

## Non-alcoholic fatty pancreas disease – practices for clinicians

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Obesity is a growing health burden worldwide, increasing the risk for several diseases featuring the metabolic syndrome – type 2 diabetes mellitus, dyslipidemia, non-alcoholic fatty liver disease and cardiovascular diseases. With the increasing epidemic of obesity, a new pathologic condition has emerged as a component of the metabolic syndrome – that of non-alcoholic fatty pancreas disease (NAFPD). Similar to non-alcoholic fatty liver disease (NAFLD), NAFPD comprises a wide spectrum of disease – from deposition of fat in the pancreas – fatty pancreas, to pancreatic inflammation and possibly pancreatic fibrosis. In contrast with NAFLD, diagnostic evaluation of NAFPD is less standardized, consisting mostly in imaging methods. Also the natural evolution of NAFPD and its association with pancreatic cancer is much less studied. Not least, the clinical consequences of NAFPD remain largely presumptions and knowledge about its metabolic impact is limited. This review will cover epidemiology, pathogenesis, diagnostic evaluation tools and treatment options for NAFPD, with focus on practices for clinicians.

**Key words:** non-alcoholic fatty pancreas; metabolic syndrome; diabetes mellitus.

### INTRODUCTION

The growing burden of obesity worldwide has led to a dramatic rise in patients suffering from metabolic syndrome. The excessive adipose tissue in obese individuals is endocrinologically active, leading to a proinflammatory state which generates several complications in target organs (liver, pancreas, heart and vessels) and even an increased risk for certain malignancies [1].

Similar to the liver, excessive lipid accumulation in the pancreas is known as steatosis. Fatty pancreas (FP), pancreatic steatosis or pancreatic lipomatosis are commonly reported in routine ultrasound examinations, but their significance is not clearly defined [1]. With the increasing epidemic of obesity, a new pathologic condition has emerged, that of pancreatic fat accumulation in the absence of alcohol use, but in association with features of the metabolic syndrome (MetS) – non-alcoholic fatty pancreas disease (NAFPD). As non-alcoholic fatty liver disease (NAFLD) is currently considered the hepatic manifestation of MetS, NAFPD could be thought of as the pancreatic equivalent of MetS.

Similar to non-alcoholic fatty liver disease (NAFLD), which has become a common cause of chronic liver disease, NAFPD comprises a wide spectrum of diseases – from deposition of fat in the pancreas (fatty pancreas, pancreatic steatosis), to

pancreatic inflammation (non-alcoholic steatopancreatitis) and possible pancreatic fibrosis [2-3]. Despite the parallelism with NAFLD, which has been extensively investigated, our knowledge about NAFPD is still at the beginning, but interest in researching it is increasing. Currently, its clinical significance, outcome, relationship with chronic pancreatitis and pancreatic cancer are not well known yet [4]. Also, diagnosis is not standardized and treatment options are not evidence-based.

In the current review, we aimed to summarize and better delineate the features of NAFPD regarding nomenclature, clinical features, diagnosis and treatment.

### LITERATURE SEARCH

For this purpose, we searched PubMed in December 2018 for all publications on NAFPD using several keywords that have been used to describe this condition – (“nonalcoholic fatty pancreas disease” OR “fatty pancreatic infiltration” OR “fatty pancreas”) AND “metabolic syndrome”. Articles were then grouped into case reports, original studies, editorials, reviews and meta-analysis. We selected 100 relevant articles on epidemiology, clinical features, diagnostic tools and treatment options and performed a narrative review (Table 1).

Table 1  
Literature search results

Search term	Number of articles
"Nonalcoholic fatty pancreas disease"	213
"Fatty pancreas" AND "metabolic syndrome"	199
"Fatty pancreatic infiltration"	263

## EPIDEMIOLOGY

First described in 1933 [5], NAFLPD has not been extensively researched so far. Its epidemiology is not very well defined because of the differences in terminology and the absence of clear diagnostic criteria. Usually, FP is an incidental finding in abdominal imaging performed for other reasons and is not thought of in front of a patient with MetS to assess for pancreatic involvement.

