Diabetes, Metabolic Syndrome and Obesity

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REVIEW

# Pathophysiological Mechanisms and Clinical Associations of Non-Alcoholic Fatty Pancreas Disease

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**Abstract:** Non-Alcoholic Fatty Pancreas disease (NAFPD), characterized by fat accumulation in pancreatic tissue, is an emerging clinical entity. However, the clinical associations, the underlying molecular drivers, and the pathophysiological mechanisms of NAFPD have not yet been characterized in detail. The NAFPD spectrum not only includes infiltration and accumulation of fat within and between pancreatic cells but also involves several inflammatory processes, dysregulation of physiological metabolic pathways, and hormonal defects. A deeper understanding of the underlying molecular mechanisms is key to correlate NAFPD with clinical entities including non-alcoholic fatty liver disease, metabolic syndrome, diabetes mellitus, atherosclerosis, as well as pancreatic cancer and pancreatitis. The aim of this review is to examine the pathophysiological mechanisms of NAFPD and to assess the possible causative/predictive risk factors of NAFPD-related clinical syndromes.

**Keywords:** non-alcoholic fatty pancreas disease, NAFPD, steatotic pancreatic disease, metabolic dysfunction-associated steatotic pancreatic disease, MASPD

## Introduction

Pancreatic fat deposition in the absence of excessive alcohol intake, described as non-alcoholic fatty pancreas disease (NAFPD),[1] is an emerging clinical entity.[2] Despite the higher susceptibility to fat deposition of the pancreas compared to the liver,[3,4] the clinical relevance and underlying pathophysiological mechanisms of pancreatic fat infiltration remain unclear in the medical literature. Robertson F. Ogilvie was the first to describe pancreatic fat deposition in obese cadavers, reporting 17% of pancreatic fat storage, as compared to 9% in lean ones.[5] Since then, excessive storage of fat in pancreatic tissue has been described with various terms, including pancreatic lipomatosis, pancreatic steatosis, lipomatous pseudohypertrophy, fatty pancreas, and more.[6,7] Currently, NAFPD is the widely accepted term, and its prevalence varies significantly among populations.[8–11]

There are many sophisticated imaging techniques used as diagnostic tools to evaluate the pancreas, with transcutaneous ultrasound being the most common,[10,12] since it is noninvasive, inexpensive, and easily performed. Nonetheless, endoscopic ultrasound (EUS),[10,13] abdominal computed tomography (CT),[14] or magnetic resonance-based techniques including abdominal magnetic resonance imaging (MRI),[15,16] and magnetic resonance spectroscopy (MRS)[17] can be used to quantify pancreatic fat content with accuracy. A direct comparison of these methods has not been performed yet. MRI enables noninvasive assessment of fat content in solid organs,[18] and with the Iterative Decomposition with Echo Asymmetry and Least squares estimation (IDEAL) method,[19] fat and water can be separated for a more precise organ assessment. EUS allows for a closer access to the pancreas; nonetheless, it is invasive and unsuitable for quantification of the entire pancreatic fat content.[10,13] In the general population and in routine medical checkup settings, invasiveness and cost-effectiveness should always be considered before examining the pancreas. As far as physiological values are

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concerned, the highest limit of normal pancreatic fat is 10 4% when assessed by MRI/MRS.[9] However, a meta-analysis showed that the upper normal limit of pancreatic fat in healthy individuals, who participated in MRI studies, was 6.2%,[20] a threshold that is recommended for future research use.

The aim of this review is to explore the pathophysiological mechanisms of NAFPD and its clinical associations, as well as to examine which of these parameters are possible causative or predictive risk factors of NAFPD.

## Pathogenesis

NAFPD is the result of several pathophysiological processes that act simultaneously (Figure 1). These processes are generated mainly from excessive deposition of fat on pancreatic cells and include the following; (1) immediate cellular damage due to direct interaction of fatty tissue with pancreatic cells, with subsequent release of free fatty acids,1,[21–23] (2) chronic oxidative stress[24,25] and local secretion of detrimental inflammatory markers,1,[26–28] (3) pathological activation or alterations in lipid-glucose metabolism, beta-oxidation, and other regulators,[29–31] and (4) an imbalance of hormone homeostasis.[32,33]

