World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i34.7660

World J Gastroenterol 2016 September 14; 22(34): 7660-7675
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Exploring the metabolic syndrome: Nonalcoholic fatty pancreas disease

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Author contributions: Catanzaro R and Cuffari B contributed equally to this work; Catanzaro R and Cuffari B designed and performed the research, analyzed data and wrote the paper; all authors contributed to revision and approval of the final version of this paper.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Manuscript source: Invited manuscript

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Received: June 4, 2016
Peer-review started: June 4, 2016
First decision: July 12, 2016
Revised: July 25, 2016
Accepted: August 10, 2016
Article in press: August 10, 2016
Published online: September 14, 2016

Abstract

After the first description of fatty pancreas in 1933, the effects of pancreatic steatosis have been poorly investigated, compared with that of the liver. However, the interest of research is increasing. Fat accumulation, associated with obesity and the metabolic syndrome (MetS), has been defined as "fatty infiltration" or "nonalcoholic fatty pancreas disease" (NAFPD). The term "fatty replacement" describes a distinct phenomenon characterized by death of acinar cells and replacement by adipose tissue. Risk factors for developing NAFPD include obesity, increasing age, male sex, hypertension, dyslipidemia, alcohol and hyperferritinemia. Increasing evidence support the role of pancreatic fat in the development of type 2 diabetes mellitus, MetS, atherosclerosis, severe acute pancreatitis and even pancreatic cancer. Evidence exists that fatty pancreas could be used as the initial indicator of "ectopic fat deposition", which is a key element of nonalcoholic fatty liver disease and/or MetS. Moreover, in patients with fatty pancreas, pancreaticoduodenectomy is associated with an increased risk of intraoperative blood loss and post-operative pancreatic fistula.

Key words: Metabolic syndrome; Nonalcoholic fatty liver disease; Pancreatic steatosis; Pancreatic lipomatosis; Nonalcoholic fatty pancreas disease; Fatty pancreas; Pancreatic fat; Pancreatic fatty replacement; Pancreatic fatty infiltration; Pancreatic cancer

Core tip: Nonalcoholic fatty pancreas disease is a very common yet neglected pathological condition. It can be considered an early marker of the metabolic syndrome and, as so, its clinical significance spaces between internal and surgical diseases, such as type 2 diabetes mellitus, atherosclerosis, acute pancreatitis and even pancreatic cancer. This review collects current knowledge of worldwide opinion leaders and

researchers of this matter.

Catanzaro R, Cuffari B, Italia A, Marotta F. Exploring the metabolic syndrome: Nonalcoholic fatty pancreas disease. *World J Gastroenterol* 2016; 22(34): 7660-7675 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i34/7660.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i34.7660

INTRODUCTION

The spreading of obesity is one of the most concerning problems of modern medicine. According to the World Health Organization (WHO), worldwide obesity has nearly doubled since 1980, and in 2008 more than 10% of the world's adult population was obese[1]. About 3.4 million adults die every year because of overweight or obesity, which are more deaths than underweight.

According to the International Diabetes Federation, the association of abdominal (central) obesity with hypertension, elevated fasting plasma glucose, high serum triglycerides, and low high density lipoproteins (HDL) define the metabolic syndrome (MetS), also known as syndrome X, cardiometabolic syndrome or insulin resistance syndrome. This condition is associated with a pro-inflammatory, pro-thrombotic state, and leads to an increased risk of developing cardiovascular disease and type 2 diabetes mellitus (T2DM)[2,3].

In the last years, more research is focusing on understanding obesity, MetS and the diseases associated.

Obesity, especially when associated with a higher waist circumference, causes ectopic fat deposition in certain organs, such as the liver (nonalcoholic fatty liver disease - NAFLD), heart, muscles, kidney and pancreas[4]. This is called steatosis[5].

As the liver is a key organ in the metabolism, its fatty infiltration has been the most investigated. Large evidence supports the hypothesis of NAFLD as both cause and consequence of the MetS[6].

Although the pancreas is also an important organ in the metabolism, the effects of fatty infiltration of this organ has been less investigated than that of the liver.

RESEARCH

The following research was performed on MEDLINE/PubMed: "pancreatic steatosis" or "pancreatic lipomatosis" or "NAFPD" or "fatty pancreas" or "pancreatic fat" or "pancreatic fatty replacement" or "pancreatic fatty infiltration". A total of 210 results were found and abstracts were examined. Thirty-four papers were excluded because the main topic was not pancreatic fat. While reviewing, further references were added.

HISTORY

The first description of pancreatic fat was made by Ogilvie in 1933[7]. He compared 19 pancreas derived from obese patients with 19 controls. Obese cadavers showed a greater mean pancreatic adiposity (17.1%, range 0%-48.5%) than the controls (9.3% range 2.5%-23.6%).

After more than 40 years, in 1978, Olsen[8] performed a larger study over 394 autopsies. The cadavers were divided into three groups: below normal weight, normal weight and above normal weight. He found a relationship between the content of fat and age, and confirmed the relation with obesity.

Across the years, many synonymous have been used to refer to "pancreatic fat accumulation", with many different meanings. Those terms have been very well reviewed in 2011, and are summarized in Table 1. According to the authors, the limit of this nomenclature is the lack of distinction between the accumulation of triglycerides in acinar cells, β-cells or intrapancreatic adipocyte tissue[9,10].