There is limited data in the literature regarding the epidemiology of NAFLPD. Studies in Asian populations have shown prevalence data ranging from 16 to 35% [6-8]. However, there is a clear strong association between NAFLPD and NAFLD, which has been shown in several studies – 50-80% of NASH patients have FP on ultrasound examination, according to reported data [9-10], which makes NAFLD a risk category for NAFLPD. Thus, considering the association of NAFLD with MetS, every patient with MetS should be evaluated for both NAFLD and NAFLPD. Despite this close epidemiological relationship and similarities with liver pathology, there is also some data that differentiate between the two: (1) some imaging studies have found no association between NAFLD and NAFLPD; (2) although there is significant pancreatic and liver fat loss in bariatric surgery-treated patients, liver fat loss seems to be higher [13] and, not in the least, (3) pancreatic fat correlated with NAFLD activity score, but after adjusting for BMI the relationship was not seen anymore [14, 11-16].

With respect to demographic characteristics, male gender, hispanics, older age and higher BMI have been reported to be associated with a higher prevalence of NAFLPD [4, 7, 17-21]. Also, it is believed that maternal obesity can induce NAFLPD in the offspring [4, 20].

There is also a lack of solid epidemiological data regarding the relationship of NAFLPD with pancreatic diseases [1]. NAFLPD has been reported to exacerbate the severity of acute pancreatitis (AP) and to increase complications after pancreatic surgery [22]; its role as a risk factor for chronic pancreatitis and pancreatic cancer is not clearly defined yet.

With regard to the relationship between NAFLPD and acute pancreatitis (AP), studies have shown there is a direct toxic effect of fat on pancreatic acinar cells and islets, with fat infiltrates adjacent to acinar cells generating severe parenchymal damage in AP [23-24]. Although Sepe *et al.* found no association between FP and amylase/lipase serum levels [25], pancreatic steatosis has been reported to worsen the inflammation in AP. Studies have shown that the most severe damage is seen in necrosed adipocytes, with surrounding parenchymal necrosis, proving the direct connection between the severity of necrosis and location of fat in the proximity of acinar cells [23, 26]. Thus, patients previously diagnosed with NAFLPD who develop AP should be managed as potentially severe AP.

Concerning pancreatic surgery, one of the most common and potentially severe complications is pancreatic fistula (PF). Several studies have addressed the risk factors for PF formation in order to get insight into possible preventive measures, and FP has been identified as one of them. Rosso *et al.* have reported that fat infiltration of the pancreas > 10% represents a significant risk factor for PF [27] and thus patients considered for pancreatic surgery should undergo preoperative assessment for FP in order to stratify their risk for PF formation.

Not in the least, while evidence is building up for MetS as a risk factor for several types of cancer, concerns have been raised about the possible association of NAFLPD with pancreatic neoplasia. Data on this association is however limited, Tomita *et al.* showing that fatty changes associated with inflammation in the pancreas constitute a predisposing factor for pancreatic carcinoma [28].

## PATHOLOGY

From a pathological point of view, there should be a clear distinction between two phenomena which generate pancreatic steatosis – on the one hand there is fat accumulation associated with MetS, namely *fatty infiltration* which defines NAFLPD, and, on the other hand, there is *fatty replacement* characterized by death of acinar cells, which get replaced by adipose tissue.

"*Fatty replacement*" occurs as a consequence of pancreatic cell apoptosis, caused by numerous factors, leading to adipocyte replacement. The leading factors for pancreatic parenchymal necrosis consist in: congenital diseases such as Cystic fibrosis, Shwachman-Bodian-Diamond syndrome, Johanson-

Blizzard syndrome, heterozygous carboxyl-ester-lipase mutations, alcohol abuse, viral infections (reovirus), iron overload (represented mainly by hemochromatosis, when the surplus iron is stored in the liver, heart, pancreas, and other organs), medications (corticosteroids, gemcitabine, rosiglitazone) or duct obstruction (obstructive chronic pancreatitis).

