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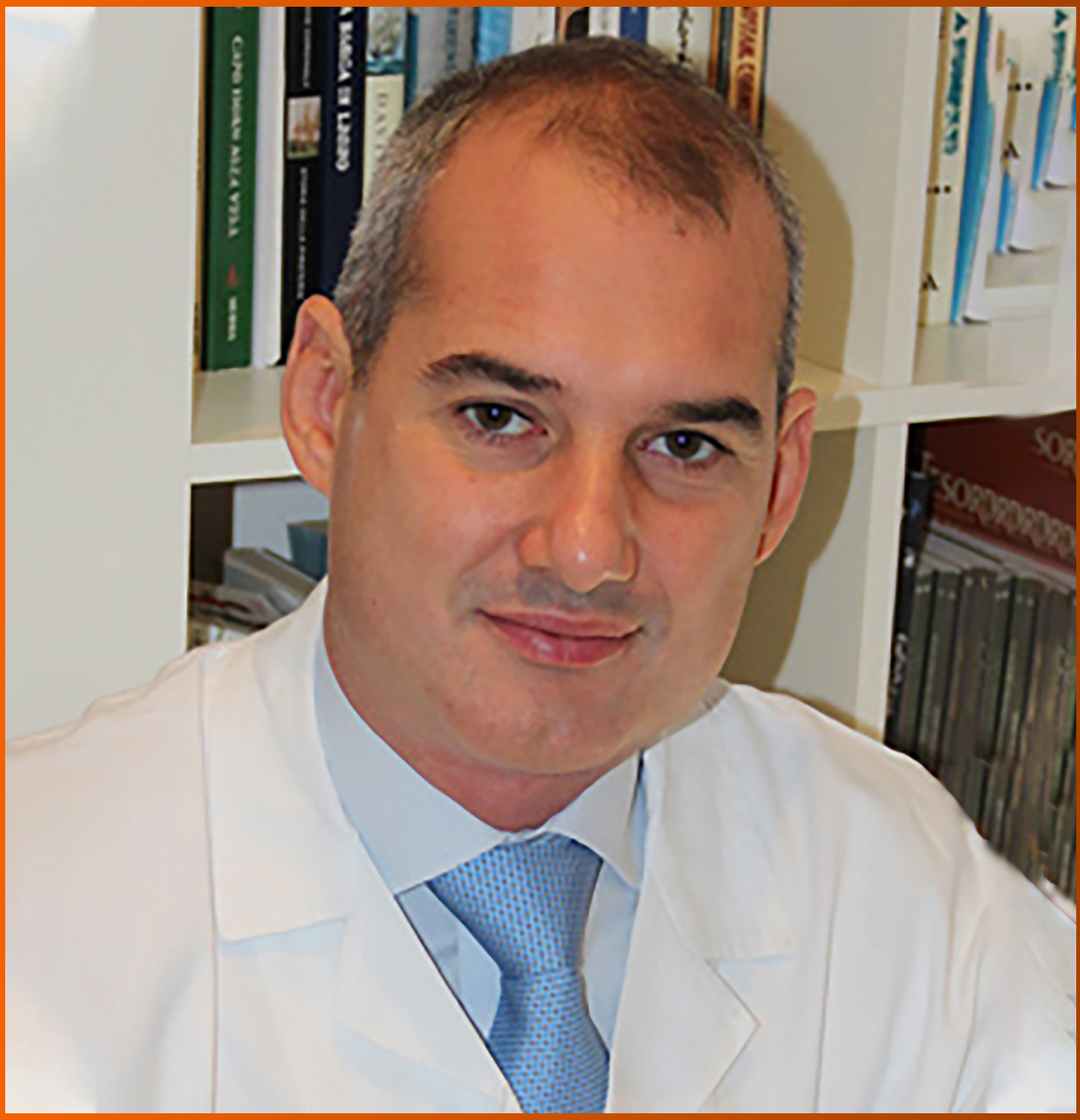