### Fat Replacement and Fat Accumulation

The main pathogenetic mechanism of NAFPD involves fatty replacement, which can either be intralobular or interlobular, followed by fat accumulation within the pancreatic tissue.[21] In most cases, excessive weight gain gradually leads to the storage of surplus adipose tissue in non-adipose organs, including the pancreas, where fat accumulates intracellularly in both acinar and pancreatic islet cells, causing dysfunction.[21] The fatty replacement phase is characterized by an accumulation of intralobular fat in the form of lipid droplets in both endocrine and acinar cells,[34,35] provoking acinar cell

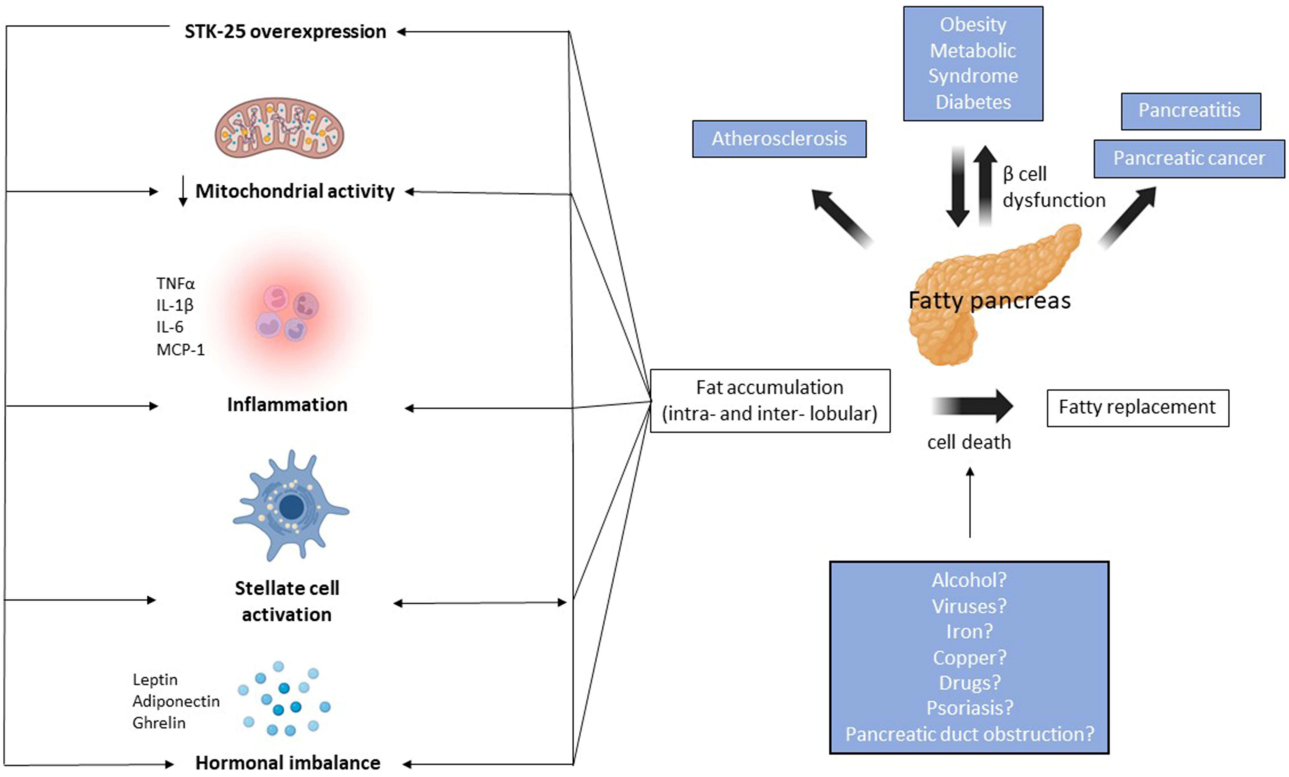


**Figure 1** Pathogenetic mechanisms behind fatty pancreas. The main pathogenetic mechanism behind non-alcoholic fatty pancreas diseases (NAFPD) is fatty accumulation (intra- or inter- lobular), followed by fatty replacement and, ultimately, β cell dysfunction. The main risk factors associated with NAFPD are obesity and metabolic syndrome (including dyslipidemia), while alcohol, viruses, iron deposition, drugs, gut hormones, psoriasis and pancreatic duct obstruction represent potential secondary;hits' which participate in cell death and replacement of pancreatic tissue with fat. Mechanisms associated with fat accumulation include reduction in mitochondrial activity, inflammatory cell infiltration with production of inflammatory cytokines (eg TNFα, IL-1β, IL-6, MCP-1), activation of stellate cells, hormonal imbalance (with perturbed leptin and adiponectin levels), as well as STK-25 pathway overexpression, which further exacerbates all the aforementioned mechanisms. NAFPD, in turn, is associated with various conditions including diabetes, pancreatitis, pancreatic cancer, as well as atherosclerosis.

death and their consecutive replacement by adipocytes, while pancreatic β-cells decrease and become dysfunctional.[1,3,36–41] Hence, fatty accumulation follows fatty replacement and acinar cell necrosis.[7,34,41,42] Fatty replacement occurs unevenly throughout the pancreatic tissue, with the anterior aspect being more prone.[7] Of note, the term fatty replacement denotes irreversible damage, not fully correctable with medications or weight reduction.[43] In parallel, interlobular fat, that is fat around large vessels and ducts, involves adipocytes and lipid droplets in inactive stellate cells, which become stimulated.[22,34] In addition, deposition of pancreatic fat ensues secondary to increased levels of free fatty acids in the plasma,[1] a process similar to the hepatic free fatty acid influx noted in non-alcoholic fatty liver disease (NAFLD).[44] Following such pancreatic insults, acinar cell apoptosis leads to rapid pancreatic volume decrease, but eventually, fatty restoration causes volume replacement until the pancreas becomes prominent and enlarged. In an animal model study, accumulation of fat tissue in the pancreas induced apoptosis, stellate cell activation, fibrosis, and, ultimately, a decrease in β/α islet cell ratio with loss of architecture.