Review Article

From NAFPD to MAFPD: a literature review of implications of a nomenclature change

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Background and Objective: Obesity is a global health issue closely linked to multiple cardiovascular and metabolic conditions. The renaming of nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD) has sparked discussions about renaming nonalcoholic fatty pancreas disease (NAFPD). This narrative review explores the potential benefits and challenges of renaming NAFPD to metabolic dysfunction-associated fatty pancreas disease (MAFPD) and its potential clinical implications.

Methods: The review employs a narrative approach, synthesizing existing literature and expert opinions to evaluate the rationale behind and the possible implications of renaming NAFPD to MAFPD.

Key Content and Findings: NAFPD is increasingly recognized worldwide but lacks standardized diagnostic criteria, hindering its independent classification as a disease. Renaming NAFPD to MAFPD may enhance diagnostic accuracy, prognostic prediction, and personalized treatment strategies. It may also facilitate global epidemiological research, data sharing, and collaboration. Major challenges include establishing uniform diagnostic guidelines for promoting and educating about the newly proposed terminology.

Conclusions: The proposed renaming from NAFPD to MAFPD may offer promising benefits despite challenges. It may also lead to improved management and understanding of the disease, potentially benefiting global healthcare strategies aimed at addressing obesity-related pancreatic complications.

Keywords: Metabolic dysfunction-associated fatty liver disease (MAFLD); nonalcoholic fatty liver disease (NAFLD); metabolic dysfunction-associated fatty pancreas disease (MAFPD); nonalcoholic fatty pancreas disease (NAFPD); metabolic syndrome (MetS)

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Introduction

Obesity is a major healthcare problem worldwide, as approximately 605 billion adults and ~108 million children suffer from overweight or obesity (1,2). Obesity leads to multiple adverse health consequences, such as type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), and cardiovascular disease (3). Adipose tissue (AT) exerts multiple functions in the body, serving primarily as a storage site for excess energy while also functioning as an endocrine organ that secretes various hormones regulating metabolic homeostasis (4). In overnutrition states, AT stores excess lipid, and when subcutaneous AT reaches its maximum storage capacity or when it is incapable of expansion as in lipodystrophy, lipid 'overflow' leads to deposition of lipids in different ectopic sites (such as the liver, skeletal muscle, heart, and pancreas) (5,6).

Recently, there has been a global push to rename diseases using terms that point to their pathophysiological origin. For instance, the "old" term nonalcoholic fatty liver disease (NAFLD) suggests that this disease has nothing to do with underlying metabolic dysfunction (7). However, NAFLD is closely linked to metabolic disorders, including obesity, insulin resistance (IR), T2DM, MetS, and atherosclerosis (8). Consequently, the NAFLD terminology has been recently changed to metabolic dysfunction-associated fatty liver disease (MAFLD), better reflecting the pathophysiology and cardiometabolic implications of this highly prevalent liver disease (9,10). Similar to the situation in the liver, observational studies showed that pancreatic fat accumulation is closely associated with metabolic abnormalities, such as obesity, IR, and MetS (11,12). In addition, many studies reported a positive association between pancreatic and hepatic fat contents (13-16). Therefore, we suggest that excess lipid deposition in the pancreas could be named metabolic dysfunction-associated fatty pancreas disease (MAFPD).

This narrative review aimed to discuss our present understanding of pancreatic fat accumulation, taking the naming process for MAFLD as a point of reference. We have also explored the advantages and potential clinical implications of renaming nonalcoholic fatty pancreas disease (NAFPD) to MAFPD. We present this article in accordance with the Narrative Review reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-284/rc).

Methods

We searched PubMed databases from inception up until June, 2024 for publications in English, by use of the terms "nonalcoholic fatty liver disease", "NAFLD", "fatty liver", "pancreatic diseases", "pancreas", "metabolic syndrome", "metabolism", "lipid metabolism", "diabetes mellitus", "Insulin Resistance", "diabetes", "adiposity", "obesity". Articles resulting from these searches and relevant references cited in those articles were reviewed. The search strategy is described in *Table 1*.