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REVIEW

Nonalcoholic fatty pancreas disease: An emerging clinical challenge

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Abstract

Nonalcoholic fatty pancreas disease (NAFPD) is an emerging disease that has gained an increasing amount of attention in recent years. It describes fat accumulation in the pancreas with insignificant alcohol consumption, but the pathogenesis is largely unknown. A wide range of terms have been used to describe the phenomenon of pancreatic fat accumulation, but NAFPD remains an under-recognized and non-independent disorder. Obesity, age, sex, race, and unhealthy lifestyle are established independent risk factors for NAFPD, which is strongly associated with metabolic syndrome, type 2 diabetes, pancreatitis, pancreatic fistula, pancreatic cancer, and nonalcoholic fatty liver disease. At present, imaging techniques are common diagnostic aids, but uniform criteria and consensus are lacking. Therapeutically, healthy diet, weight loss, and exercise are the mainstays to reduce pancreatic fat accumulation. It can be seen that there is a limited understanding of NAFPD at this stage and further exploration is needed. Previous studies have revealed that NAFPD may directly affect diagnosis and clinical decision-making. Therefore, exploring the pathophysiological mechanism and clinical associations of NAFPD is a major challenge for researchers and clinicians.

Key Words: Nonalcoholic fatty pancreatic disease; Pancreatic steatosis; Obesity; Metabolic syndrome; Pancreatic disease; Pancreas

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Core Tip: Just as obesity is a global problem, nonalcoholic fatty pancreas disease (NAFPD) has attracted an increasing amount of attention from researchers and clinicians. In this review, we have summarized the recent progress of NAFPD, including risk factors, pathogenesis, diagnosis, and clinical consequences. The value of NAFPD as early indication of diagnosis and intervention in patients with metabolic syndrome, type 2 diabetes, and pancreatitis is important. In the future, it is reasonably expected that large cohort and multi-center basic and clinical research can deepen our knowledge of NAFPD, so that the early diagnosis and treatment of NAFPD and clinical associations can be made possible.

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INTRODUCTION

Obesity has become the most important global health problem, with the proportion of obese people increasing at an unprecedented rate. Overweight in adults is defined by the World Health Organization as body mass index (BMI) ≥ 25 kg/m^2, and obesity as BMI ≥ 30 kg/m^2. As of 2016, > 1.9 billion adults were overweight, > 650 million were obese, and at least 2.8 million deaths were occurring yearly from overweight or obesity. Multiple comorbidities associated with obesity result in a global health burden and exhibit a variety of disorders, including metabolic syndrome (MetS), cardio/cerebrovascular diseases, psychiatric disease, and malignancy[1,2]. Recently, studies have focused on ectopic fat deposition in organs induced by obesity, known as steatosis[3,4]. Large studies have investigated hepatic fatty infiltration, which contributes to the 30% prevalence of nonalcoholic fatty liver disease (NAFLD)[5,6]. Continuous progression of NAFLD may lead to nonalcoholic steatohepatitis (NASH), cirrhosis, and liver cancer. Although NAFLD has been extensively researched and its relationship with metabolic disorders has been determined, ectopic fat accumulation in the pancreas and its clinical significance have received little attention until recently.

Correlation between pancreatic weight and total body weight was first described by Schaefer in 1926[7]. The concept of pancreatic steatosis was first described in 1933 when Ogilvie[8] observed that the quantity of pancreatic fat was double in obese individuals compared with that in nonobese individuals. Years later, Olsen[9] found an increased amount of pancreatic fat in a direct relationship to age after an autopsy study of 394 cases. Subsequently, Stamm[10] reached the same conclusion and found a significant relationship between pancreatic steatosis and the risk of type 2 diabetes mellitus (T2DM) and atherosclerosis when the pancreatic fat content was > 25%. Several synonyms have been used for pancreatic fat accumulation (Table 1) (adjusted according to Smits and van Geenen[11] and Tariq *et al*[12]). Nonalcoholic fatty pancreas disease (NAFPD) is defined as pancreatic fat accumulation associated with obesity and absence of significant alcohol consumption[11]. Significant alcohol consumption is considered to be > 20 g/d.