On the other hand, obesity is considered to be the main factor involving “*fatty infiltration*”, leading to adipocyte infiltration in the pancreas, resulting in non-alcoholic fatty pancreas disease (NAFPD) [2, 25].

As such, when assessing for NAFPD, one should exclude conditions associated with fatty replacement – congenital diseases, steatogenic medications, viral infections, iron overload and obstructive pancreatitis [29] (Table 2).

*Table 2*  
Mechanisms of fat deposition in the pancreas and related diseases

<b>Fatty infiltration</b>	<b>Fatty replacement</b>
NAFPD = FP + MetS features	Congenital diseases Viral infections Iron overload Drug-induced Obstructive pancreatitis

Adipose tissue acts as an endocrine organ, sending signals to the brain, liver, skeletal muscle and pancreas. In conditions of weight gain, when adipose tissue expansion limit is exceeded, excess lipid is deposited in visceral and peripheral non-adipose tissue organs [30] such as the muscle, the liver and more recently the pancreas, causing visceral fat. At the same time, adipose tissue secretes less of the liporegulatory adipokine (TNF- $\alpha$ , IL-6 and adiponectin), and more of the proinflammatory cytokines [31-32].

Compared to adipocytes, non-adipose cells have a limited capacity for free fatty acid storage [33]. When the storage capacity is exceeded, non-adipose cells become hypertrophic and undergo necrosis recruiting macrophages. Recruited macrophages infiltrate the hypertrophic adipose tissue and acquire the proinflammatory M1 phenotype causing a low grade inflammatory state [34].

Fatty infiltration of the pancreas is observed as ectopic adipocytes infiltrating the pancreatic tissue, causing initially pancreatic hypertrophy and hyperplasia [1] resulting in insulin resistance and dysfunction of pancreatic  $\beta$ -cells, with the risk of type 2 diabetes mellitus (T2DM) [21].

Unlike hepatic steatosis, where fat accumulates in hepatocytes, in “*fatty infiltration*” of the pancreas, triglycerides accumulate in adipocytes in the pancreatic tissue [35].

Histologically, two types of pancreatic adipocyte infiltration have been described: intralobular fat (accumulating with a scattered pattern) [4] and interlobular fat (with fat in the area between pancreatic lobules, mostly perivascular), the last type being specific for fatty infiltration in humans [36-37].

Microscopic analysis showed that in massive pancreatic steatosis, only pancreatic islet cells are resistant to fatty infiltration [38] raising the theory that exocrine pancreatic insufficiency might be the first manifestation of NAFPD. But the  $\beta$ -cell is also vulnerable to the lipotoxic effects of excess lipid flux to pancreatic islets, as well as to the damaging effects of the proinflammatory cytokines deriving from visceral obesity [2, 39-40].

It seems that ectopic fat deposition in non-adipose tissues and systemic low-grade inflammation activates the insulin resistance mechanism in insulin target tissues [21], which result in the metabolic syndrome phenotype [41-43]. FP is considered by some authors the first site of ectopic lipid deposition and as such, an early marker of insulin resistance [43].

## DIAGNOSING NAFPD

With respect to diagnosis, it is important to note that not every fatty pancreas detected on ultrasound means NAFPD. According to its definition as obesity-associated accumulation of pancreatic fat, NAFPD diagnosis requires evidence of fatty infiltration of the pancreas and the associated MetS features, according to NCEP ATP III or IDF criteria (Table 3), in the absence of conditions associated with fatty replacement [44].

In contrast with NAFLD, there is currently no reliable biomarker to detect NAFPD and the diagnosis is mainly based on imaging methods [1]. Imaging tests aim at detecting and quantifying pancreatic fat, but this is not always easy to achieve non-invasively. Evaluation of pancreatic fat is even more challenging if we consider that the pancreatic parenchyma has variable shapes and sizes, margins are not always well demarcated and fatty distribution can be heterogenous [45] and not least, normal fatty degeneration occurs with increasing age [46-47]. Also, when using any imaging modality to evaluate pancreatic fat, we should acknowledge that there is a normal fatty infiltration of the pancreas, of up to 6.2% according to Singh *et al.*, and only excessive fat accumulation over this cut-off should be considered FP.