From NAFLD to MAFLD and MASLD: the redefining and renaming of fatty liver disease

Liver fat deposition resulting in hepatic steatosis was previously known as NAFLD. NAFLD is histologically defined as an accumulation of liver fat in more than 5% of hepatocytes in the absence of significant alcohol consumption, viral hepatitis or other competing risk factors for hepatic steatosis (17,18). However, this exclusive definition has many limitations and overlooks the pathogenic role of metabolic dysfunction in the development of this liver disease (19). Further, using alcohol consumption as a criterion for assessing liver health is inaccurate. For example, the standards for determining the daily amounts of alcohol that affect human health are not well defined (20). Some studies have even found that moderate alcohol consumption (less than 20 g/day) may protect against NAFLD, while others indicate the converse. There is also the question of why there should be any mention of alcohol consumption when defining a primarily metabolic liver disease (21). In 2020, an international panel of experts proposed the definition of MAFLD, highlighting the crucial role of metabolic dysfunction in the pathogenesis of this liver disease (7,22). In 2023, another panel of experts introduced the term metabolic dysfunction-associated steatotic liver disease (MASLD). Both fatty liver disease nomenclatures aim to provide a more accurate description

Table 1 The search strategy summary

Items	Specification
Date of search	January 2023, June 2024
Databases searched	PubMed
Search terms	"nonalcoholic fatty liver disease", "NAFLD", "fatty liver", "pancreatic diseases", "pancreas", "metabolic syndrome", "metabolism", "lipid metabolism", "diabetes mellitus", "Insulin Resistance", "diabetes", "adiposity", "obesity"
Timeframe	From inception to June 2024
Inclusion criteria	Publications in English. The search strategy was designed to identify relevant studies for an in-depth review, providing valuable insights into the renaming of NAFPD and its potential benefits and challenges
Selection process	W.Z. conducted the selection, and all authors revised the manuscript to identify potential studies based on their expertise

NAFLD, nonalcoholic fatty liver disease; NAFPD, non-alcoholic fatty pancreas disease.

of this complex liver disease and seek to offer targeted guidance for its prevention and treatment (23).

Numerous research reports have highlighted the advantages of the proposed "positive" diagnostic criteria for MAFLD in clinical practice (*Table 2*) (19,24-33). Firstly, the MAFLD definition accurately reflects the underlying pathophysiology, allowing greater attention to the range of its metabolic associations (34). Patients with MAFLD may fluctuate between isolated steatosis and steatohepatitis over a relatively short time (35), while steatohepatitis can progress at varying rates to advanced fibrosis and cirrhosis (or reverse) (36). This reflects the highly dynamic disease process in the liver, a consequence of the impact of varying lifestyle factors. This new framework is essential for adequately understanding the progression and regression of MAFLD and for timely treatment; hence, the MAFLD definition has superior clinical utility (37). Secondly, the MAFLD definition better identifies individuals at high risk for liver disease progression than the NAFLD definition. A large cohort study using the National Health and Nutrition Examination Survey (NHANES) III database found that participants diagnosed with MAFLD also had a higher proportion of metabolic comorbidities (including T2DM and hypertension) and a worse prognosis than those diagnosed with NAFLD (24). Thirdly, the MAFLD definition allows the diagnosis of this metabolic liver disease in the context of other coexisting liver diseases (38). This approach is a novel way of thinking about fatty liver disease and establishes a framework to consider other etiologies that may contribute to and worsen liver disease (39). The proposed terminology change from NAFLD to MAFLD will hopefully remind clinicians to identify and treat all coexisting metabolic diseases in patients in a holistic manner and treat them promptly.

From NAFPD to MAFPD: redefining pancreatic steatosis

Definition of pancreatic steatosis

Fat deposition in the pancreas is the most common pancreatic pathology, affecting at least 16% of the global population (40). Nevertheless, our understanding and knowledge(s) of this disease remains poorly understood. As early as 1926, Schaefer reported an association between pancreatic weight and body weight (41). In subsequent studies, researchers reported an association between pancreatic fat accumulation and MetS (abdominal obesity, hypertension, atherogenic dyslipidemia and IR or T2DM) (42,43). With the introduction of imaging techniques, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), the associations between pancreatic fat content and various metabolic disorders, such as the MetS, prediabetes and T2DM, have been confirmed (44). Thus, the coexistence of multiple metabolic disorders typically characterizes both MAFLD and pancreatic fat accumulation.