Nowadays, with the development of more sophisticated imaging techniques and data suggesting the clinical importance of obesity and the MetS, the interest of researchers is increasing, as shown in Figure 1.

Table 1 Nomenclature according to Smits and van Geenen[9]

Name	Definition
Pancreatic steatosis Pancreatic lipomatosis Fatty pancreas	General term for pancreatic fat accumulation
Lipomatous pseudohypertrophy	Extreme variant of pancreatic fat accumulation when the pancreas is enlarged uniformly or focally, the exocrine system is replaced by fat, and when no association can be found with obesity[10]
Fatty replacement	Death of acinar cells with subsequent replacement with adipocytes
Fatty infiltration	Infiltration of adipocytes owing to obesity
NAFPD	Pancreatic fat accumulation in association with obesity and metabolic syndrome
NASP	Pancreatitis owing to pancreatic fat accumulation

NAFPD: Non-alcoholic fatty pancreas disease; NASP: Non-alcoholic fatty steatopancreatitis.

HOW TO ASSESS PANCREATIC FAT

Anatomical pathology

Mild or massive pancreatic steatosis can be assessed by simple inspection of the organ. That can be useful in the surgical setting, as further explained[11].

Histological examination is the most common way to assess pancreatic fatty infiltration in animal models[12-28]. Human specimen can be obtained from autopsies, operatory remnants or, rarely, fine needle aspiration cytological (FNAC) examination[7,8,16,29-40].

Fat accumulation may be even or uneven[41-43]. Four different types of uneven pancreatic lipomatosis have been described: (1) Type 1a (35% of cases):

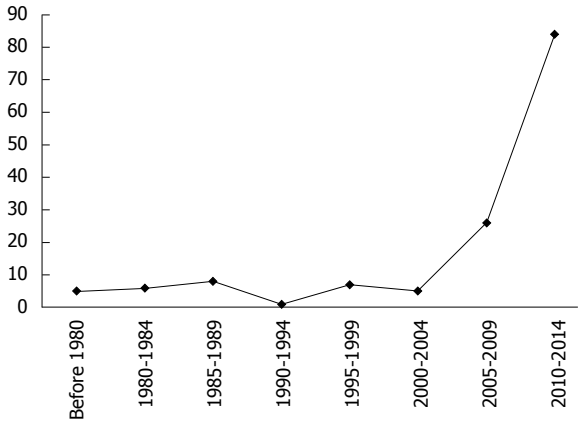

Figure 1 MEDLINE/PubMed findings about pancreatic fat.

replacement of the head with sparing of the uncinate process and peribiliary region; (2) Type 1b (35%): replacement of the head, neck, and body, with sparing of the uncinate process and peribiliary region; (3) Type 2a (12%): replacement of the head, including the uncinate process, and sparing of the peribiliary region; and (4) Type 2b (18%): total replacement of the pancreas with sparing of the peribiliary region[41,44].

Unlike the liver, where the triglycerides accumulation is mainly intracellular, pancreatic steatosis is histologically characterized by an increased number of adipocytes (Figures 2 and 3)[5,16]. However, intracellular fat accumulation can be visualized by electronic microscopy or immunohistochemistry in both acinar and islet cells and may precede adipocytes infiltration[12,13,16,18,21,23,45-48]. It is unknown if intracellular or extracellular triglycerides have a different clinical significance, but it is possible that adipocytes influence the function of acinar and/or islet cells by a paracrine effect, while intracellular lipids may lead to lipotoxicity and therefore islet or acinar cells injury, as further discussed[9].

Thus now, there is not a shared score to grade the severity of fatty infiltration on histological examination, so each group have used arbitrary subjective parameters, or computer-based morphometric analysis, which gives an objective quantification of pancreatic fat[8,30,31,33,34,38,48-50].

To our knowledge, the only scoring system that has been validated on patients by a rastering method is the pancreatic lipomatosis score (PLS), developed by van Geenen *et al*[9,33].

PLS modifies the classification made by Olsen in 1978[8], based on the percentage of adipocytes per microscopic field: (1) Group 1: $\geqslant$ 51%; (2) Group 2: $\geqslant$ 26%; (3) Group 3: $\geqslant$ 15%; and (4) Group 4: $\geqslant$ 8%.

The group numbers were shifted and a group for patients with less than 8% fat was added. Furthermore, intralobular fat, interlobular fat and total fat were scored separately. A last group was added for pancreases with > 75% of total fat.

Radiological assessment

The majority of radiological techniques available have been used to study pancreatic steatosis. So far, there is not cut-off points validated on patients, nor valid comparative trials that are able to assess which technique is the most accurate.

Ultrasonography: Both transabdominal ultrasound and endoscopic ultrasound (EUS) can be used to observe the pancreas[42,51-66]. A fatty pancreas looks hyperechogenic (hyperechogenic pancreas - HP) compared to the liver or, if the liver is also hyperechogenic, with the spleen or the kidney. Since the kidney and the pancreas cannot often be seen in the same window, one could use an indirect comparison between the kidney with the liver, and then the liver with the pancreas[57,58].

By EUS, the echogenicity of the pancreas can also be compared with the one of retroperitoneal fat[65]. In addition, EUS may also be associated with FNAC for cytological analysis[36].

Some authors have even graded the severity of pancreatic fat infiltration basing on echogenicity only, or on a grading system based on the aspect of the pancreatic duct and the presence of parenchymal "salt and pepper" dots[56,59].