[45] Likewise, in another animal study, where obese mice were investigated for pancreatic cellular changes, intralobular and interlobular fat storage was responsible for a heavier pancreas, larger pancreatic islet cells, and atypical cellular structure.[28] These modifications may have occurred in an attempt of β-cells for compensation; β-cells compensate against initial cellular and metabolic fluctuations, presenting an enhancement in their secretory activity, an expansion of their β-cell mass, or both.[29] Overall, this might explain why pancreatic cells with chronically elevated fat content will become hypertrophic and hyperplastic.[46] Deposition of fat tissue in the pancreas, in combination with free circulating fatty acids, causes β-cell dysfunction,[23] with a baseline increase in insulin release, an impaired glucose-stimulated insulin secretion of β-cells[29,47,48] and the generation of oxidative stress with consequent organ injuries.[1,23,49] After the increase of basal insulin secretion, there is a subsequent decrease, a state that cannot be repealed with the induction of compensatory proinsulin biosynthesis.[50] Therefore, clinical conditions, such as insulin secretion impairment and diabetes, might arise.[23,46] Many of these mechanisms are supported in a human study, where Tushuizen et al[17] showed a negative correlation between pancreatic fat content with β-cell function in subjects without diabetes.

## Oxidative Stress and Inflammatory Processes

Chronic oxidative stress is implicated in metabolic syndrome, diabetes mellitus and atherosclerosis. Indeed, oxidative stress is referred to as a "second hit" in cases of steatohepatitis,[12] so a similar process in the case of NAFPD may be hypothesized.[51]

Increased body weight provokes chronic cortisol release[24] and activation of the hypothalamic-pituitary-adrenal (HPA) axis,[24,25] thus increasing metabolic syndrome and atherosclerotic disease risk.[52] Fat storage induces local pancreatic inflammatory cell infiltration,[26] further inducing β-cell function deterioration and destruction. Pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and 6 (IL-6), monocyte chemotactic protein-1 (MCP-1) are released, leading to inflammation, fibrosis, and insulin resistance.[1] Free fatty acids are released via lipolysis of visceral adipose tissue,[22,27,28,53] but also due to inflammatory responses,[27] altogether resulting in histopathological alterations and secondary pancreatic acinar cell atrophy and fibrosis.[38,54] Of importance, the role of copper in pancreatic disease was investigated in an animal study.[55] The authors stated that pancreatic atrophy is more pronounced in males compared with females, while the endocrine male pancreas is also more susceptible to dietary copper deprivation than the female rat.[55] Similarly, copper is also important in NAFLD. In a cross-sectional study that included 100 obese patients with hepatic steatosis detected by ultrasound, it was shown that an altered copper bioavailability predicts early atherosclerosis.[56] Moreover, older studies demonstrated that pancreatic fatty deposition is also accompanied by leukocyte infiltration,[57] although more recent ones did not corroborate these findings.[1]

