

Nonalcoholic Fatty Pancreas Disease: Clinical Consequences

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Keywords

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Abstract

Metabolic syndrome and its components such as obesity, hypertriglyceridemia, type-2 diabetes mellitus (DM-T2), and arterial hypertension are unequivocally serious problems for every society. This is especially true in economically developed countries where the imbalance in lifestyle between caloric intake and caloric output still gets greater and greater. This fact is not only a concern for the adult population but for children as well. However, metabolic syndrome does not only affect society and health in regards to cardiovascular diseases, it significantly concerns gastroenterology where it is classified as nonalcoholic fatty pancreas disease (NAFPD). The data gained from several trials show that the prevalence of NAFFP is 33% (95% CI 24–41%). When it comes to the diagnostic procedures concerning the presence of pancreatic fat, a whole spectrum of suitable methods are recommended. Probably, the most exact method is the use of magnetic

resonance imaging. However, for common clinical practice, the abdominal sonographic examination based on the comparison of the pancreatic parenchymatous echogenity versus renal or hepatic echogenity is used. The clinical consequences of pancreatic steatosis and steatopancreatitis are significant. These diseases are connected with DM-T2 and insulin resistance. In recent years, changes of exocrine pancreatic function, particularly its decrease, have also been described. It is known that there is a close correlation between NAFFP and nonalcoholic hepatic steatosis and also with the increased thickness of aortic intima-media. There is also an important relationship between NAFFP and pancreatic carcinoma. Pancreatic steatosis, and especially its NAFFP form, is a serious state which can be treatable by the possible effective management of metabolic syndrome parameters, including obesity.

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Introduction

Fatty storage in the pancreas is mentioned under various names. Similarly, the etiology of the state is various. Pancreatic steatosis was first described by Ogilvie [1]. In their

Table 1. Nomenclature of the fat in the pancreas

Name	Definition
Pancreatic steatosis Pancreatic lipomatosis Fatty pancreas	General terms for pancreatic fat accumulation
Fatty replacement	Death of acinar cells – replacement with adipocytes
Fatty infiltration	Infiltration with adipocytes due to obesity
NAFPD	Pancreatic fat accumulation + obesity and metabolic syndrome
NASP	Pancreatitis due to pancreatic fat accumulation

NAFPD, nonalcoholic fatty pancreas disease; NASP, nonalcoholic fatty steatopancreatitis.

set of observed obese patients, he described the presence of pancreatic fat in 17% of the obese patients, while in the slim patients, it was present only in 7%. In 1978, Olsen [2] examined a group of 394 autopsied patients and found an increased amount of pancreatic fat in a direct relationship to age. Similarly, Stamm [3] proved an increase of pancreatic fat associated with higher age. They also found a significant relationship between pancreatic steatosis when fatty content in the pancreas is at 25% or more, and the risk of development of type-2 diabetes mellitus (DM-T2) and atherosclerosis. In 2010, van Geenen et al. [4] expressed the hypothesis that obesity and its association with insulin resistance play an important role in pancreatic infiltration with adipocytes, leading to steatosis of the gland. Insulin resistance also leads to peripheral lipolysis, and subsequently to a flux of fatty acids into the hepatic parenchyma and the onset of nonalcoholic fatty liver disease (NAFLD).

Pezzilli and Calculli [5] assumed that the most suitable name for fatty accumulation in the pancreas is the term pancreatic steatosis. This term also characterizes the fatty accumulation in the pancreas as a reversible process. The terminology dealing with fatty accumulation in pancreatic tissue is clearly summarized in Table 1 (adjusted according to Smits and van Geenen [6, 7]). The epidemiological data are not numerous. Epidemiological trials performed between 2014 and 2016 state the prevalence of nonalcoholic fatty pancreas disease (NAFPD) as being between 16 and 35%. This is mostly based on the results gained in the Asian population [8–10]. Only one epidemiological trial which was published in 2016 [11] dealt with pediatric population and puts the prevalence of pancreatic steatosis at 10%. The limiting factor of this work is the fact that it was performed entirely on hospitalized children, not on the general pediatric population.

Pathogenesis and Risk Factors

There are basically 2 mechanisms leading to fatty accumulation in the pancreas [6].

The first is the death of acinar cells and their substitution by adipocytes. In this case, the state is called “fatty replacement”. The second is fatty accumulation called “fatty infiltration”. Both of these states are succeeded by the presence of DM-T2, metabolic syndrome, and/or obesity.