Transabdominal ultrasound is cheap, fast and non-invasive, but the pancreas can't always be visualized, especially in obese patients. Another limitation of both transabdominal and endoscopic ultrasonography is that they are operator dependent.

More important, HP may not be a certain indicator of pancreatic fat infiltration, as a fibrotic pancreas is also hyperechogenic[60]. Therefore, it has been suggested that ultrasonography (US) shouldn't be used as a screening tool for pancreatic fat content, and that computed tomography (CT) or magnetic resonance imaging (MRI) should be the second step to confirm the diagnosis[9,60].

CT: CT imaging is widely used to study all abdominal organs. A fatty pancreas will be hypodense in hounsfield units (HU) compared to the spleen[39,67-69]. In severe fatty replacement, the attenuation can be compared with the adjacent retroperitoneal fat[42]. When the condition is severe, differentiation between lipomatosis and pancreatic agenesis can be made by evaluating the ductal system, which will be present in fatty replacement and absent in agenesis[44]. Unenhanced CT should be preferred, as the normal pancreatic parenchyma between fatty areas could exhibit contrast enhancement, and focal fatty replacement could simulate a true mass[70].

To validate CT for the diagnosis of pancreatic steatosis, Saisho *et al*[30] showed that the fat/parenchyma ratio calculated from CT is analogue to histological evaluation. Moreover, in 2014, Kim *et al*[39] found

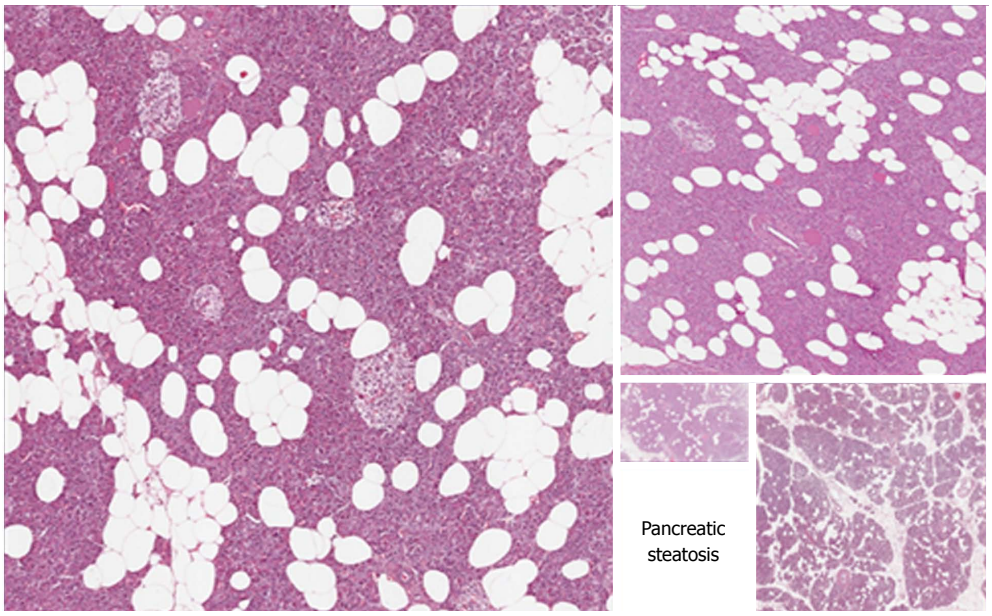

Figure 2 Pancreatic steatosis. Courtesy of Prof. Vasquez E and Dr. Angelico G, Anatomical Pathology Department, University of Catania -Catania, Italy.

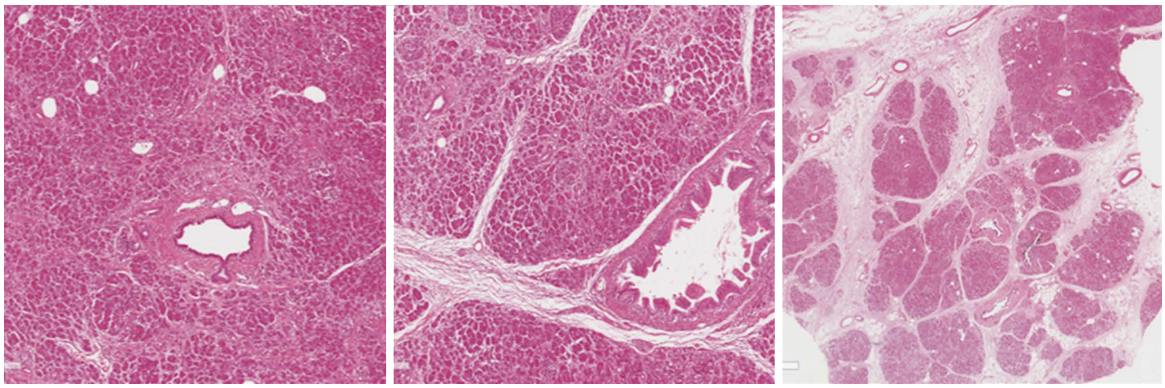

Figure 3 Normal pancreas. Courtesy of Prof. Vasquez E and Dr. Angelico G, Anatomical Pathology Department, University of Catania -Catania, Italy.

that pancreatic fat fraction in histological evaluation was significantly correlated with the difference between pancreatic and splenic attenuation ($P < 0.01$) and the pancreas-to-spleen attenuation ratio ($P < 0.01$).