Currently, many terms have been used to describe pancreatic fat accumulation; the different criteria have

Table 2 Comparison between MAFLD and NAFLD definitions

Author (ref)	Study design	Number of patients included	Clinical significance
Wang *et al.* (19)	Cross-sectional study	1,223	Patients with NAFLD and MAFLD had intermediate/high cardiovascular risk, with a high rate of CVD events. Patients with MAFLD and concomitant viral infection had significantly increased cardiovascular risk and CVD events compared to those without viral infection
Lin *et al.* (24)	Cross-sectional study	13,083	MAFLD definition is more practical for identifying patients with fatty liver disease with high risk of disease progression
Yamamura *et al.* (25)	Cross-sectional study	765	MAFLD definition better identifies individuals with fatty liver and significant fibrosis (evaluated by non-invasive tests)
Lee *et al.* (26)	Case-control study	9,584,399	Compared with NAFLD, MAFLD better correlates with CVD
Sun *et al.* (27)	Cross-sectional study	12,571	Compared with NAFLD, MAFLD is more accurate for identifying patients with CKD
Fukunaga *et al.* (28)	Cross-sectional study	124	MAFLD, particularly non-obese MAFLD, is a stronger risk factor for colorectal adenoma than NAFLD
Nguyen *et al.* (29)	Case-control study	2,997	Compared with NAFLD, MAFLD criteria identified individuals with more comorbidities and a worse prognosis
Tsutsumi *et al.* (30)	Case-control study	2,306	Compared with NAFLD, MAFLD better identifies patients with high CVD risk
Yoo *et al.* (31)	Cohort study	701	MAFLD is associated with increased CVD mortality
Kwon *et al.* (32)	Cohort study	21,713	Switch from NAFLD to MAFLD criteria identifies a greater number of individuals at high risk of CKD
Yu *et al.* (33)	Cohort study	30,633	Compared with NAFLD, the MAFLD definition identifies more fatty liver patients with high-risk diseases

MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; CVD, cardiovascular disease; CKD, chronic kidney disease.

some specific characteristics (*Table 3*). Fat accumulation in islet or acinar cells is known as "pancreatic steatosis" (45). Conversely, the term "fat replacement" refers to the irreversible situation in which pancreatic acinar cells are damaged or die due to various insults such as viral infection or pancreatic duct ligation, and are replaced by fat cells (46). "Fatty infiltration" refers to the accumulation of adipocytes within the pancreas caused by excess adiposity and may be reversible through body weight loss and administration of certain medications (47). "Pancreatic lipomatosis" is used as a term referring to the fatty replacement of pancreatic exocrine tissue (48). "Lipomatous pseudohypertrophy" is an extreme variant of pancreatic fat accumulation characterized by an increase in pancreatic volume and replacement of exocrine tissue by AT, even to the extent of the whole pancreas (49). The term "nonalcoholic fatty pancreas disease" is used to describe the occurrence of pancreatic fat degeneration associated with obesity and MetS in the absence of significant alcohol consumption or other competing causes for pancreatic steatosis (45). Despite the widespread acceptance of the acronym NAFPD, many inaccuracies persist in the terminology. Thus, establishing a more accurate definition of pancreatic fat deposition has become a clinical and research priority.

Epidemiology of NAFPD

Due to the lack of unified diagnostic criteria, epidemiological data on the global prevalence of fatty pancreas are very limited. However, the prevalence of pancreatic fat accumulation appears to be steadily increasing. A cohort study involving 42,599 participants found a prevalence of 17.9% (50). Among 250 individuals in the United States who underwent endoscopic ultrasound (EUS) examinations, 27.8% were diagnosed with fatty pancreas (51). In Jakarta, a study of 901 adult medical check-

Table 3 Common nomenclatures for pancreatic steatosis

Name	Definition
Pancreatic steatosis	Fat accumulation in islet or acinar cells
Fatty replacement	Acinar cell death with subsequent adipocyte replacement
Fatty infiltration	Adipocyte infiltration
Pancreatic lipomatosis	Fatty replacement of pancreatic exocrine tissue
Lipomatous pseudohypertrophy	Exocrine pancreas replaced by adipocytes and not associated with excess weight
Nonalcoholic fatty pancreas disease (NAFPD)	Pancreatic fat accumulation in the absence of significant alcohol consumption (<20 g/day) and other competing causes for pancreatic steatosis

up patients reported a NAFPD prevalence of 35.0% (52). Moreover, NAFPD can also occur in children. A retrospective study revealed that among 232 pediatric subjects aged 2 to 18 years undergoing abdominal CT scan, approximately 10% had NAFPD (53). Given the increasing global rates of obesity in the general population, it is foreseeable that the prevalence and incidence rates of NAFPD will continue to rise globally.