Epidemiological data are not numerous due to the lack of standardized tests. The prevalence of NAFPD ranges from 16% to 35% in Asians[13]. A study of 4419 Chinese adults found a prevalence of NAFPD of 11% and a higher incidence with age and a gender difference in adults < 55 years[14]. A meta-analysis, pooling data on NAFPD from 11 studies (12675 individuals), yielded a prevalence of 33% (95% confidence interval, 24%-41%)[15]. Although epidemiological data are scarce, such a high prevalence cannot be ignored. A cross-sectional study from Medistra Hospital, Jakarta showed that NAFPD had significant associations with metabolic factors such as fasting plasma glucose, triglyceride (TG), and cholesterol levels, which might play an important role in the risk of malignancy[16]. NAFPD is strongly associated with metabolic risk factors as a significant manifestation of MetS and obesity[17]. Currently, with the development and application of advanced diagnostic techniques, clinical data on NAFPD will be widely acquired and receive more attention.

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 steatopancreatitis.

RISK FACTORS AND PATHOGENESIS

To this day, several risk factors of NAFPD have been identified, with obesity being widely accepted as the most important[18]. Under the condition of obesity, two mechanisms contribute to pancreatic fat accumulation. The first is called fat replacement, in which dead acinar cells are substituted by adipocytes. The second is called fat infiltration, which refers to fat accumulation[11]. Experimental studies in mice have shown that maternal obesogenic diets during pregnancy and lactation induce alterations in endoplasmic reticulum stress, such as the unfolded protein response, and also lead to alterations in circadian metabolic patterns through biological clock-molecular core circadian genes, resulting in NAFPD[19,20].

In addition to obesity, age is another significant risk factor. Epidemiological studies have shown a positive association between age and NAFPD[14,21], and men may have a higher risk of NAFPD[22]. This does not mean, however, that the risk of NAFPD in children can be overlooked[23]. As a major associated disease, NAFLD has been implicated as a significant risk factor leading to NAFPD. A study of 293 patients with NAFPD found a 67.9% concurrence rate with NAFLD and a negative predictive value for NAFLD of 96.4% with a normal pancreas[22]. Multiple regression analysis concluded that NAFLD is the strongest predictor for NAFPD[24]. There appears to be a link between NAFPD and NASH, with 50% of NASH patients suffering from NAFPD[25]. A previous study indicates that NAFPD is significantly associated with advanced fibrosis but not NASH. The authors stated that NAFPD is a safe, inexpensive index to rule out advanced fibrosis as the negative predictive value of NAFPD for advanced fibrosis is 93%[26]. In addition to this, hypertension, lower serum lipase activity, hyperferritinemia, and lifestyle factors (*e.g.*, sedentary, smoking, and frequent meat consumption) might be relevant for NAFPD[24,27-31].

With regard to NAFPD pathogenesis, some evidence indicates that NAFPD may be associated with adipocyte-derived inflammatory factors, especially those induced by free fatty acids (FFAs). The expression of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein-1 increase in rats with FFA-induced hyperlipidemia, and the levels of body and epididymal fat increased significantly[32,33]. Treatment of SZ95 sebocytes with palmitic acid, a major saturated FFA, resulted in a significant increase in intracellular fat levels and upregulated expression of IL-6 and IL-8 messenger RNA, as well as secretion of these inflammatory cytokines[34]. Similarly, palmitic acid induces monocyte chemoattractant protein-1 secretion and monocyte infiltration in renal tubular epithelial cells, which aggravates the inflammatory response[35]. However, not all FFAs have the same effect, which may be due to the differences in unsaturated double bonds and spatial conformation. A recent study has shown that saturated fatty acids (palmitic acid) and polyunsaturated fatty acids (γ-linolenic acid and arachidonic acid) have minor effects on the gene expression of inflammatory factors (IL-6, TNF-α, and cyclooxygenase-2) in peripheral blood mononuclear cells, while monounsaturated fatty acids (oleic acid), polyunsaturated fatty acids (α-linolenic acid), and docosahexaenoic acid decreased the gene expression of inflammation[36]. In addition, pancreatic fat accumulation and inflammatory response are aggravated in splenectomy-treated obese mice, which are inhibited by targeted administration of anti-inflammatory cytokine IL-10[37]. Overexpression of serine/threonine protein kinase 25 in transgenic mice exacerbates high-fat-diet-induced pancreatic fat accumulation and is accompanied by inflammatory cell infiltration, apoptosis, and a marked decrease in islet β/α-cell ratio[38]. Current research is focusing on epidemiology and clinical complications of NAFPD, but there is a lack of fundamental research literature on genetics and molecular mechanisms. This could be

related to the lack of clear awareness, and more comprehensive and in-depth research is needed.