The use of ionizing radiation limits CT as a research method, but recent evidence suggests that preoperative CT evaluation of pancreatic fat may be of importance in predicting the clinical outcome in pancreatic surgery, or as a prognostic marker for pancreatic adenocarcinoma[67,68,71].

MRI: MRI is sensible, noninvasive and safe. For those reasons, it's currently the most used method to study fat content of the pancreas, especially in prospective studies. Single-voxel magnetic resonance spectroscopy (MRS) is considered almost equivalent to histology and biochemical measurements, and therefore is currently the criterion standard for the determination of pancreatic lipomatosis[72-79].

There are several methods to measure pancreatic fat fraction (PFF) in the pancreas using MRI.

The most used method utilize the frequency shift between the water and the fat resonances to generate in-phase and opposed-phase images, in which the signal of the water and fat net magnetization vectors are at a maximum or a minimum[80].

The Dixon method consist of a post-processing of the in-phase and opposed-phase spin echo images that uses the chemical shift difference between protons in water and fat, leading to water-selective and fat-selective images[81]. However, the results can be affected by T1 and T2 relaxation effects[82]. The novel and fast two-point mDixon exhibits a good correlation with MRS for assessment of PFF, with limited sensitivity for assessing lower fat content[76].

Spectral-spatial excitation technique combine chemical shift selectivity with simultaneous slice-selective excitation in gradient-echo imaging sequences. Apparently, this method is as good as in-phase/opposed-phase imaging on determinate the PFF[80], and is particularly good for determining small amounts of fat[83].

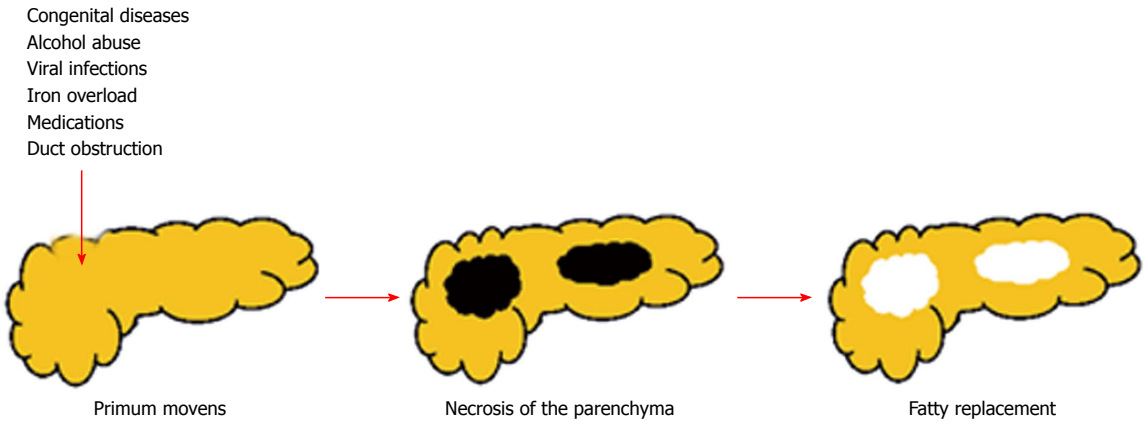

Figure 4 Pathogenesis of "fatty replacement".

A recently developed method is the three dimensional iterative decomposition with echo asymmetry and least squares estimation (IDEAL), which produces separated fat and water images, optimal in signal-noise ratio. Hu *et al*[73] reported that this method may be even superior to MRS in the measurement of PFF.

Finally, the newest automated intra-subject registration-based segmentation is potentially suitable for the quantification of abdominal and organ fat and achieves comparable quantitative endpoints with respect to manual segmentation[84].

EPIDEMIOLOGY

Only few epidemiologic studies have been performed to assess the prevalence of pancreatic steatosis. The estimated prevalence is between 16% and 35% in Asian populations[64,85,86].

In 2016, Pham *et al*[87] published the first study on which the prevalence of pancreatic steatosis was assessed in a pediatric population, which was 10%. However, this result may not be extended in general pediatric population, as it was assessed on hospitalized patients.

However, even considering the limits of those studies, all of them suggest a large prevalence in general population.

PATHOGENESIS AND RISK FACTORS

There are at least two mechanisms that can lead to a pancreatic fat accumulation[9]: (1) death of acinar cells and replacement by adipocytes - "fatty replacement" (Figure 4); and (2) fat accumulation associated with obesity and type 2 diabetes mellitus - "fatty infiltration" or "NAFPD".

Fatty replacement

Theoretically, any noxa strong enough to cause necrosis of the acinar cells can lead to fatty replacement[9]. Despite that, only little evidence can be found in literature.

Congenital diseases: Cystic fibrosis (CF) or mucoviscidosis is an autosomal recessive disorder. It is caused by the presence of mutations in both copies of the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR), involved in the production of pancreatic juice. CF results in a more dense pancreatic secretion, which eventually leads to pancreatic damage and replacement with adipocytes[88-101].

Shwachman-Diamond syndrome or Shwachman-Bodian-Diamond syndrome (SBDS) is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency with fatty replacement, bone marrow dysfunction, skeletal abnormalities, and short stature. The gene mutated in this syndrome is called SBDS, and its function is probably involved in RNA metabolism or ribosome assembly, although it's uncertain. Therefore, the pathogenesis of pancreatic damage is still unclear[51,102-108].