Currently, there is no consensus regarding the first line imaging method to diagnose FP as the

diagnostic accuracy is widely variable, but availability, costs and drawbacks also should be taken into account. Comparative head-to-head trials

with different imaging methods have not been carried out so far, nor cut-off values validated for each imaging tool [29].

*Table 3*  
Metabolic syndrome definition according to NCEP ATP III and IDF criteria

International Diabetes Federation	National Cholesterol Education Program Adult Treatment Panel III
1. Central obesity (defined as waist circumference)	
ethnicity specific values	Males >102 cm (> 40 in) Females >88 cm (> 35 in)
2. Triglycerides $\geq$ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality	
3. Reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females	
4. Systolic blood pressure $\geq$ 130 or diastolic blood pressure $\geq$ 85 mm Hg	
5. Fasting plasma glucose $\geq$ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes	
<b>Metabolic syndrome definition</b>	
Central obesity <i>plus</i> any 2 of the remaining factors	Any 3 criteria

#### *Transabdominal ultrasound*

Transabdominal ultrasound (US), the most widely available, non-invasive tool for abdominal imaging, is frequently limited by the suboptimal visualization of the pancreas due to its deep retroperitoneal location, with interposition of the stomach or bowel content anteriorly. Some have reported lack of pancreas visualization in 1 out of 7 cases, particularly in obese individuals [7] – meaning the exact population in which we're looking for NAFLD. Pancreatic steatosis has been defined as an increased echogenicity of the pancreatic parenchyma compared to the liver or kidney (to the latter indirectly, first comparing hepatic and renal echogenicity, then comparing liver and pancreas echo contrast, as the pancreas and the kidney cannot be visualized in the same acoustic window) [43]. Severe pancreatic steatosis has also been defined when the parenchymal brightness is similar to that of the retroperitoneal fat [2]. Another confounder in US evaluation of the pancreas is that fibrosis also appears as hyperechoic, which can be misleading. Not least, the major limit of US is the fact that its operator dependent – in the study by Wang CY *et al.* reported mean interobserver percentage of agreement for ultrasound diagnosis of fatty pancreas was only 72% ( $\kappa = 0.63$ ) [19]. Some authors have tried using some quantitative methods to assess pancreatic echogenicity – such as pancreato-perihepatic fat index, which has proved a strong association with MetS [48].

#### *Endoscopic ultrasound*

Compared to conventional US, endoscopic ultrasound (EUS) brings a higher frequency probe in close proximity of the pancreas, which translates

into higher resolution and better visualization of the pancreas. Thus, EUS provides quality images for assessing the echotexture of the pancreas, but its major drawback is that it is invasive and carries associated procedural risks [49]. Several studies have researched factors associated with hyperechoic pancreas on EUS and have shown strong association with fatty liver, BMI  $\geq$  30, male gender, age over 60 years and hypertension [10, 25, 50]. As for transabdominal US, EUS is also operator-dependent and there is always the confounder that pancreatic hyperechogenicity does not always represent fatty infiltration and a differential with pancreatic fibrosis should be made [51].

Add-on EUS modules such as real-time elastography (RTE) have provided semiquantitative or quantitative information in several pancreatic diseases [52] and expectations were made for pancreatic steatosis too. However, RTE during EUS as a measure of pancreatic elasticity has proven to be correlated with pancreatic fibrosis, but not with fatty infiltration staged by histology [53-54].

#### *Computed tomography*

Computed-tomography (CT) is a good tool for assessing the pancreatic parenchyma. A non-contrast study is sufficient to evaluate for fatty infiltration of the pancreas, which will appear hypodense compared to the liver or spleen. Quantification of pancreatic steatosis is feasible by measuring the density (HU) in a selected region of interest (ROI). Its use for assessing FP is however limited by the radiation exposure, except for preoperative assessment in patients proposed for surgery, in whom the degree of pancreatic fat predicts clinical outcomes [55-57].

