FATTY PANCREATIC DISEASE

The management of NAFPD focusses on the early reduction of pancreatic fat buildup through balanced diet, weight reduction, and exercise regimen.[84] Patients with NAFPD may benefit from lifestyle changes, including reducing meat consumption and calories.[85] Weng *et al*. documented an insignificant association between NAFPD and smoking and sedentary behavior;[20] however, others argue that a lifestyle change can be helpful.[18]

Studies on animals and humans have provided evidence that NAFPD is reversible. In mouse models, troglitazone and orlistat administration have been found to substantially decrease organ failure and death, thereby preventing and reversing inflammation and fat deposition in the pancreas. While metformin has no discernible impact on NAFPD, new hypoglycemic drugs, such as liraglutide, are used to induce weight loss in obese individuals. Liraglutide has been demonstrated to lessen the severity of NAFPD.[86,87] Administration of sitagliptin and telmisartan can effectively slow the development of NAFPD.[88] Berberine and cinnamic acid, which are traditional Chinese remedies, have also been reported to reduce the risk of NAFPD via blocking fat deposition.[89] In addition to pharmacological treatment, animal and human models have examined how weight reduction after bariatric surgery reduces pancreatic fat deposition and enhances pancreatic cell function.[90,91] However, it was noted that the degree of decrease in the pancreatic fat content does not correspond well with the decrease in body weight, indicating variations in metabolic phenotype.[71]

CONCLUSION

NAFPD and obesity are significant concerns that have piqued the interest of diabetologists, internists, and nutritionists.

Although different mechanisms have been proposed for the pathogenesis of NAFPD, none have been established. Age, obesity, sex, ethnicity, unhealthy lifestyle, and, likely, inflammation are all risk factors. Although a confirmatory diagnosis of NAFPD can only be made through tissue histology, invasive and noninvasive radiological diagnostic methods have been developed using transabdominal US, MRI, and EUS elastography. Advances in diagnostic techniques would allow to better understand the alterations involved in NAFPD pathophysiology and the microscopic pathological link between NAFPD and other pancreatic conditions. In patients with MeTS, it is crucial to assess the amount of pancreatic fat accumulation as a prognostic indicator for exocrine pancreatic insufficiency, chronic pancreatitis, pancreatic cancer, and early signs of ectopic fat deposition and insulin resistance. Early diagnosis of fatty pancreas is important for reducing and preventing the epidemic of MeTS and treating fatty pancreas. Further studies are required to determine the causative relationship and association between NAFPD and MeTS.

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