## Dysregulation of Metabolic Pathways

In terms of dysregulated pathways, fatty accumulation of the pancreas influences multiple regulatory pathways. First, fat deposition impairs pancreatic β-cell cAMP production and, as a result, it inhibits islet cell adaptation to the disturbed metabolic milieu.[29,30] Another probable mechanism is the augmented phospholipid saturation of the mitochondrial membrane, which results in diminished mitochondrial function,[58] peroxisomal fatty acid metabolism, cytochrome P450 CYP-2E1 induction, and the subsequent production of free oxygen radicals, as in the case of NAFLD.[59,60] This

leads to further activation of stellate cells that attract neutrophils and cause an inflammatory reaction.[61] Additionally, in the context of chronic fatty pancreas accumulation, overexpression of the serine/threonine-protein kinase 25 (STK-25), a novel negative regulator of lipid and glucose metabolism, occurs.[62] STK-25 can be overexpressed when feeding mice with high-fat diets, aggravating lipid accumulation in cells and impairing skeletal muscle mitochondrial function, thereby diminishing insulin sensitivity.[62–64] In skeletal myocytes of patients with type 2 diabetes mellitus, STK-25 mRNA levels were significantly elevated, compared with healthy controls.[62] The overexpression of STK25 in NAFPD exacerbates all the aforementioned pathophysiological mechanisms, including inflammatory pancreas infiltration,[45,65] stellate cell activation, β-cell loss, and pancreatic destruction.[45] Indeed, STK25 is considered to play a key role in both the pathogenesis and progression of NAFLD.[66] Overexpression of STK25 induces lipogenesis, triglyceride secretion and suppressed beta-oxidation.[66] A similar mechanism may be adopted by pancreatic cells in cases of STK25 overstimulation highlighting that NAFLD and NAFPD are two closely related conditions. Beta-oxidation is severely impaired during fatty accumulation.[31] When there is an impediment in fatty acid catabolism, fat will also accumulate in zone 3 of hepatocytes, giving rise to NAFLD.[12] In pancreatic tissue, parameters like hyperglycemia and hypertriglyceridemia induce cellular free fatty acid increase, loss of β-cell mass, as well as decreased beta-oxidation.[53] Increased glucose levels augment malonyl-coenzyme A via the tricarboxylic acid cycle, thus inhibiting carnitine palmitoyltransferase-1 and diminishing mitochondrial β-oxidation while stimulating triglyceride production in β-cells.[53] In correlation with that, when obese mice were studied,[1] accumulation of cholesterol and free fatty intoxication were observed. Through this process, triglyceride accumulation in β-cells is promoted, which, in combination with lipid peroxidation, leads acinar and islet cells to destruction.[27,28,53] When triglycerides continue to accumulate inside pancreatic cells, insulin gene expression is downregulated, and glucose-stimulated insulin secretion is impaired.[22,28,53]

## Dysregulation of Hormonal Homeostasis

Adipocytokines, which consist of adipose tissue released cytokines, adipokines and chemokines, are valuable bioactive substances that maintain metabolic homeostasis and protect against metabolic overload.[32,33] Decreased levels of adiponectin in obese patients signify the loss of insulin sensitivity modulation, and the decrease of fatty acid oxidation in body tissues.[33] In contrast, regulation of leptin levels in obese patients is a more complex pathway. It is thought that leptin levels and obesity are reversibly correlated; when leptin increases, it leads to the expression of suppressor-of-cytokine-signaling (SOCS-3) pathway, which thereafter inhibits leptin signaling.[67] In obesity, adipocytokines like leptin and adiponectin may differentially affect pancreatic tissue.[33] It has been shown that adiponectin levels are positively correlated with plasma insulin and negatively associated with plasma triglycerides and insulin resistance.[68]