CT can provide quantitative assessment of pancreatic fat, with good correlation with histology – such quantitative tools validated in studies are fat/parenchymal ratio, difference between pancreatic and splenic attenuation and the pancreas-to-spleen attenuation ratio [58-59].

#### *Magnetic resonance imaging (MRI)*

Being a non-irradiating, non-invasive and safe method and having better accuracy for detecting lipomatosis, MRI is the preferred tool for evaluation of FP. There are several protocols to measure pancreatic fat using MRI, with MR spectroscopy being considered equivalent to histology [29]. Other studies have also shown comparable diagnostic accuracy of MRI with histology, which makes it the imaging method of choice for diagnosing pancreatic lipomatosis [29, 60-62].

#### *Histological assessment*

Histology remains the gold standard for assessing pancreatic fat content, but routine biopsy sampling to evaluate for FP is not feasible, even with minimally invasive techniques such as EUS-guided fine needle aspiration (EUS-FNA).

Unlike NAFLD, when triglycerides accumulate mainly intracellular, in NAFPD there is an increased number of adipocytes, although intracellular fat accumulation in acinar and islet cells can also be found [29]. It is not well known if there is a different significance for intracellular or extracellular fat accumulation, but both mechanisms can induce pancreatic dysfunction – adipocytes by influencing acinar/islet cells by paracrine effect, while intracellular fat by inducing direct injury to these cells, as previously discussed [29].

Currently there is a histologic scoring system called pancreatic lipomatosis score (PLS), developed by van Geenen *et al.* [2, 14], which modifies the classification of Olsen [63].

### CLINICAL SIGNIFICANCE

#### *Metabolic risk*

By definition, NAFPD includes features of MetS, which translates into strong association with type 2 DM, NAFLD and cardiovascular risk.

Although studies results, showing higher pancreatic fat deposits in patients with impaired glucose metabolism [20, 64], suggested that NAFPD might be a risk factor in developing type 2 DM, independent association of NAFPD and future type 2 DM evolution remain still under discussion [4, 21, 65].

Regarding "fatty pancreas" and "fatty liver", recent studies showed that there is a significant association between these two entities. Patients with NAFLD also often suffer from NAFPD, while the presence of NAFLD in NAFPD patients is debated [7, 20].

Also, Kim *et al.* showed that fatty pancreatic infiltration is associated with a higher risk of carotid atherosclerosis in non-obese patients with type 2 DM [66].

#### *Acute and chronic pancreatitis*

There is indirect evidence with respect to the relationship between NAFPD and AP, considering that obesity and MetS features are known risk factors for AP. Moreover, some studies have shown that fatty infiltration of the pancreas promotes more severe inflammation in AP [2, 23, 26].

With regard to its relationship with chronic pancreatitis (ChP), there is currently no evidence that NAFPD could cause ChP. In fact, studies have shown no correlation or even inverse correlation of FP with pancreatic fibrosis [67]. Recurrent acute pancreatitis in dysmetabolic patients can lead to morphologic changes of ChP, but this by reduction in parenchyma and substitution with adipocytes and fibrosis, and not by fatty infiltration which defines NAFPD.

There has also been a debate in the literature about pancreatic hyperenzymemia and FP. Some authors have theorized that pancreatic hyperenzymemia in apparently healthy individuals could be due to FP and dyslipidemia, while others have shown that there is no connection to FP [19, 25, 68-69].

#### *Exocrine pancreatic insufficiency (EPI)*

Given the toxic effect of fat on acinar cells, EPI could occur in the evolution of NAFPD, at least theoretically. However, there is currently no study looking at EPI in patients with pancreatic steatosis; only case reports of patients with severe fatty replacement who developed EPI were found in the literature search [70-73]. On the other hand, there are several studies reporting on EPI in type 2 DM patients; about one fifth of diabetics have exocrine insufficiency as measured by fecal elastase-1 (FE-1) [74-76], but FE-1 values do not seem to correlate with pancreatic steatosis [77].