DIAGNOSIS OF NAFPD

Given pancreatic fat accumulation as the dominating feature of NAFPD, histological biopsy is the gold standard for diagnosis[39-42]. A meta-analysis of mean pancreatic fat content in healthy volunteers suggested that a cutoff point of 6.2% may be recommended to distinguish normal pancreatic tissue from pancreatic fat accumulation[15]. It is unclear whether the normal state is lower than 6.2%, and whether 6.2% can be considered as the threshold NAFPD associated diseases (such as NASH). More studies with larger sample sizes are needed to determine the rationality, and further prospective studies are required to validate the applicability of this threshold. More importantly, due to the complex anatomical location of the pancreas and invasive operation, histological biopsy is inadequate for routine clinical applications, likely conferring adverse outcome in patients. Additionally, the inhomogeneity of pancreatic fat accumulation has been suggested in imaging studies[43], causing challenges in sampling and analysis of histological biopsy.

Consequently, noninvasive diagnostic methods for NAFPD may be the optimal way for clinical application. Transabdominal ultrasonography (TUS) is a widely available method with low cost and risk. The pancreas can be partially visualized with TUS because of gas inside the gastrointestinal tract. At the same time, this is also a challenge in obese patients to exhibit an apparent pancreas[44]. Pancreatic fat accumulation appears hyperechoic as compared with liver or kidney accumulation, a reference point for diagnosis[45,46]. Some studies have established that echogenicity of retroperitoneal fat suggests a higher amount of pancreatic fat deposition, using a grading system[22,25,7]. However, another limitation is that pancreatic fibrosis may also appear hyperechoic, which does not necessarily indicate pancreatic fat accumulation[48-50].Until now, there is no generally accepted method for quantitative assessment of pancreatic echotexture[51]. Endoscopic ultrasonography (EUS), as an invasive method, provides better assessment of the pancreas and has other features, such as biopsy and elastography, overcoming the visual and anatomical barriers of TUS[52]. However, it would not be appropriate to diagnose pancreatic fat accumulation solely on EUS, and further investigations of clinical implications need to be highlighted.

Computed tomography (CT) is considered to be a preferred imaging technique for abdominal organs and has a wide variety of clinical applications. Hounsfield units (HUs) are used to measure the severity of pancreatic fat accumulation, showing low-density compared with the spleen[53]. CT without contrast is recommended because the pancreatic parenchyma absorbs the contrast medium and is suspected to be a solid lesion[54]. The threshold of pancreatic fat accumulation is proposed to be 36 HU[55], but it has not gained wide acceptance[22,55,56]. However, pancreatic fat accumulation is usually not evenly distributed, posing difficulty in distinguishing fat in adipocytes from parenchymal cells, and it may not be able to assess accurately pancreatic fat content[57]. A previous study has found that CT using fat/parenchyma ratio is a reliable method[58], but further clinical data are needed for verification.

Magnetic resonance imaging (MRI) is an imaging technique combining spatial, anatomical, and quantitative data. Its signal arises from water and fat molecules within different organs, producing small differences in the resonance frequencies, thereby allowing quantification. MRI has many advantages as a diagnostic method, given its noninvasiveness, safety, and high sensitivity, and is applicable in to children [59]. In this way, MRI is the preferred method for diagnosis of pancreatic fat accumulation[60,61]. Proton magnetic resonance spectroscopy (1H-MRS) is considered to be the gold standard for noninvasive quantitative assessment of pancreatic fat accumulation. It deduces the spectrum of proton signaling by MRS acquired using point-resolved spectra or stimulated echo acquisition mode sequencing, and its diagnostic accuracy is comparable with histology[62,63]. However, the smaller size of the pancreas and inaccurate positioning while breathing might lead to detection errors. MRI chemical-shift imaging acquires the imaging signals using the chemical shift between water and fat within different organisms, completing detection in a single breath hold and thereby reducing errors due to breathing[64-66]. In recent years, based on the reconstruction algorithm, a new technique called iterative decomposition of echo asymmetry of water and fat with least squares estimation (IDEAL) has been developed. IDEAL can be used for evaluation of pancreatic fat content with accuracy