Johanson-Blizzard syndrome (JBS) is caused by mutations in the *UBR1* gene, which encodes one of several ubiquitin ligase enzymes of the N-end rule pathway. It is associated with developmental errors, impaired apoptosis, and both prenatal and chronic inflammatory damage, necrosis and fibrosis of the pancreatic acini. Pancreatic exocrine insufficiency in JBS can additionally stem from congenital replacement of the acini with fatty tissue[109-114].

Finally, heterozygous carboxyl-ester-lipase mutations are associated with fatty replacement of the pancreas and maturity onset diabetes of the young, probably due to a protein misfolding[55,115].

Those genetic conditions can also be associated with exocrine pancreatic insufficiency (EPI), as a result of the destruction of exocrine pancreatic parenchyma.

Alcohol abuse: It has been suggested that alcohol abuse may be associated with abnormal mitochondrial function, which may account for the fat accumulation observed in pancreatic acinar cells[116]. However, evidence don't support this theory, and it is more probable that alcohol abuse leads to pancreatic lipomatosis *via* acute and/or chronic pancreatitis and/or

the upregulation of transcription factors involved in the synthesis of cholesterol and triglycerides[12,13,57,59,116-118]. Also, alcoholism is associated with malnutrition, which is also a cause of pancreatic steatosis[13].

Viral infections: Viral infections with Reovirus, may lead to duct obstruction and therefore necrosis of the parenchyma and subsequent substitution with fatty tissue[9,49,119]. In support of this pathogenic pathway, pancreatic duct legation actually leads to fatty replacement[120,121].

Iron overload: The most important causes of iron overload are hereditary hemochromatosis, a genetic disorder, and transfusional iron overload, which can result from repeated blood transfusions. Iron mainly accumulates in reticuloendothelial system, liver, heart, and endocrine or exocrine glands, pancreas included. When the pancreas is involved, iron leads to oxidative stress of acinar and islet cells, apoptosis and substitution with adipocytes. This has been described in patients with transfusion-dependent diseases as myelodysplastic syndrome and cooley's anemia (β-thalassemia major)[122-125].

Medications: Although it's theoretically valid, evidence that medications can cause pancreatic tissue necrosis and subsequent substitution with fatty tissue is scarce and mainly based on case reports or animal models. drugs reported are corticosteroids, gemcitabine, rosiglitazone and, more recently, octreotide[17,49,126-130].

Chronic liver disease: Yoshimura *et al*[131] and Sasaki *et al*[132] suggested that lipomatous pseudohypertrophy of the pancreas might be caused by chronic advanced hepatic lesions, which lead to ductal obstruction. Thus now, only case reports of patients with chronic hepatitis B and liver cirrhosis support this hypothesis[49,132,133].

Stronger evidence exists that pancreatic steatosis is associated with NAFLD[33,56,57,59,64,75,134-137]. However, the pathogenesis of this association is more likely due to metabolic pathways than pancreatic injury, and it will be discussed in the appropriate section.

Malnutrition: Malnutrition, as seen in alcoholism, kwashiorkor and AIDS is associated with changing in pancreatic structure, including pancreatic lipomatosis[13,29,138]. However, the lack of evidence makes the pathogenesis still unclear.

Pancreatitis: It is theoretically possible that necrotizing pancreatitis leads to fatty replacement, but, to our knowledge, this association has never been reported. In contrast, Recurrent Acute Pancreatitis (RAP) may lead to reduction of the parenchymal mass and substitution with adipocytes[139-141]. Moreover, an increased number of intrapancreatic adipocytes can be observed in pancreata of lean patients with nonhereditary or hereditary chronic pancreatitis[142-144].

Moreover, NAFPD has been associated with an increased risk of developing severe acute pancreatitis, as discussed in the appropriate section.

Nonalcoholic fatty pancreas disease

The most important risk factor for developing NAFPD is obesity. This relation was suggested in the first study by Ogilvie and has been widely confirmed[145]. Experimental models report that maternal obesity and postnatal obesogenic diets can result in a NAFPD by inducing an endoplasmic reticulum imbalance and alteration in circadian metabolic patterns[25,146]. In addition to obesity, studies on sufficiently wide populations (> 1000 subjects) suggest also increasing age, male sex, hypertension, dyslipidemia, alcohol consumption, low serum lipase activity as important risk factors, although data must be considered still insufficient[30,64,86,147]. T2DM and NAFLD are often reported as risk factor. However, data are sometimes contrasting, as further discussed. Wong *et al*[148] found also a positive correlation between fatty pancreas and hyperferritinemia.

Recently, different ethnicity has been suggested as an independent risk factor of developing pancreatic steatosis. Hispanics and Caucasians showed an increased risk to develop pancreatic fat infiltration than the African Americans[149,150]. More important, PFF may predict the outcome of insulin resistance in African Americans, but didn't show the same accuracy for Hispanics[151]. However, more research is needed.

The relation with age and low serum lipase activity is probably due to a fatty degeneration of the pancreas, which may be considered paraphysiological[147,152].