The risk induction factors of steatopancreatitis include:

- (a) Congenital diseases (Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, cystic fibrosis, heterozygous carboxyl-ester lipase mutation)
- (b) Alcohol abuse
- (c) Infections (viral infection with Reovirus)
- (d) Hemochromatosis
- (e) Medicines (rosiglitazone, corticosteroids, octreotide, gemcitabine)
- (f) Malnutrition
- (g) NAFLD, chronic hepatitis B?
- (h) Necrotizing pancreatitis?, recurrent acute pancreatitis?, hereditary chronic pancreatitis?

One of the signs of the presence of risk factors is the manifestation of steatopancreatitis, which is evidently caused by different mechanisms. The trials performed on patients and animal trials show the coexistence of NAFPD with NAFLD [4, 12]. Both NAFPD and NAFLD are closely connected with obesity and the increased presence of visceral adipose tissue [13, 14].

NAFPD is a disease where obesity or obesity as a part of metabolic syndrome is the essential risk factor. The experimental trials show that maternal obesity and post-

natal obesogenic diet lead to the onset of NAFLD. The inducers are endoplasmic reticulum, disbalance, and the alteration of circadian metabolic processes [15]. In our clinical trial, we proved that metabolic syndrome and its components (obesity, arterial hypertension, hypertriglyceridemia, the changes of HDL cholesterol, and DM-T2) are all significant factors of NAFLD development [16].

The generally true correlation between the finding of NAFLD and NAFLD is not however absolutely valid [13]. Although hepatic fat is localized mainly intracellularly, pancreatic fat is connected to the presence of adipocytes which infiltrate its parenchyma. Therefore, for example, during a bariatric surgical intervention, the mentioned hepatic fat and pancreatic fat change and disappear quite independently of each other [17]. Despite this, it cannot be ruled out that NAFLD and NAFLD influence each other regarding disease onset and progression.

Diagnosis of Pancreatic Steatosis

There is not a clear consensus as to the diagnostic methods concerning the presence of pancreatic fat. The optimum method should be able to simultaneously determine the presence of fat in the gland and its quantity in a noninvasive way. The imaging methods play the most important role in diagnostics.

Transabdominal ultrasonographic examination is a noninvasive and widely available method. Pancreatic steatosis is defined as an image of increased echogenicity in the pancreatic parenchyma, when compared with the renal echogenicity or liver echogenicity, where the possible presence of hepatic steatosis is the limitation of evaluation. Therefore, it is first recommended to compare the hepatic and renal echogenicity and then, using the same acoustic window, compare the pancreatic echogenicity with the renal or hepatic echogenicity. With respect to the possible presence of hepatic steatosis, it seems to us that for this purpose comparison only with renal echogenicity is better. One limitation of this type of examination can be excessive obesity, and it can be emphasized that the examination is operator dependent. The method for quantitative evaluation of pancreatic echogenicity was not generally accepted [18].

Endoscopic ultrasound is an endoscopic invasive method, which enables a very good visualization and evaluation of the examined gland. The evaluation of texture in the pancreatic parenchyma is quite exceptional.

Various trials have shown the relationship between increased pancreatic echogenicity and the presence of fatty liver, obesity with BMI >30.0, and usually also with arterial hypertension and even age higher than >60 years [19, 20]. This method is also operator dependent. The increased echogenicity of pancreatic parenchyma is not always the image of an increased fatty presence in the pancreas, but it can be caused by the presence of pancreatic fibrosis, which is considered as a method limitation [21].

Computed tomography. A typical fatty pancreas is hypodense in Hounsfield units compared to the spleen [22]. The method is operator dependent, and the evaluation of its diagnostic profit is not uniform [23, 24]. Saisho et al. [25], for example, found computed tomography examination using the evaluation of fat/parenchyma ratio to be a reliable method when compared with the histological diagnosis.

Magnetic resonance imaging (MRI) is the most preferred method at present. The advantage of MRI is its noninvasivity, safety, and high sensitivity. The various trials showed that its accuracy in the identification of fat presence is comparable with histological examination, and in this way, it is the preferred method in the diagnostics of pancreatic lipomatosis [17, 26].

MRI proton density fat fraction. This method enables a highly accurate quantification of the amount of fat present in the pancreatic parenchyma [27]. At present, this method is also indicated for the quantitative determination of fat in the adjacent parenchymatous organs, not only in a pancreas [28].

Ultrasound elastography can evaluate organ's stiffness. In pancreatology, it has been useful in diagnostics of pancreatic diseases, that is, elastography via endoscopic ultrasound predicts exocrine pancreatic insufficiency in chronic pancreatitis [29]. There are some limitations in diagnosing steatopancreatitis, especially the retroperitoneal location of the pancreas and its small size, which can decrease the diagnostic accuracy.