and less signal contamination. It has been validated in animal models and is expected to replace MRS as the gold standard for quantifying pancreatic fat accumulation[59,67]. MRI proton density fat fraction (MRI-PDFF) is one of the state-of-the-art techniques, which addresses limitations of multipoint Dixon quantification and allows accurate quantification of pancreatic fat accumulation[68]. A previous study has suggested a diagnostic cutoff value for NAFPD of 10.4% using MRI-PDFF[29]. Currently, this approach has been applied not only to the pancreas but also to adjacent parenchymal organs in quantitating fat content[68].

Magnetic resonance elastography (MRE) can provide a quantitative assessment of the elasticity and structure of tissues by collecting dynamic propagation signals of vibration waves. MRE is now used for evaluating fibrosis, inflammation, and edema of tissues. This is the most accurate method for assessing hepatic fibrosis and correlates well with histological staging of fibrosis[69-71]. As mentioned earlier, the anatomical location and size of the pancreas can create challenges for the operator. MRE might be used as a noninvasive tool for detecting pancreatic fat accumulation, enhancing the ability to distinguish between pancreatic and retroperitoneal fat[72]. In previous MRE studies, the better credibility and repeatability of investigating pancreatic tissue have been identified[72]. However, there has been no relevant study on MRE evaluation of pancreatic fat accumulation. As mentioned above, it would not be appropriate to diagnose pancreatic fat accumulation solely by EUS. To complement EUS, elastography *via* EUS has been developed to evaluate pancreatic tumors and lymph nodes that are hard to reach. This adds dynamic quantification of elasticity of the target tissue, differentiates benign and malignant tissue, and predicts the exocrine dysfunction of chronic pancreatitis[69]. Clinical practice guidelines for pancreatic elastography have been published[73]. The high precision of pancreatic elastography will improve with continued technological advancement.

Although the imaging techniques mentioned above can be used to evaluate pancreatic fat accumulation, the limited research has limited their clinical use[74]. Moreover, further studies on the indications, sensitivity, specificity, and cut-off values of these imaging techniques are awaited. The latest developed technique of organ segmentation is promising for evaluating the distribution of interlobular and intralobular septal pancreatic fat[75]. However, whole-organ segmentation and automatic analysis have greater trouble in technology.

CLINICAL CONSEQUENCES OF NAFPD

MetS

Unhealthy lifestyle and eating habits lead to the increasing prevalence of MetS. MetS is a group of complex metabolic perturbations, consisting of abdominal obesity, insulin resistance, hypertension, hypertriglyceridemia, and low plasma high-density lipoprotein–cholesterol levels; three of which must be fulfilled for diagnosis of MetS [76]. The risk of diabetes and cardiovascular disease are at high levels in individuals with MetS, which is closely correlated with progression of NAFLD. In recent years, several reports have revealed that a correlation exists between NAFPD and MetS and suggest that it must be part of the definition of MetS[77-79]. Altered metabolism of fatty acids, induced by abdominal obesity, is a risk factor for cardiovascular disease and gastrointestinal disorders, including of the pancreas[80,81]. Whether the association of NAFPD and MetS is directly causal, or is a result of obesity, remains unclear and awaits further investigation.

Endocrine dysfunction

Obesity is a widely accepted significant risk factor for T2DM[82]. The fact that obesity has become a top global health problem may also explain, to some extent, the increasing incidence of T2DM[83]. NAFPD lies at the junction of obesity and T2DM. Endocrine dysfunction induced by NAFPD, including β-cell dysfunction and insulin resistance, is directly responsible for the development of T2DM. Insulin resistance due to pancreatic beta cell dysfunction contributes to the development of T2DM, which is thought to be the driving force behind the alarming prevalence of T2DM[21,84].