How obesity leads to ectopic fat (EF) accumulation is not clear yet. Some individuals are more susceptible to accumulate EF for Body Mass Index (BMI). Although it may seem paradoxical, it has been suggested that those patients may have an impaired subcutaneous fat storage capacity, which leads to visceral and ectopic fat accumulation. An extreme example of this phenomenon is Lipodystropy, also known as Berardinelli-Seip syndrome (BSS). Patients with BSS have a scarce subcutaneous fat storage, but a greater amount of visceral and ectopic fat. On the other hand, several studies prove that healthy individuals with high subcutaneous fat content have low levels of visceral and ectopic fat. Subcutaneous fat may even have a protective action regarding ectopic fact accumulation[153]. In an experimental model, transplantation of normal adipose tissue in the subcutaneous region of lipoatrophic mice, removes their excess of EF and insulin resistance[154].

More efforts have been made to explain ectopic fat accumulation in the liver (NAFLD). It has been hypothesized that insulin resistance facilitates the transport of free fatty acids (FFA) from adipose tissue to the liver, and their storage in hepatocytes. Steatosis occurs when the rate of import and fatty acid synthesis

exceed the rate of export and catabolism[155].

An interesting finding of a prospective study on 293 patients[56] is that about 68% of cases with fatty pancreas concurrently had fatty liver, but most subjects (97%) with fatty liver had fatty pancreas. Although the positive predictive value of fatty liver in fatty pancreas was 69.4%, the negative predictive value of fatty liver in normal pancreas was 96.4%. Our group is currently involved in a retrospective CT-based study which preliminary results on 47 patients lead to the same results (Catanzaro R, Cuffari B, Palmucci S et al, unpublished). This implies that fatty pancreas could be used as the initial indicator of EF deposition.

As NAFLD and NAFPD are often associated, one could assume that they could share a common pathway[33,56,57,59,64,75,134-137].

Actually, important information must be taken in account: (1) some studies have found no correlation between NAFLD and NAFPD[80,156]; (2) hepatic fat is mainly intracellular, while NAFPD is a consequence of adipocytes infiltration[5,16]; (3) when patients are treated with bariatric surgery, fat loss in the liver and the pancreas seem to be independent, suggesting tissue-specific mobilization of these ectopic fat stores[77]; and (4) when corrected for BMI, the association between hepatic and pancreatic steatosis can't be found anymore[33,134,137].

It could be correct to assert that, according with current evidence, the association between NAFLD and NAFPD is a consequence of obesity only. Therefore, hypothesis used to explain hepatic steatosis may not be suitable for NAFPD. However, it is possible that pancreatic and hepatic steatosis affect each other and more research should focus on the different pathways that lead to one or the other condition[135,157].

In conclusion, the pathogenesis of NAFPD is still unknown, and no satisfactory theories have been proposed yet. Therefore, more research will be needed.

CLINICAL SIGNIFICANCE

T2DM

About 347 million people worldwide have T2DM, and numbers are increasing[158]. The WHO projects that diabetes will be the seventh leading cause of death in 2030[159].

Since T2DM is increasing problem worldwide, and pancreatic islets have a key role in the metabolism of glucose, one of the main issues in NAFPD research is whether or not pancreatic steatosis is a risk factor for T2DM.

In vitro and animal studies suggest that pancreatic lipomatosis may contribute to β-cell lipotoxicity and lipoapoptosis, with consequent loss of function[160-162]. However, data on humans are inconsistent.

Using proton MRS and oral glucose tolerance tests, Tushuizen *et al*[163] found that pancreatic fat correlated negatively with β-cell function parameters in nondiabetic subjects. Heni *et al*[156] found the same association in patients with impaired glucose metabolism and, in a stepwise multivariate regression analysis, pancreatic fat resulted a stronger determinant of impaired insulin secretion than visceral fat. More recently, Della Corte *et al*[157] found a positive correlation between NAFPD and homeostatic model assessment - insulin resistance (HOMA-IR) in a pediatric population with NAFLD. In contrast with these results, two studies performed using the gold standard hyperglycemic clamp, found no relation between pancreatic fat content and β-cell function in subjects with impaired glucose metabolism[74,164].

Data about patient with full-blown T2DM are even more challenging. Tushuizen *et al*[163], found no association between pancreatic fat and β-cell dysfunction in diabetic patients. That may suggest that once diabetes occurs, other factors cause further β-cell impairment. However, they found that diabetic subjects had a significantly higher pancreatic fat content than nondiabetic, association confirmed by Lingvay *et al*[72].

Saisho *et al*[30], using computed tomography on 1721 nondiabetic and 165 subjects with T2DM, observed that pancreatic fat was not significantly increased in T2DM.

Wang *et al*[64], in 2014, studying a cohort of 8097 subjects, found that the fatty pancreas group had an increased risk of diabetes (OR = 1.593) than non-fatty pancreas group ($P < 0.001$).

Finally, a recent study[165] found a significant higher average fat content in the pancreas of patients with newly diagnosed T2DM compared with healthy controls.

Summarizing, three hypotheses can be made about β-cell dysfunction in pancreatic steatosis: (1) the increased amount of triglycerides in pancreatic β-cells can lead to their dysfunction, probably with a mechanism of lipotoxicity, at least in subjects with an already impaired glucose metabolism; (2) intrapancreatic adipocytes may have a negative paracrine effect on β-cells; and (3) NAFPD and T2DM are just consequences of obesity.

According to current evidence, the majority of the authors support the last theory, but more research should focus on this topic and meta-analysis will be required[145].