The necessity for redefining NAFPD

Similar to the NAFLD definition, the prerequisite for a diagnosis of NAFPD involves excluding an arbitrary amount of "significant" alcohol consumption. The latter as a diagnostic criterion is problematic as it inaccurately assesses health based on the amount of alcohol consumed. A wealth of information suggests that there is no safe limit for daily alcohol consumption, and even moderate alcohol consumption can be potentially harmful (54). In addition, substantial individual differences in response to alcohol intake highlight the unreliability and lack of utility of setting an absolute threshold for alcohol intake for any given individual (21). Furthermore, "alcoholic" may be stigmatizing for many subjects. For example, in many societies, alcohol drinking is prohibited for religious or cultural reasons, making the issue even more problematic. In these situations, asking about daily alcohol consumption can be misconstrued as provocative and seen as a moral judgment, bringing many difficulties to diagnosis and treatment (55).

Another concern is that NAFPD fails to emphasize the pathogenic role of metabolic dysfunction in its development. Accumulating evidence suggests a close association between NAFPD and MetS features (51,56). Metabolic dysfunction in NAFPD may result from multiple putative mechanisms, such as greater IR, abnormal lipid homeostasis, low-grade inflammation, increased endoplasmic reticulum (ER) stress, oxidative stress, and mitochondrial dysfunction (*Figure 1*). These mechanisms are discussed below.

Abnormal lipid homeostasis

Numerous studies have demonstrated a persistent elevation of non-esterified fatty acids (NEFA) and triglyceride-rich lipopolysaccharides (TL) as pivotal in the occurrence of IR and pancreatic beta cell dysfunction (57,58). Extended exposure of pancreatic islets to NEFA impairs pancreatic beta cell secretion and insulin gene expression and increases beta cell apoptosis (59,60). Among the NEFAs, increased saturated fatty acids (primarily palmitic acid) are crucial for inducing lipotoxicity in pancreatic beta cells (59,61). When the amount of palmitic acid in cells exceeds the capacity of the mitochondria to oxidize them, palmitic acid is converted to potentially toxic fatty acid-derived lipids, such as diacylglycerol (DAG) and ceramide (62). DAGs may affect PI3K/Akt pathway signaling, leading to the development of IR, while ceramide inhibits Akt by activating protein phosphatase 2a and PKA isoform zeta (ζ), promoting IR (63). Furthermore, pancreatic beta cells respond to palmitate through the Toll-like receptor pathway, triggering the production of multiple chemokines such as interleukin (IL)-8, IL-6, and monocyte chemotactic protein-1 (MCP1) that recruit M1-polarized pro-inflammatory monocytes/macrophages to pancreatic islets, thus activating inflammatory processes and inducing the functional deterioration of pancreatic beta cells (64,65).

Low-grade, chronic inflammation

Inflammatory responses are an important manifestation of NAFPD. Many inflammatory cytokines, including leptin, adiponectin, IL-1β, and IL-6, are involved in the