NAFLD and Clinical Consequences

Metabolic Syndrome and Cardiovascular Diseases

Metabolic syndrome belongs to the serious civilizational diseases befalling around 30% of the population. After previous discussions concerning its definition, the so called harmonized definition of metabolic syndrome

was accepted in 2009 which is characterized by the total of 5 components, the presence of 3 of which is necessary to make the diagnosis of metabolic syndrome [30]. The components of metabolic syndrome include DM with insulin resistance, arterial hypertension, obesity, and dyslipidemia (hypertriglyceridemia, decrease of HDL cholesterol). Obesity is the main important factor which can be considered a pandemic across societies. Abdominal obesity is characterized by dysfunction of adipose tissue, when the metabolism of esterified fatty acids is altered and this, together with DM, is a risk factor for the development of cardiovascular diseases [31]. Adipose tissue is an important endocrine organ producing adipocytokines and inflammatory mediators, for example, TNF- α [32]. Because of that obesity is an important risk factor not only for cardiovascular diseases but also for gastrointestinal diseases, including afflictions of liver and pancreas.

Ectopic fat deposits are in close correlation with cardiovascular diseases, NAFLD and epicardial adipose tissue [33]. Kul et al. [34] published a trial where they observed the role of NAFLD, the presence of epicardial adipose tissue, and changes in the thickness of the aortic intima-media. They proved that the presence of NAFLD is connected with an increased occurrence of increased aortic intima-media thickness and epicardial adipose tissue.

There is no doubt that metabolic syndrome and its components are in close correlation with NAFLD, as was confirmed in a trial evaluating 13 publications with a total of 49,329 subjects [35].

Insulin Resistance

The results of the trials performed evaluating the association between NAFLD and insulin resistance are still controversial. Della Corte et al. [36] found a higher level of insulin resistance, circulating tumor necrosis factor α , and interleukin 1 β only in obese children with NAFLD, but not in the children with NAFLD. Moreover, HOMA-insulin resistance was found in those patients with NAFLD namely in connection with a higher BMI [37]. However, these results are challenged by the scientific works published by Le et al. [38] and Rossi et al. [14], which show them to be controversial. The authors found a relationship between the content of pancreatic fat and markers of insulin resistance. The question is if pancreatic steatosis really is the cause of insulin resistance, or if it is only a part of the other possible etiological factors.

Type-2 Diabetes Mellitus

DM-T2, formerly known as noninsulin dependent or adult onset diabetes, belongs to the components of metabolic syndrome and its relationship to obesity and insufficient physical activity has been clearly described [39]. Some investigations have shown that fatty infiltration of the pancreas leads to the loss of beta cells and their function, which was designated as the driving force in the development of DM [40]. The most frequent explanation concerning the relationship between NAFLD and the dysfunction of pancreatic beta-cells is based on the glycolipotoxic phenomenon. Hyperglycemia in the beta cells inhibits the beta-oxidative mitochondrial process through a cascade of enzymatic processes, which ultimately leads to the intracellular accumulation of triglycerides as its final consequence. Insulin resistance simultaneously reduces the inhibitory insulin activity in lipolytic processes and leads to the increase of circulating free fatty acids [41]. Tushuizen et al. [42] evaluated the pancreatic fat content and beta cell function in men with and without DM-T2. The pancreatic fat content was compared between the diabetic patients and the controls. The fat content was significantly higher in the set of patients with DM [42]. Ou et al. [40] found an important relationship between NAFLD and the development of prediabetes in men [39]. The negative association between the quantity of pancreatic fat and insulin secretion in patients with prediabetes was described by Heni et al. [13]. van der Zilj et al. [43] proved that those patients with prediabetes have a higher content of pancreatic fat; however, they did not find a relationship between fatty pancreas and insulin secretion.

Pancreatic Cancer

Publications documenting the influence of obesity and insufficient physical activity on the development of various tumorous diseases including those of the pancreas began to appear as early as in the first decade of this century [44, 45]. The presence of the pancreatic inflammatory process in the terrain of pancreatic steatosis is the most important predisposing factor for the development of pancreatic adenocarcinoma [46]. The carcinogenetic mechanism in fatty pancreas has still not been fully elucidated.

In 2017, Lesmana et al. [47] showed an increased prevalence of NAFLD in his set of patients suffering from pancreatic carcinoma. He evaluated NAFLD as one of the significantly important risk factors for the development of pancreatic carcinoma.

Various authors focusing on patients who were operated on for ductal pancreatic adenocarcinoma reported

significantly higher risk of postoperative complications, mainly the development of pancreatic fistulas, in association with increased presence of fat in the pancreatic tissue [48–50].