MetS

The MetS is a major and increasing clinical and social issue worldwide, as a result of changing in lifestyle which include high-caloric and high-fat diet and decreasing physical activity. MetS is associated with a 5-fold increase risk of T2DM, 2-fold risk of developing cardiovascular disease, 2- to 4-fold increased risk of stroke, 3- to 4-fold increased risk of myocardial infarction, and 2-fold mortality caused by coronary events[3].

NAFLD is considered the hepatic manifestation of

MetS. High levels of FFA and insulin resistance are considered key pathogenic factors in the development of fat accumulation in the liver[3].

There is an increasing evidence of association between NAFPD and all the components of the MetS in animal models and humans[20,56,59,62,148,166].

Weather pancreatic steatosis is a key organ in the development of the MetS or just a marker or that condition (mediated by general obesity), we believe that the assessment of pancreatic fat infiltration will have an increasing role in the clinical management of the syndrome.

Cardiovascular risk

As discussed, MetS itself is associated with an increased incidence of cardiovascular diseases. Recently, one study[167] found that pancreatic steatosis may be an independent risk factor on the development of carotid atherosclerosis in non-obese subjects with T2DM. Therefore, it could be a marker of a higher risk of cardiovascular disease, especially in non-obese subjects.

Acute and chronic pancreatitis

Obesity and the MetS are associated with the incidence and severity of acute pancreatitis[168-171]. Thus now, this association was explained by the fact that both obesity and the MetS are linked with other well-known risk factors for acute pancreatitis, such as gallstones, alcohol abuse, cancer, hypertriglyceridemia, use of medications, moreover, as already pointed out, the MetS may be associated with a pro-inflammatory state which may exacerbate inflammation after the trigger is pulled[172].

There is speculation that pancreatic steatosis may have a key role in the pathogenesis of pancreatitis in obese patients. In analogy with NAFLD leading to non-alcoholic steato-hepatitis (NASH), the term non-alcoholic steato-pancreatitis (NASP) has been proposed[48].

The existence of NASP has not been proved yet, but there is biological plausibility, and evidence is increasing. Adipocytes may generate a local and systemic pro-inflammatory state by producing pro-inflammatory adipokines and cytokines, such as leptin, interleukin 1β and tumor necrosis factor, or toxic fatty acids that may make the pancreas more susceptible to inflammation[28,157,173].

Pokhrel *et al*[174] found that increased pancreatic fat on MRI was not an independent predictor of post-ERCP pancreatitis, however, data is scarce and more research will be required.

An excellent review by Acharya *et al*[175] points out that intra-pancreatic fat have a role in the severity of acute pancreatitis: lipases released by acinar cells after the first injury, cause a local and systemic lipolysis, which results in increasing of FFAs, especially unsaturated fatty acids (UFAs). The spread of UFAs in the pancreatic parenchyma has a direct toxic effect on acinar cells (lipolytic flux), causing acinar necrosis. In post-mortem studies, more severe necrosis of the parenchyma occurred closer to necrotizing fat (peri-fat acinar necrosis: PFAN)[143,176]. In 2011, Smits and van Geenen[9] published preliminary results of a CT-based study that show a significant relationship between pancreatic steatosis and severity of pancreatitis ($P < 0.03$). The use of lipases inhibitors (Orlistat) to prevent conversion of mild into acute pancreatitis may be therefore justified and studies are evaluating its efficacy, with encouraging results[177].

As already discussed, RAP can cause chronic pancreatitis and morphological changes, which include fatty replacement. However, no evidence exists that NAFPD can cause chronic pancreatitis.

Pancreatic fibrosis

Chronic liver inflammation as seen in NASH, leads to necrosis of hepatocytes and liver fibrosis. Theoretically, in the pancreas, NASP could determinate the same changes, but data are inconsistent.

Matsuda *et al*[26], found that in Zucker Diabetic Fatty rats fed with a chronic high-fat diet, fat accumulates in pancreatic acinar cells, and this fatty change seems to be related to subsequent pancreatic fibrosis and acinar cell injury. However, in Ossabaw swines, another animal model for the MetS, pancreatic steatosis was not associated with other histological abnormalities[20].

In humans, patients with chronic pancreatitis have both an increased amount of pancreatic fat and fibrosis, however, van Geenen *et al*[35]. found no relationship between pancreatic fibrosis and NAFPD ($P = 0.916$) in a study over 900 autopsies, and Mathur *et al*[31] found that pancreatic fat correlated even negatively with fibrosis ($P < 0.001$).

Therefore, according to current evidence, fatty replacement and pancreatic fibrosis seem to be both independent consequences of chronic inflammation in patients with chronic pancreatitis.

Pancreatic cancer

Several studies show that obesity is one of the leading risk factors for pancreatic cancer (PC)[178-184]. However, the pathophysiological pattern of this association is not clear yet. Several mechanisms have been discussed[172]: Evidence exists that the increase of certain hormones in obese patients, such as insulin, adipokines and resistine and systemic oxidative stress may have a role in the development of pancreatic adenocarcinoma[172,185-188].

NAFPD has been independently associated with an increased risk to develop PC[38]. A recent study[40] observed a correlation between pancreatic intraepithelial neoplasia (PanIN) and extra- ($P < 0.01$) and intralobular ($P < 0.0001$) pancreatic fat. No clear metabolic pathways have been identified to explain this association, but speculation is possible.