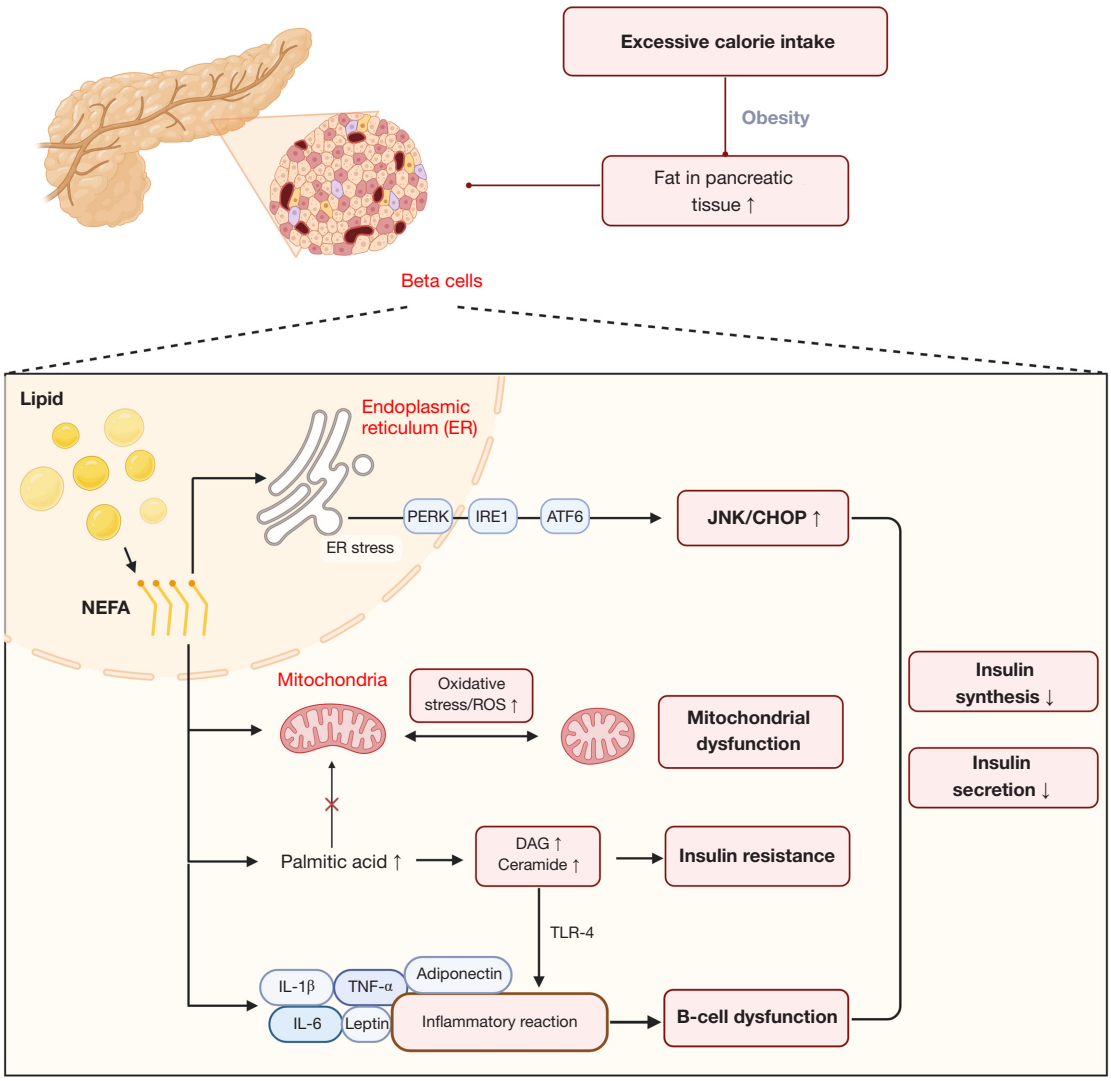

Figure 1 Pathophysiological hypotheses on the association between NAFPD and MetS. The association between them is the result of multifactorial interactions. Firstly, pancreatic fat accumulation can lead to pancreatic islet cell damage and decreased insulin secretion, resulting in abnormal elevation of plasma glucose and lipid concentrations, thereby increasing the risk of MetS. Furthermore, pancreatic fat accumulation exacerbates the development of MetS through mechanisms including IR, low-grade inflammation, and neuroendocrine regulation that impact lipid metabolism and adipocyte function (Created with BioRender.com). ER, endoplasmic reticulum; PERK, PKR-like ER kinase; IRE1, inositol-requiring transmembrane kinase/endonuclease 1; ATF6, activating transcription factor 6; CHOP, C/EBP homologous protein; JNK, c-Jun N-terminal kinase; ROS, reactive oxygen species; DAG, diacylglycerol; IL, interleukin; TNF-α, tumor necrosis factor-alpha; NAFPD, non-alcoholic fatty pancreas disease; MetS, metabolic syndrome; IR, insulin resistance.

development of IR and pancreatic dysfunction (66-68). While the primary functions of leptin and adiponectin are to regulate eating behavior and energy expenditure, these adipokines may also regulate inflammatory responses (69). Adiponectin stimulates insulin secretion and beta-cell survival by activating adiponectin receptor 1 (ADIPOR) on pancreatic beta cells. Leptin inhibits pancreatic insulin secretion by activating the leptin receptor (LEP-R) (70). Among the pro-inflammatory and immune-regulatory cytokines, IL-6 is the most extensively characterized and may impair fat metabolism and potentially contribute to IR (67). Thus, insulin-resistant obese individuals

have higher serum IL-6 levels than insulin-sensitive individuals matched for body mass index (BMI) (71). Elevated serum IL-6 levels, reflecting obesity-related IR, correlate positively with AT hyperplasia (72). TNF-α is another proinflammatory cytokine in obesity-related AT dysfunction. In the AT, TNF-α is primarily secreted by macrophages in the stromal vascular fraction. In insulin-resistant individuals, circulating TNF-α levels and TNF-α gene expression in ATs are increased (73).