Animal experiments have shown that high-fat diet is a risk factor for pancreatic fat accumulation and β-cell apoptosis[85]. Long-term high-fat diet induces MetS in mice and eventually leads to insulin resistance, NAFPD and NAFLD[79]. Therefore, the correlation between NAFPD and β-cell dysfunction has been validated in animal models. The role of glucotoxicity and lipotoxicity is widely accepted in the pathogenesis of β-cell dysfunction[86]. Glycotoxicity induced by hyperglycemia

hinders the process of mitochondrial β-oxidation and results in the accumulation of TGs in β-cells[87]. Likewise, the significant increase of FFA in the pancreas due to high-fat diet triggers pancreatic lipotoxicity, which leads to damage of pancreatic acinar and islet cells by inflammatory reaction[88].

Similarly, NAFPD is strongly associated with T2DM in humans. The pancreatic fat content of T2DM patients is significantly higher than that of patients without T2DM (measured by MRS)[89,90]. In contrast, the proportion of T2DM is significantly higher for NAFPD patients, comparing with control group[27]. NAFPD is independently related to prediabetes and diabetes in men[21], and the pancreatic fat content is negatively associated with insulin secretion in prediabetes[62]. A cross-sectional study enrolling 8097 subjects not only found a higher prevalence of NAFPD in the general population but also revealed an association between NAFPD and T2DM[27]. NAFPD may be another independent risk factor for the development of T2DM in addition to NAFLD[21]. To date, only one 7-year longitudinal population-based retrospective cohort study has investigated the association between NAFPD and the incidence of T2DM. NAFPD was positively associated with increased T2DM incidence. However, after adjustment for confounders, including BMI and liver attenuation, this association disappeared. Therefore, further studies with a longer follow-up period as well as studies in other ethnic groups are needed to confirm these findings[91]. In addition, there appears to be an ethnic predilection for the phenomenon of crosstalk between glucose and FFA. This predilection is reflected in obese Hispanics, who have higher pancreatic TG levels compared with African Americans and a greater decline of β-cell function compared with Caucasians with similar pancreatic TG levels[92]. The mechanism of this ethnic predilection remains unclear, and further studies are needed to determine how this occurs.

The association between NAFPD and insulin resistance is still controversial. Using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and euglycemic clamp to measure insulin resistance, the positive correlation between insulin resistance and the severity of NAFPD was observed in patients with impaired fasting glucose and/or impaired glucose tolerance[22,93]. Other investigations have also found an association between NAFPD and markers of insulin resistance[94,95]. However, it remains controversial whether this association is independent of obesity and NAFLD. A previous study has found higher levels of insulin resistance, IL-1 β, and TNF-α in obese children with NAFLD but lower levels in children with NAFPD[96]. In a multivariate logistic regression analysis, the association between NAFPD and HOMA-IR disappeared after further adjustment for visceral fat, rather than overall adiposity or pancreatic fat, suggesting that the former mediates the association between NAFPD and insulin resistance[22]. Consequently, the real issue is whether NAFPD really is the cause of insulin resistance, or if it is only a part of the abnormalities in the process of obesity.

Exocrine dysfunction

Exocrine pancreatic dysfunction is a deficiency of enzyme secretion due to several pathological factors and can be secondary to pancreatectomy or pancreatic diseases, especially chronic pancreatitis. NAFPD may also be a potential factor in exocrine dysfunction[53,97]. Several studies have pointed to the fact that NAFPD is the second leading cause of pediatric pancreatic insufficiency and coexists with exocrine dysfunction, which is frequently present in a few childhood syndromes such as Johanson-Blizzard syndrome and Schwachman-Diamond syndrome[98]. To date, there have been few reports regarding NAFPD and exocrine dysfunction[99-102]. A recent study enrolling 43 patients with NAFPD found a significant reduction of fecal elastase-1, a widely utilized indicator of pancreatic exocrine function, in patients with NAFPD in comparison to those patients without NAFPD[103]. Patients with endocrine dysfunction develop symptoms of malabsorption such as steatorrhea, bloating, abdominal pain, and weight loss, while complete fatty replacement is seen on imaging studies[101,104,105]. In addition, NAFPD has been also confirmed as a major cause of chronic pancreatitis and ductal stones[106]. The oxidative stress resulting from NAFPD could lead to exocrine dysfunction. Furthermore, adipocytes probably enact a paracrine effect, decreasing pancreatic exocrine function[40,41,107]. Nevertheless, these mechanisms have only been studied *in vitro* and require *in vivo* studies for confirmation.