Notably, it has been demonstrated that the gut-brain axis may also play a role in NAFPD, and more specifically overexpression of ghrelin may contribute to increased intra-pancreatic fat deposition in individuals with acute pancreatitis.[69] Similarly, gut hormones may contribute to NAFLD pathogenesis, but the association between intrahepatic fat deposition and gut hormones remains to be elucidated.[70]

## Human-Based Studies and Correlation with Molecular Abnormalities

Even though the pathophysiological mechanisms between fatty pancreas and β-cell dysfunction/apoptosis have been thoroughly discussed, recent findings from human studies do not come in accordance with previous conclusions. In a recent large cohort study of adult Chinese subjects, who had undergone fatty pancreas evaluation by MRI, an association of fatty pancreas and β-cell function was found.[9] However, this association disappeared after adjusting for BMI and intrahepatic triglycerides. Although this cohort did not show an independent association between fatty pancreas and β-cell function, pancreatic fat accumulation was still associated with insulin resistance, even after adjusting for hepatic fat content and BMI.[9] Likewise, in another human-based comprehensive analysis of interlobular, intralobular and parenchymal pancreatic fat and their effects on β-cell performance, no relationship was found between total and intralobular pancreatic adipose tissue infiltration with β-cell function.[71] In some small case series that compared pancreatic fat among patients with diabetes with that of normal controls, an association of fatty pancreas with weakened β-cell function and insulin secretion was noted.[17,72] Nevertheless, we cannot conclude whether this β-cell dysfunction was established beforehand or if it was a direct consequence of fatty accumulation. Ozturk et al,[73] while studying the

association between NAFLD and atherosclerosis, emphasized that insulin resistance appeared among their study population in the absence of obesity and diabetes mellitus. In a study of 106 subjects with new-onset of type 2 diabetes, no significant correlation was noted between the amount of pancreatic fat deposition and islet cell function.[74] The controversial results of previous studies either drive us towards the existence of more pathophysiological cascades that make fatty accumulation a causative factor of β-cell dysfunction, or to genetic polymorphisms, which are not yet under investigation. Other "hits" that can lead to pancreatic cell death include fibrosis of the pancreas, extreme alcohol intake, viral infections, iron overload, medications, or an obstruction of the pancreatic duct.[42]

# Clinical Associations of NAFPD

## Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) occurs when hepatocytes are infiltrated with fat, in the absence of excessive alcohol consumption.[75] As mentioned above, obesity is the main causative risk factor, not only for NAFPD but also for NAFLD,[75] making these two clinical syndromes closely related. In general, fat deposition is linked to multiple diseases like metabolic syndrome, diabetes, and atherosclerosis.[2,76]

In a large cross-sectional study where NAFPD and its risk factors were examined, authors compared pancreatic echogenicity with that of the liver and demonstrated that fatty pancreas and fatty liver composition were found in combination in almost 26% of patients, whereas fatty pancreas alone was found in 16%.[11] In a prospective study almost 68% of the included patients with fatty pancreas presented with fatty liver, but 97% of patients initially diagnosed with fatty liver presented concurrently with a fatty pancreas, making fatty liver a strong predictive factor of fatty pancreas disease.[8] In a Chinese study, 67% of non-diabetic subjects with fatty pancreas had simultaneous fatty liver changes.[8] In this study, fatty liver was an independent risk factor for NAF-PD.8 Likewise, in another analysis among 60 patients with hepatic steatosis, 57% were found with NAFPD.[12] The amount of fat in liver tissue is significantly correlated with pancreatic fat in numerous other studies,[77–79] signifying that both clinical entities share similar risk factors, pathogenetic mechanisms and disease progression pathways. In a clinical trial including 121 obese/overweight children and adolescents, 48% of those with confirmed fatty liver disease of any severity exhibited NAFPD, while, in subjects with steatohepatitis the percentage of NAFPD increased to 80%.[78]

On the contrary, some studies did not manage to find an association between pancreatic fat and liver fat.[4,17,72,80] In a study of subjects with and without diabetes,[17] those with diabetes had higher liver fat content, but there was no statistically significant association between liver and pancreatic fat content. These contradictory results focusing on the correlation between NAFLD and NAFPD might imply that, despite that both syndromes share similar pathological mechanisms, organ fat accumulation may be distributed differently due to unknown mechanisms.