ER stress

The ER is the primary site for protein folding and transport within the cell, and it synthesizes nearly all secretory proteins (74). Within the ER, proteins that fail to fold or modify appropriately undergo ubiquitination at the ER membrane, leading to their degradation. This phenomenon is denoted as ER-associated degradation (ERAD) (75). When accumulated misfolded proteins are insufficient to be eliminated by ERAD, the ER activates an unfolded protein response (UPR) (76). As a complex signaling pathway, the UPR attempts to reduce the synthesis of new proteins, enhance folding capacity, and degrade terminally misfolded proteins (77). If these mechanisms cannot restore ER homeostasis, the cell undergoes apoptosis (78).

In the presence of lipotoxicity or IR states, there is a substantial increase in the body's metabolic demands. To sustain the substantial stores of insulin granules in response to these metabolic demands, pancreatic beta cells must generate significant amounts of proinsulin, the precursor to insulin and C-peptide. Proinsulin biosynthesis contributes as much as 30–50% of total cellular protein synthesis in pancreatic beta cells. This places significant stress on the secretory pathway of beta cells, particularly in the ER (79). When the synthesis of proinsulin exceeds the processing and folding capacity of the ER, a large amount of unfolded/unprocessed proinsulin accumulates, inducing the UPE and activating the three major signaling pathways of the UPR: PERK (PKR-like ER kinase), IRE1 (inositol-requiring transmembrane kinase/endonuclease 1), and ATF6 (activating transcription factor 6), respectively (80,81). Long-term persistent ER stress can lead to prolonged UPR activation, which promotes cell death signals (82). In addition, NEFAs may activate C/EBP homologous protein (CHOP) and c-Jun N-terminal kinase (JNK), i.e., key signals in the apoptosis pathway, mainly through the UPR (83).

Oxidative stress and mitochondrial dysfunction

Studies have found that increased NEFA levels may impair pancreatic beta-cell function by inducing oxidative stress. Specifically, in isolated rat islets, NEFAs induce reactive oxygen species (ROS) generation and reduce pancreatic insulin secretion and insulin content, thereby increasing pancreatic beta-cell apoptosis (84). Additional support for the involvement of oxidative stress in lipotoxicity is derived from intervention studies with antioxidants. Both metformin and troglitazone (i.e., a peroxisomal proliferator-activated receptor-gamma agonist since withdrawn) have antioxidant properties and prevent hyperglycemia in Zucker diabetic fatty rats (85,86). Administration of antioxidants, such as N-acetyl cysteine, partially alleviates NEFA-induced decreases in *in-vivo* glucose-stimulated insulin secretion (GSIS) in rats and averts the NEFA-induced impairment of both GSIS and insulin gene expression *in vitro* (87).

Moreover, since NAFPD may increase the risk of acute pancreatitis, chronic pancreatitis, pancreatic fibrosis and pancreatic cancer (*Figure 2*) (44,88), timely interventions and early treatments of triggering factors for NAFPD may reduce pancreatic fat infiltration and prevent related complications (89).

Reconsideration of the definition of "pancreas fat"

Widespread research on metabolic diseases, particularly the redefinition of NAFLD, has prompted a reconsideration of the definition of "pancreas fat." Can we use the NAFLD-MAFLD experience to create a new definition for pancreas fat? As discussed earlier, studies suggest a significant correlation between increased pancreatic and liver fat content, and both conditions share common metabolic risk factors (such as overweight/obesity, IR, and MetS) (90,91). Fatty degeneration in the liver may also occur in other organs, including the pancreas. The pathophysiological alterations arising from hepatic fat accumulation might similarly occur in different organs where fat accumulates (90) (*Figure 3*). Epidemiological studies and meta-analyses have demonstrated a strong correlation between hepatic fat accumulation and an increased risk of pancreatic fat degeneration. For example, in a cross-sectional study of 42 obese patients examining the association between pancreatic fat accumulation and various fat depots (including hepatic fat and visceral AT) with IR and other metabolic abnormalities, Targher *et al.* reported a significant association between pancreatic fat accumulation, hepatic fat levels, IR and metabolic abnormalities, predominantly influenced by visceral AT (16). The results of another small cross-sectional study also reported a significant association between hepatic