Acute pancreatitis

As a major risk factor for severe acute pancreatitis, obesity is closely associated with multiple organ failure[108-110]. Obese mice develop more severe pancreatitis after hyperstimulation of pathogenic factors than lean mice do[111]. In addition, NAFPD is

associated with organ failure[112], local complications[113], prolonged hospitalization [114], and increased mortality in patients with pancreatitis[109,115].

Mechanistic hypotheses regarding the causal relationship between obesity and acute pancreatitis have been previously presented, including that pancreatic microcirculation in NAFPD patients is reduced, with a consequent reduction in local oxygen content and ischemic injury. The second is that hepatic dysfunction associated with obesity might enhance the systemic inflammation, and local inflammation due to NAFPD is usually located in the pancreatic fat[116]. Adipocytes can secret chemokines and cytokines, an imbalance of which causes a developing inflammatory state[117, 118]. The cytokines (IL-1β and TNF-α) produced by adipocytes in combination with free radicals derived from fatty acids create a proinflammatory milieu that leads to acinar cell injury and exacerbates the severity of acute pancreatitis[96,110,119]. Analogous to the association of NAFLD and NASH, the condition of pancreatitis owing to NAFPD has been termed nonalcoholic steatopancreatitis[78,120,121].

Pancreatic fistula

Pancreatic fistula is a potentially life-threatening complication after pancreatoduodenectomy[122]. Mathur *et al*[42] were the first to report that NAFPD significantly increased the risk of developing postoperative pancreatic fistula (POPF). Subsequently, the relevance of NAFPD to POPF has been confirmed[123-126]. It has been shown that pancreatic fat content > 10% is a significant risk factor for POPF[127], while the prognosis of patients is significantly associated with pancreatic fat content [53]. Currently, preoperative evaluation of risk factors has been considered to be a viable approach in preventing POPF. The high incidence of NAFPD in patients with POPF detected by preoperative CT has led to the proposal that preoperative assessment of NAFPD by CT could be used as a noninvasive method to predict POPF [128]. Guo *et al*[129] retrospectively evaluated the relative weights of several factors, including NAFPD, and established a simplified scoring model for precise prediction of POPF. Next, multicenter prospective studies, as well as improvement in the accuracy of scoring model, should be performed with a view to application in the preoperative assessment of pancreatoduodenectomy.

Pancreatic cancer

With obesity becoming the top global health problem, there is increasing evidence that obesity is a risk factor for pancreatic cancer[130-133]. Whereas obesity is strongly associated with NAFPD, similar to NAFLD, it is thought that NAFPD may drive the progression of pancreatic cancer by nonalcoholic steatopancreatitis or fibrosis[134]. Several findings support this view, but evidence is still limited. A retrospective study has reported a prevalence of NAFPD in patients with pancreatic cancer by EUS, which is the most sensitive for NAFPD. Compared with other risk factors, NAFPD is the only significant risk factor for pancreatic cancer in regression analysis[135]. There is a direct association between NAFPD and the incidence of intraepithelial neoplasia and pancreatic ductal adenocarcinoma, as shown by histopathology[136,137]. Currently, NAFPD is independently associated with the risk of pancreatic cancer[136]. In addition, NAFPD promotes the dissemination of pancreatic cancer[138] and significantly increases the risk of postoperative complications[139] and mortality[140].