#### *Pancreatic fistula*

Considering its close association with MetS, NAFPD seems to be a pathology for internal/general medicine, but there is something in it for surgeons too. One of the most fearful complications of

duodenopancreatectomy is formation of PF. Over the years, several modifiable and non-modifiable risk factors for PF development have been studied and addressed by technique improvement, drug interventions or post-operative management. Of these, fatty infiltration of the pancreas has been proven to be a significant risk factor for PF formation and preoperative evaluation for pancreatic steatosis is now considered a rational step for risk stratification of patients [27, 29].

#### *Pancreatic cancer (PC)*

While evidence is building up that metabolic disturbances are associated with an increased risk for certain types of cancer [78-79], a question has emerged about the risk of PC in NAFLD. Obesity is a well-known risk factor for PC [80] and there are some preliminary data to support an association between FP and pancreatic cancer too. The proposed mechanism of carcinogenesis in NAFLD is by means of adipocyte-mediated chronic inflammation, similar to what occurs in NAFLD [2, 29].

Besides the increased risk for PC, NAFLD also seems to contribute to worse outcomes of PC by altering the tumor microenvironment, compared to patients with lean pancreas [55, 81] who develop cancer.

Taking into account the increasing trend in mortality for PC [82], further research on the association between NAFLD and cancer is warranted.

### TREATMENT

Being recently recognized as a new entity of the metabolic syndrome, research regarding NAFLD treatment is limited. In fact, until now no standard treatment has been proposed for NAFLD patients.

#### *General*

Having in mind that obesity represents the main cause for pancreatic fatty infiltration, according to several studies, weight loss with or without bariatric endoscopy/surgery [83-86] might represent the easiest way to reduce pancreatic fat content. Interestingly, despite the association between NAFLD and NAFLD, when patients undergo bariatric surgery, fat loss in the liver and pancreas occurs independently, suggesting a tissue-specific mobilization of the ectopic fat deposits [13, 29].

Lifestyle measures such as very-low-fat eating and intensive training could be expected to work in a complementary way by promoting an increased number of insulin receptors that are more functionally competent [87].

#### *Promising results for drug-based therapies*

Although until now there is no approved pharmacological therapy for NAFLD, it seems that treatment with **oral hypoglycemic agents**, such as metformin, DPP-4 inhibitors and thiazolidinediones in T2DM subjects showed encouraging results. **Metformin** is a first-line antidiabetic drug with favorable effect on lipid metabolism [88].

Studies on rats proved that metformin, by decreasing oxidative stress in pancreatic islets, might have a direct beneficial effect on insulin secretion [89]. It improves insulin resistance and suppresses the compensatory  $\beta$ -cell hyperplasia induced by high-fat diet [90], therefore it might reduce visceral fatty tissue.

**Incretin-based therapies**, especially DPP-4 inhibitors (Sitagliptin), in monotherapy and combined with metformin, reduced pancreatic adiposity [91].

**Troglitazone**, the first thiazolidinedione, withdrawn in 2000 because of the frequent adverse liver reactions, including acute liver failure, decreases hepatic glucose output and increases insulin-dependent glucose disposal in the skeletal muscle. The metabolic changes induced by troglitazone result from the increased responsiveness of insulin-dependent tissues [92] and are observed in numerous animal models of insulin resistance. Although treatment did not affect pancreatic weight or islet number, it increased granulation of the pancreatic beta cells in rodent models of insulin resistance. Several studies in mice suggest that troglitazone prevented hyperglycemia, hyperlipidemia, and the increase in 11 $\beta$ -HSD1 (an enzyme that reduces cortisone to cortisol, reducing the risk of central obesity development) [93]. Troglitazone was also associated with a 52% decrease in islet triglycerides, exerting direct lipopenic activity in normal islets and in the islets of obese prediabetic rats [94].

By suppressing inflammatory changes in the pancreas, troglitazone treatment completely prevented or reversed histological alterations such as fibrosis, fatty replacement, and inflammatory cell infiltration [95].

Studies with new generation thiazolidinedione on NAFLD are missing.

It has been shown that the activation of a local renin-angiotensin system contributes to insulin resistance and non-alcoholic fatty liver disease onset [96], therefore **Angiotensin type-1 receptor (AT1R) blockers** might mitigate insulin resistance and fatty liver by enhancing beta-oxidation, reducing lipogenesis and controlling inflammation [97].