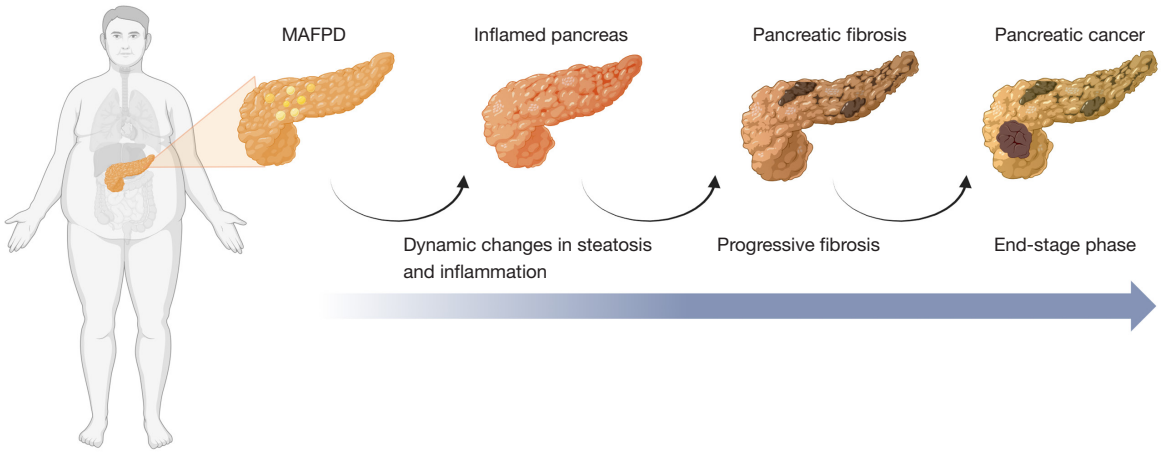

Figure 2 The disease progression of MAFPD. MAFPD exhibits a progressive course, evolving from the initial stage of fat accumulation to subsequent phases involving pancreatic inflammation, fibrosis, and the eventual development of end-stage pancreatic cancer (Created with BioRender.com). MAFPD, metabolic dysfunction-associated fatty pancreas disease.

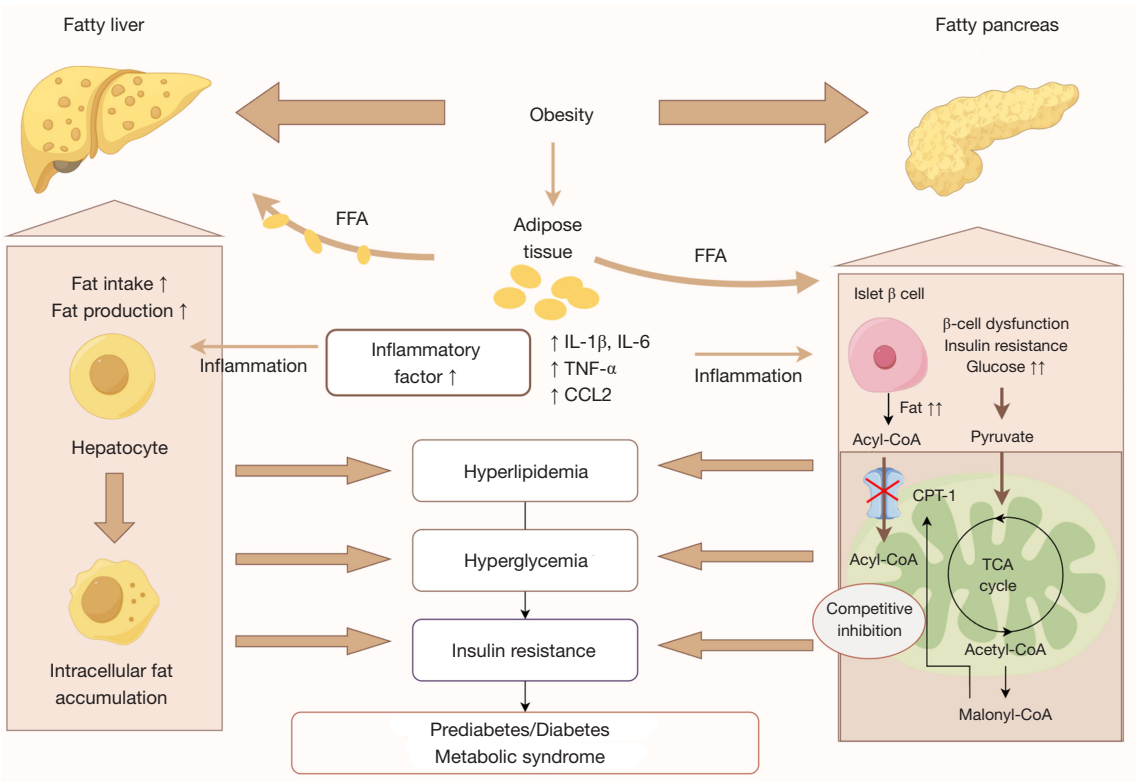

Figure 3 The link between MAFLD and MAFPD is complex, and mechanisms of mutual influence may coexist between the two conditions. These mechanisms include inflammatory response, IR, and glucose and lipid metabolism disturbances. Dyslipidemia and dysglycemia are pivotal pathological factors linking these two conditions (By figdraw.com). FFA, free fatty acid; IL, interleukin; TNF-α, tumor necrosis factor-alpha; TCA, tricarboxylic acid; MAFLD, metabolic dysfunction-associated fatty liver disease; MAFPD, metabolic dysfunction-associated fatty pancreas disease; IR, insulin resistance.

and pancreatic fat contents, as measured by magnetic resonance spectroscopy, in Dutch individuals with BMI ranging from 20.0 to 42.9 kg/m^2 (92).