It is worth mentioning that, based on recent evidence, the association between NAFPD and NAFLD is also mediated via a systemic autoimmune comorbidity, namely psoriasis. Psoriasis is well associated with metabolic disturbances, including obesity, metabolic syndrome and type 2 diabetes, all of which consist risk factors for both NAFPD and NAFLD.[81–83] In psoriatic patients, chronic inflammation, mediated by pro-inflammatory cytokines and adipokines (especially TNF-α), drives insulin resistance and plays a crucial role not only in hepatic steatosis but potentially also in pancreatic steatosis.[84] Additionally, it has been suggested that psoriasis is associated with pancreatic diseases, such as pancreatitis and pancreatic cancer, as evident in recent published data.[85]

## Obesity and Metabolic Syndrome

Obesity is a multifactorial clinical entity that can lead to the excessive and pathological accumulation of adipose tissue in non-adipose tissues such as the pancreas, liver, heart, skeletal muscle and is associated with diabetes mellitus, cardiovascular disease, hypertension, and hyperlipidemia.[86–88] Since the term NAFPD describes the accumulation of fat into the pancreas, obesity is the main driver of this condition.[75] A large number of studies link central obesity and/or increased BMI to fatty deposition of the pancreas.[9,10,20]

Metabolic syndrome is defined as the presence of at least three of the following risk factors: high blood glucose, increased levels of triglycerides, low levels of HDL cholesterol, large waist circumference and hypertension.[89] Many

studies focusing on patients' metabolic abnormalities try to correlate these with the existence of fatty pancreas. In 2009, Lee at al. studied 293 individuals from an obesity clinic with a confirmed diagnosis of pancreatic fat accumulation of various severity.[90] More than half of the patients (61.4%) were diagnosed with fatty pancreas. Results positively correlated pancreatic fat infiltration with metabolic risk factors, such as increased visceral fat and waist circumference, triglycerides, insulin resistance, correlating fatty pancreas with metabolic syndrome. Similarly, a case–control study showed that fatty pancreas was strongly associated with hypertension, increased blood glucose levels, central obesity, and increased triglycerides, but reported no association with HDL values.[91] A more recent study that systematically reviewed and analyzed data from 2675 individuals found that approximately 33% of them had NAFPD.[20] Among individuals with NAFPD, 44% of them met the criteria for metabolic syndrome.[20] In a prospective study by Sepe et al, fatty pancreas was observed in 27.8% of participants that underwent EUS for various purposes.[10] Notably, the presence of any component of metabolic syndrome was associated with a significant 37% increase in the prevalence of fatty pancreas. Individuals who fulfilled the criteria for metabolic syndrome had a 40% prevalence of fatty pancreas, rendering metabolic syndrome a strong predictive factor of NAFPD. Interestingly, a high-fat diet is associated with triglyceride accumulation mainly in pancreatic cells, rather than hepatocytes, making pancreatic steatosis an early consequence of metabolic syndrome.[3]

On the other hand, Wong et al,9 showed that, among all metabolic syndrome components, only central obesity and hypertriglyceridemia were independent risk factors of NAFPD. A Turkish clinical trial also reported an association of fatty pancreas with metabolic syndrome, which was influenced, however, by other factors such as BMI and NAFLD.[92]

## Insulin Resistance - Prediabetes - Diabetes

Pancreas has an essential role in regulating glucose metabolism and glandular secretion under various metabolic circumstances. The pathogenesis of type 2 diabetes is characterized by peripheral insulin resistance and impaired glucose secretion, gradually leading to a decline in β-pancreatic cells and, later, to their gradual destruction. A disproportionate accumulation of visceral adipose tissue is a strong risk factor for insulin resistance.[93–95] However, study results remain controversial for the association between fatty pancreas and diabetes mellitus.