Exocrine and Endocrine Pancreatic Functions

The relationship between pancreatic steatosis, steato-pancreatitis, and pancreatic functional disorder is attributed to beta-cell lipotoxicity [22]. Furthermore, as proven by Pezzilli and Calculli [5], a close relationship also exists between obesity and steatopancreatitis, and obesity and DM-T2. In the trial of Miyake et al. [51], the authors confirmed that the presence of a fatty pancreas is an independent risk factor, extremely important for the relationship with endocrine pancreatic function. Therefore, it is necessary to further study the clinical course of patients with endocrine pancreatic impairment due to a fatty pancreas.

Exocrine pancreatic insufficiency can be defined as insufficient activity of pancreatic enzymes in the duodenum as a result of insufficient pancreatic secretion or premature enzyme destruction. The other conditions associated with exocrine pancreatic insufficiency include chronic pancreatitis, pancreatic carcinoma, coeliac disease, DM, or pancreatic resection. Pancreatic steatosis can also be an influencing factor in exocrine pancreatic function [22, 52]. There are theoretically 3 possible mechanisms leading to exocrine functional pancreatic disorder in patients suffering from pancreatic steatosis. These include:

- (a) Lipotoxicity of acinar cells
- (b) Adipocyte-mediated negative paracrine effect
- (c) Direct destruction of acinar cells

Tahtaci et al. [53] published their results gained from a group of 43 patients suffering from pancreatic steatosis and a group of 48 persons without diagnosed pancreatic steatosis. These cohorts were examined by MRI, and the value of fecal elastase-1 was determined. Those persons suffering from diagnosed chronic pancreatitis, alcohol abuse, DM, coeliac disease, inflammatory bowel disease, and those who had had surgical pancreatic intervention were excluded from this study. The authors found a significant reduction of fecal elastase-1 in patients with diagnosed pancreatic steatosis in comparison to those patients without steatosis. However, the authors found no differences in the relationship between NAFLD and the patients with or without diagnosed pancreatic steatosis. Therefore, the authors assumed, in contrast to the conclusions from, for example, d'Assignies et al. [54], that the relationship between NAFLD and NAFPD does not exist. This may be because NAFLD represents a different group among the patients with pancreatic steatosis.

Microbiome and NAFPD

We have not found any recently published work considering a relationship between a possible role of microbiome and NAFPD. However, there is a well-known described role between a gut microbiome and metabolic syndrome. In metabolic syndrome, a fat accumulation occurs in the pancreas, due to which there is also a relationship with NAFPD. Thus, the effect of a similar microbiome on the development of NAFPD can be assumed as in the metabolic syndrome [22, 55].

Chronic Pancreatitis

It's clear that alcoholic steatosis of the pancreas can develop into chronic pancreatitis – probably due to chronic inflammation.

Acute pancreatitis or recurrent acute pancreatitis may lead to a reduction of the parenchymal mass and substitution with adipocytes. An increased number of pancreatic adipocytes can be observed in the pancreases of lean patients with nonhereditary/hereditary chronic pancreatitis [56].

That NAFPD progresses into chronic pancreatitis was not clearly described in the literature, but we know that recurrent acute pancreatitis is a risk factor for a chronic form of pancreatitis development. van Geenen et al. [57] found no relationship between pancreatic fibrosis and NAFPD. According to current evidence, fatty replacement and pancreatic fibrosis seem to both be independent consequences of chronic inflammation in patients with chronic pancreatitis [57].

Conclusion

NAFPD is a hot topic in gastroenterology. Just as obesity and metabolic syndrome are global problems, pancreatic steatosis especially in the form of NAFPD is an important challenge for pancreatologists, diabetologists, and nutritionists.

NAFPD should have consideration in clinical practice. The evaluation of steatopancreatitis as early marker of ectopic fat accumulation and insulin resistance in persons with metabolic syndrome, as a prognostic marker for exocrine pancreatic insufficiency, chronic pancreatitis, and/or pancreatic cancer is important.

The growing incidence and prevalence of obesity, including metabolic syndrome, is a world health problem.

Common risk factors for the development of NAFLD – as in older age, high body mass index, dyslipidemia, or metabolic syndrome with metabolic dysfunction – insulin resistance, are a real challenge for multidisciplinary research.

There is no doubt that systematic and extensive research as well as multicentric trials in these fields can be expected. The clinical consequences concerning NAFLD are not only numerous but also important from a practical standpoint. This is especially true if in our population >30% of the people are obese and about 30% have metabolic syndrome.

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Statement of Ethics

The authors declare that they have no ethical conflicts to disclose.

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