Nevertheless, no clear consensus can be reached on the definitive mechanism for pancreatic cancer linked to NAFPD. MetS, oxidative stress, adipocytokine imbalance, and inflammation may contribute to the development of pancreatic cancer[141]. Abnormally increased adipocytes in the setting of NAFPD result in an adipocytokine imbalance, creating a proinflammatory milieu that aggravates the risk of recurrent pancreatitis, which is considered a major risk factor for pancreatic cancer. More fundamental mechanistic studies as well as prospective cohort studies with long-term follow-up are needed to clarify the causal link between NAFPD and pancreatic cancer.

NAFLD

The pancreas and liver are from the same embryonic endoderm, which may explain to some extent the similarities and links of fat accumulation in both NAFPD and NAFLD [142]. However, the pancreas seems to be more susceptible to fat accumulation compared with the liver[41]. Data from TUS, MRS, and histopathology have demonstrated a significant positive correlation between NAFPD and NAFLD[15,22, 61], with NAFPD present in nearly 70% of patients with NAFLD and associated with its well-known risk factors including MetS, T2DM, and obesity[27,143,144]. NAFPD is comorbid in approximately half of pediatric patients with NAFLD, corresponding to a combined NAFPD in 80% of NASH patients, and NAFLD children with NAFPD have

more severe insulin resistance and liver disease[96]. Although both NAFPD and NAFLD are associated with obesity, pancreatic fat accumulation might be the initial indicator of ectopic fat accumulation, as a strong determinant of NAFLD and MetS[27].

TREATMENT

Given the similarities with NAFLD, early treatment of NAFPD should be emphasized with the goal of minimizing pancreatic fat accumulation through healthy dieting, weight loss, and exercise[145]. Lifestyle modifications such as reducing caloric intake and meat consumption may benefit patients with NAFPD[146,147]. However, Weng *et al*[14] found a nonsignificant trend between NAFPD and sedentary habits as well as smoking.

Evidence for the reversibility of NAFPD has been found in animal and human studies. Troglitazone and orlistat administered to mouse models significantly prevent or reverse pancreatic inflammation and fat infiltration and reduce organ failure and mortality[148,149]. Liraglutide, a drug approved for obesity, has been shown to reduce the severity of NAFPD and NAFLD, while metformin has no significant effect on NAFPD[150,151]. Combination of sitagliptin and telmisartan demonstrates efficacy in controlling NAFPD progression[152]. In addition, berberine and cinnamic acid (traditional Chinese medicines) show prevention of NAFPD development by inhibiting fat accumulation[153]. Besides drug therapy, the impact of weight loss on NAFPD after bariatric surgery has been studied in animal and human models. Bariatric surgery in NAFPD patients has the benefits of decreasing pancreatic fat volume and improving β-cell function[89,127]. Of note, the degree of reduction in pancreatic fat content does not correlate with reduction in total body weight, suggesting differences in metabolic phenotype[15].

CONCLUSION

Just as obesity is a global problem, NAFPD has attracted a great deal of attention from researchers and clinicians. Understanding of NAFPD is still in its infancy since its discovery for its relation to obesity. Age, gender, race, and unhealthy lifestyle are considered as risk factors. A variety of invasive and noninvasive tools have been developed for diagnosis including 1H-MRS, IDEAL-MRI, MRI-PDFF, and EUS elastography; some of which have reached consensus guidelines. Improvement of diagnostic tools help us to understand better changes involved in NAFPD pathophysiology and the microscopic pathophysiological relationship between NAFPD and other pancreatic diseases, so as to provide the groundwork for novel therapies for NAFPD.

Because of the close correlation, NAFPD should be considered in clinical practice for related diseases, including MetS, T2DM, pancreatitis, POPF, pancreatic cancer, and NAFLD. The value of NAFPD as an early indication of diagnosis and intervention in patients with MetS, T2DM, and pancreatitis and as a prognostic marker for pancreatic surgery and postoperative complications is important. Nowadays, lifestyle modifications, including structured exercise and prudent diet, remain the cornerstones of NAFPD treatment. In the future, it is reasonably expected that systematic basic and clinical research will elucidate the pathogenesis, influencing factors, and clinical complications of NAFPD. Large cohort, multicenter investigations should be performed to deepen our knowledge of NAFPD, so that the early diagnosis and treatment of NAFPD and clinical associations can be made possible.

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