In numerous animal studies, islet cell abnormalities are related to pancreatic lipomatosis, and result in increased blood glucose levels.[48,96] A human study reported an almost 12% incidence of diabetes in the NAFPD cohort versus a 5% incidence in the non-NAFPD group. NAFPD patients had an 108% increased risk of diabetes mellitus. Pancreatic fat was also found to be negatively associated with insulin secretion in other analyses,[72] as well as with hyperglycemia and occurrence of diabetes.[17,72,97] Of note, individuals presenting with both fatty pancreas and fatty liver, had the highest levels of insulin resistance compared to those with either condition alone.[9]

Another analysis indicated that fatty pancreas at baseline is associated with an increased incidence of diabetes. However, this finding was not significant in multivariate analyses.[98] This was in line with results from a large cohort study, where, despite the high frequency of fatty pancreas in diabetes, their association did not reach statistical significance.[11] Other investigations did not support the association between fatty pancreas and diabetes mellitus or impairments in glucose levels as well.[10,90]

Conclusively, pancreatic steatosis may be an early event in the pathogenesis of diabetes,[99] but evidence pointing to an independent association is limited.

## Atherosclerosis

NAFPD has been linked with atherosclerosis risk factors including advanced age, BMI, hypertension, and hyperlipidemia[9,28,72,90,91] The effect of fatty pancreas on glucose and insulin metabolism, chronic low-grade inflammation and chronic stress may increase cardiovascular disease (CVD) risk.[100] This is amplified by the accumulation of lipids in coronary and peripheral blood vessels.

Carotid intima-media thickness (IMT) and carotid-femoral pulse wave velocity (cf-PWV) are widely used as indicators of subclinical atherosclerosis by detecting early functional and structural changes of the vascular wall.[101,102] It has been shown that NAFLD, especially in advanced stages, is correlated with increased risk of atherosclerosis and, potentially, cardiovascular events.[103–107] However, it remains to be answered whether fatty pancreas is a predictive CVD factor. A study that included patients with biopsy-proven NAFLD and healthy controls showed that patients with fatty

pancreas had significantly higher cf-PWV levels, whereas no association was found with carotid IMT. The link between cf-PWV/carotid IMT levels and fatty pancreas, nevertheless, was not observed upon adjusting for relevant variables.[92] In another case–control study, epicardial adipose tissue and aortic IMT were higher among NAFPD subjects, compared to those without NAFPD, while both epicardial adipose tissue and aortic IMT were independent risk factors of subclinical atherosclerosis.[108]

### Pancreatitis

Chronic high-fat dietary intake is associated with inter- as well as intra-pancreatic fat accumulation. As such, NAFPD progression may lead to chronic pancreatitis, and this association is expressed by the term "non-alcoholic steatopancreatitis" (NASP).[1,109] In favor of this hypothesis, a study showed that obese mice are more likely to develop severe forms of pancreatitis than lean ones.[110] Additionally, in a review by Smith et al, preliminary data link acute pancreatitis with NASP.[7] According to the authors, the uneven secretion of proinflammatory cytokines creates an inflammatory environment which promotes bouts of acute pancreatitis.[7] Finally, a recent pilot study of 189 subjects indicated that fatty pancreas is a risk factor of acute pancreatitis.[111]

### Pancreatic Cancer

Obesity is strongly associated with pancreatic steatosis and inconsistently associated with pancreatic cancer; this raises concerns for a potential relationship between fatty pancreas and pancreatic cancer.

A meta-analysis of 4400 patients showed a positive association between increased BMI and risk of pancreatic cancer in both sexes, while central obesity was associated with an increased risk of pancreatic cancer only in women.[112] It has been described that NAFPD can lead to NASP and sequentially to pancreatic cancer.[113] In a study of 102 cases of pancreatic ductal adenocarcinoma, fatty pancreas was significantly higher in cases compared to healthy individuals.[114] Findings of a retrospective cross-sectional study analyzing data from patients with pancreatic carcinoma further supported the role of fatty pancreas in the development of pancreatic cancer.[115] According to Lesmana et al, NAFPD is the only significant risk factor when it comes to pancreatic cancer, while factors like age, gender, diabetes, and pancreatitis failed to show a causative role.[113] Indeed, in a case–control study of patients who underwent total resection due to pancreatic adenocarcinoma, patients with fatty pancreas had higher mortality.[116]

At present, however, there is not enough evidence to decisively support the relationship between NAFPD and pancreatic cancer, and several studies have failed to detect an association. A study by Sepe et al did not find an association between fatty pancreas and pancreatic malignancy.[10] Wu et al also found no association between pancreatic carcinoma markers and NAFPD.[91]