Based on this fact, some authors used Telmisartan, Sitagliptin and Metformin in monotherapy or in combinations (telmisartan + metformin,

telmisartan + sitagliptin, sitagliptin + metformin) to evaluate their effects on insulin resistance and on pancreatic and hepatic adipose tissue distribution in mice fed on a high-fat diet. All drug treatments had the effect of reducing body weight, and also pancreatic and hepatic steatosis. The best results were observed with telmisartan and sitagliptin, associated or as monotherapies [98]. In a follow-up study, complete reversal of pancreatic steatosis was achieved using telmisartan and sitagliptin combination [99].

Another study on obese rats highlighted that **Sandostatin** (somatostatin analogue) might improve pancreatic fatty infiltration, lipid disorder, insulin resistance, and alleviate pancreatic injury by down-regulating the expression of adipose differentiation-related protein in the pancreas [100].

Studies have also researched IL-10 and some homeopathic remedies such as berberine and cinnamic acid [101-104], but further evidence to support their benefits in FP is needed.

## CONCLUSIONS

NAFPD is a new but very common pathological entity which is not readily recognized in

clinical practice, although easily diagnosable with good imaging of the pancreas. It could be considered the pancreatic manifestation of MetS and it should be searched for in each patient who meets criteria for MetS. It is not just another target for ectopic fat deposition, but it has significant metabolic consequences. Diagnostic work-up includes pancreatic imaging, starting with routine ultrasound and confirming with advanced imagery. There is no standard treatment for NAFPD, but weight control by lifestyle measures or bariatric endoscopy/surgery and antidiabetic drugs showed promising results.

**Conflict of Interest disclosure:** The authors declare that there are not conflicts of interest.

**Abbreviations:** NAFPD: non-alcoholic fatty pancreas disease; NAFLD: non-alcoholic fatty liver disease; FP: fatty pancreas; MetS: metabolic syndrome; BMI: Body Mass Index; AP: acute pancreatitis; PF: pancreatic fistula; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; IL-6: Interleukin 6; T2DM: type 2 diabetes mellitus; US: transabdominal ultrasound; EUS: endoscopic ultrasound; RTE: real-time elastography; CT: computed-tomography; MRI: magnetic resonance imaging; FNA: guided fine needle aspiration; ChP: chronic pancreatitis; EPI: exocrine pancreatic insufficiency; FE-1: fecal elastase-1; PC: pancreatic cancer; DPP-4: dipeptidyl peptidase 4; 11 $\beta$ -HSD1: 11 $\beta$ -hydroxysteroid dehydrogenase type 1; AT1R: angiotensin type-1 receptor; IL-10: Interleukin 10.

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*Obezitatea reprezintă o povară din ce în ce mai mare la nivel mondial, crescând riscul pentru mai multe patologii care intră în componența sindromului metabolic – diabetul zaharat tip 2, dislipidemia, ficatul gras non-alcoolic și bolile cardiovasculare. Odată cu creșterea frecvenței obezității, o nouă entitate patologică s-a conturat în cadrul sindromului metabolic, cea a pancreasului gras non-alcoolic (NAFPD). Similar cu ficatul gras non-alcoolic (NAFLD), NAFPD cuprinde un spectru larg de afectare pancreatică – de la steatoză până la inflamația pancreasului și posibil fibroză pancreatică. Spre deosebire de NAFLD, testele diagnostice pentru NAFPD sunt mai puțin standardizate, constând în metode imagistice. De asemenea, evoluția naturală a NAFPD și asocierea acesteia cu cancerul pancreatic este mult mai puțin cunoscută. Nu în ultimul rând, consecințele clinice ale NAFPD rămân în mare parte prezumții, iar cunoștințele impactului său metabolic sunt limitate. Acest review sumarizează cunoștințele actuale despre epidemiologia, patogenеза, testele diagnostic și opțiunile de tratament pentru NAFPD, cu accent pe practica clinică.*

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