The increased numbers of adipocytes in NAFPD could promote cancerogenesis indirectly by NASP, as occurs in the liver[9].

Persistent organic pollutants (POPs) are lipophilic toxics able to bio-accumulate in fatty rich tissues of animals, especially those higher in the food chain, humans included. Evidence exists that accumulation of POPs in adipose tissue may be associated with PC occurrence, and it is possible that a higher concentration of pancreatic fat, and consequently of POPs, can partially explain the linkage between NAFPD and PC[172].

Along with an increased risk to develop PC, patients with increased pancreatic fat have a poorer outcome than those who develop cancer in a lean pancreas. In particular, NAFPD promotes dissemination and lethality of PC[32,67]. Mathur *et al*[32] suggested that "pancreatic steatosis alters the tumor microenvironment, enhances tumor spread, and contributes to the early demise of patients with pancreatic adenocarcinoma".

In addition, pancreaticoduodenectomy in patients with fatty pancreas is associated with an increased risk of intraoperative blood loss and post-operative pancreatic fistula, which contributes with the poor outcome in those patients[31,34,37,50,68,71,189-191]. Therefore, assessment of pancreatic steatosis by preoperative CT or MRI or intraoperative histological evaluation on the frozen sections may have a role, in the future, in the prognostic evaluation of patients with PC[37,67,68,71,189,190].

Pancreatic transplant

The first pancreatic transplant was performed in 1966 in the United States[192]. It is a very effective and yet the only definitive option for curing insulin-dependent diabetics. However, the spreading of this technique is restricted by the significant rate of surgical complications resulting in graft failure/loss and recipient morbidity and mortality.

Increasing obesity and age, of both recipient and donor, increase the risk of technical complications like graft pancreatitis, graft thrombosis, intra-abdominal infections, gangrene and pancreatic fistula. However, if the transplantation is successful, there is not an increased risk of allograft failure[193,194]. Older patients with higher BMI are more likely to have steatosis, and that could explain the association.

Certain transplant surgeons do not use pancreas that are infiltrated by fat on inspection, since the procedure is technically more difficult when using a fatty pancreas, but a more objective measurement could avoid to waste organs that would be suitable for transplant. Verma *et al*[11] propose the IDEAL scanning on the sole organ as a possible solution. Furthermore, "defatting" of the organ is possible and a successful case has been reported in 2004[195].

Pancreatic hyperenzimemia

In 1996, Gullo *et al*[196] first reported a benign syndrome characterized by increased levels of serum amylase, pancreatic isoamylase, lipase and trypsin. This condition is nowadays called Gullo's syndrome and has been better characterized[196,197].

Cavallini *et al*[198], in a US based study, found that HP was related with hyperamylasemia. However, Gullo *et al*[54] found no correlation in a MRI based study. More recently, Wu *et al*[62] found that amylase levels in patients with pancreatic lipomatosis were even lower than controls.

Exocrine function

In theory, pancreatic steatosis can lead to EPI with different mechanisms: (1) fat droplet accumulation in acinar cells and consequent lipotoxicity; (2) negative paracrine effect mediated by adipocytes; and (3) death of acinar cells as cause of both EPI and fatty replacement.

However, the exocrine function in patients with NAFPD has never been extensively investigated. Therefore, data are mainly based on case reports of extreme cases of complete fatty replacement of pancreas with fatty tissue[36,52,199-201].

In one recent study[202], fecal level of pancreatic elastase (PE-1) was evaluated in patients with T2DM. EPI was more frequent in patients with high HbA1c, but did not correlate with pancreatic steatosis.

THERAPY

Since NAFPD has been only recently extensively studied and its clinical significance is not clear, no clinical trials have validated any medications yet. Anyway, evidence exist that it is reversible.

Pancreatic fat can be reduced by weight loss, with or without bariatric surgery, and that is associated with improvement of insulin sensibility[203].

Moreover, specific treatment showed efficacy *in vitro* or on murine models: (1) Troglitazone[204]; (2) combination of Telmisartan and Sitagliptin[21]; and (3) Berberine and Cinnamic Acid, as components in Jiaotai Pill, a traditional Chinese medication[27,205].

We hope that increasing evidence on the clinical significance of pancreatic steatosis will support further research.

CONCLUSION

Pancreatic steatosis, which comprehends fatty replacement and fatty infiltration of the pancreas, is a very common condition, easily diagnosable but often neglected by physicians and researchers.

Its clinical significance ranges widely in Internal Medicine and Surgery, and more correlations may be found in future. Nevertheless, evidence is not exhaustive and the pathophysiology is yet unknown.

We believe that, according to current literature, pancreatic steatosis should have stronger consideration

in clinical practice, in particular: (1) as an early marker of ectopic fat accumulation and insulin resistance in the MetS; (2) in the differential diagnosis with pancreatic fibrosis, especially when the pancreas is observed with US or EUS; (3) as a prognostic and/or predictive marker for acute pancreatitis and PC; (4) in pre-operatory evaluation before pancreaticoduodenectomy or pancreatic transplant; and (5) as a possible cause of unexplained exocrine pancreatic insufficiency.

More research, in future, should focus on the clinical consequences of pancreatic steatosis, in order to understand its impact on human health, its patho-physiology and eventually support clinical trials.

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P- Reviewer: Antonini F, Peng SY **S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Ma S

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ISSN 1007-9327