## Pathogenetic Mechanisms and Clinical Entities Associated with NAFPD

The main risk factors associated with NAFPD are obesity and metabolic syndrome (including dyslipidemia), while alcohol, viruses, iron deposition, drugs and pancreatic duct obstruction represent potential secondary;hits' which participate in cell death and replacement of pancreatic tissue with fat.[41,90,91,100] The main pathogenetic mechanism of NAFPD is fatty replacement, followed by fatty accumulation (intra- or inter-lobular) and, ultimately, β-cell dysfunction.[21] Mechanisms associated with fat accumulation include reduction in mitochondrial activity, inflammatory cell infiltration with production of inflammatory cytokines (eg, TNFα, IL-1β, IL-6, MCP-1), activation of stellate cells, hormonal imbalance (with perturbed leptin and adiponectin levels, overexpression of ghrelin), as well as STK-25 pathway overexpression, which further exacerbate all the aforementioned mechanisms.[34,70] B-cell dysfunction, as well as hormonal imbalance, in turn, can lead to insulin resistance, prediabetes and diabetes, while reduction in mitochondrial activity, inflammatory cell infiltration and activation of stellate cells, can lead to pancreatitis and pancreatic cancer.

## Treatment of NAFPD

Despite the growing prevalence of NAFPD, its understanding remains limited and effective management strategies are still being explored. The effectiveness of current treatments for NAFPD is limited, as there is no approved pharmacologic

therapy. To date, the most effective treatments are lifestyle modifications, including dietary changes, regular exercise, and weight-management programs.[117] Calorie restriction has been suggested as the potential means of normalizing β-cell function and reducing pancreatic fat content.

Troglitazone, a member of the thiazolidinedione class with insulin-sensitizing and anti-inflammatory properties[118] which has been withdrawn from the market,[119] has been implicated in NAFPD. Specifically, animal models have shown that troglitazone can reverse changes in tissue structure such as fibrosis and fatty accumulation, while reducing infiltration of inflammatory cells.[120] However, this effect has not been assessed by clinical trials. Glucagon-like peptide-1 (GLP-1) agonists have the potential to lessen the severity of NAFPD, by modulating the ER stress pathway and the subsequent signaling of apoptosis in mice models, and to alter regional adiposity in humans.[121,122] Moreover, the synergistic activity of sitagliptin, a dipeptidyl peptidase (DPP) 4 inhibitor which prolongs the action of GLP-1 and insulin secretion from pancreatic β-cells, with telmisartan, which modulates inflammatory responses and improves endothelial function, exhibits remarkable efficacy in effectively managing the progression of NAFPD in mice.[123] Based on evidence from experimental models, GLP-1 agonists consist the most promising class of drugs for the treatment of NAFPD122 and prospective trials are needed to verify these data.

It has also demonstrated that bariatric surgery can lead to significant reductions in fat accumulation within the pancreas.[124] Nonetheless, education regarding healthy dietary habits and regular exercise should be the mainstay for reducing the NAFPD risk, as well as for treating those already diagnosed with it.

## Nomenclature of NAFPD

The term "non-alcoholic fatty pancreas disease" is misleading, since many subjects with obesity may simultaneously consume alcohol, while it may also be stigmatizing. Similar to a recent proposal for NAFLD nomenclature,[125–127] we propose the term "Steatotic Pancreatic Disease" (SPD) in order to generally describe the accumulation of fat within pancreatic tissue, and the term "Metabolic dysfunction-associated Steatotic Pancreatic Disease" (MASPD) for describing the accumulation of fat within pancreatic tissue when this is associated with obesity or the metabolic syndrome.

## Conclusion

NAFPD has been associated with a number of clinical entities, including metabolic syndrome, diabetes mellitus and atherosclerosis, but also with pancreatitis and pancreatic cancer. Similar clinical associations are observed in NAFLD. However, due to the scarcity of data on NAFPD, further studies are awaited to better determine related biological processes and metabolic sequelae.

## Disclosure

Theodosios D. Filippatos reports participation in advisory boards for Lilly and lecture honoraria from Boehringer Ingelheim, Mylan, Astra Zeneca, Lilly, Recordati, Bausch Health, Servier, Viatris, Omega-Pharma and Innovis; personal fees from Perrigo, Innovis, and Servier, outside the submitted work. The remaining authors, Antonia Pagkali, Anastasios Makris, Kalliopi Brofidi, and Aris P. Agouridis have no conflict of interest to declare.

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