A new nomenclature: MAFPD

Building on the established association between pancreatic fat and MetS, and considering the close association between pancreatic and liver fat contents, by the name rules set by MAFLD, we suggest the term "metabolic-associated fatty pancreas disease" (MAFPD) to describe the presence of pancreatic fat accumulation. Thus, similarly to the criteria proposed for diagnosing MAFLD, we suggest the following diagnostic criteria for MAFPD: evidence of pancreatic fat accumulation (mainly based on imaging methods) with at least one of the following metabolic risk abnormalities: overweight/obesity, the presence of T2DM, or evidence of metabolic dysfunction. Being overweight is defined as a BMI ≥25 kg/m^2, and T2DM is defined as an HbA1c level ≥6.5% (≥48 mmol/mol) or the use of any glucose-lowering drugs. Metabolic dysfunction is defined as the presence of at least two metabolic risk abnormalities in lean individuals who do not have T2DM, including: (I) waist circumference ≥90 cm for men and ≥80 cm for women; (II) blood pressure ≥130/85 mmHg or specific drug treatment; (III) plasma triglyceride concentrations ≥150 mg/dL or specific drug treatment; (IV) plasma HDL cholesterol concentrations <40 mg/dL in men, <50 mg/dL in women or specific drug treatment; (V) prediabetes (fasting glucose concentration of 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c 5.7–6.4%); (VI) homeostasis model assessment-IR (HOMA-IR) score ≥2.5; and (VII) plasma high-sensitivity C-reactive protein level >2 mg/L (22,93).

We have used the term MAFPD rather than metabolic dysfunction-associated steatotic pancreas disease (MASPD) because there is not global consensus on nomenclature to define fat in the pancreas linked to metabolic dysfunction. The APASL nations, which includes more than half the world's population and over 60% of the world's burden of chronic liver diseases and liver cancers, do not consider the term 'fatty' to be stigmatizing, when it refers to fatty liver disease (MAFLD). Indeed, APASL and over 77 associations worldwide have endorsed the term MAFLD (https://maiden-apasl.com/). That said, Younossi *et al.* recently undertook a global cross-sectional survey study to assess stigma in NAFLD among patients and healthcare providers from around the world. These authors showed that there was a disconnect between physicians and patients related to stigma and related nomenclature, and the perception of NAFLD stigma varied among patients, healthcare providers, geographic locations and sub-specialties (although more than two thirds of the participants of this global survey did not believe that the term "fatty" was stigmatizing) (94).

It is undeniable that alcohol consumption significantly endangers pancreatic health. Not only does it promote pancreatic fat accumulation (95), but it also triggers complications, such as pancreatitis, pancreatic cancer, and T2DM (96-98). Therefore, we suggest proposing a new term, "alcohol-associated fatty pancreas disease" to describe pancreatic fat disease in individuals with excessive alcohol consumption but without coexisting metabolic risk factors.

Finally, we propose that imaging techniques, such as CT and MRI (*Figure 4*), can be used to non-invasively assess the severity of pancreatic fat accumulation (99-102). Pancreatic histological examination is the "gold standard" for MAFPD diagnosis but is impractical in routine clinical practice.

Potential implications and advantages of renaming NAFPD to MAFPD

Clinical applicability is the only criterion for judging any new disease name. It includes the utility of the diagnostic criteria for practice and evaluating the natural history of pancreatic fat accumulation and its associated complications.

MAFPD identifies the disease based on factors such as overweight/obesity and metabolic disorders, regardless of whether (or not) the individual drinks alcohol; this significantly facilitates disease diagnosis. Secondly, focusing on the role of "metabolic abnormalities" in the development of MAFPD is anticipated to encourage additional studies into the disease's etiology and pathogenesis and generate new ideas for treating and managing the disease. Meanwhile, excluding excessive alcohol intake as a confounding factor can focus the research on the specific impact of different metabolic factors on pancreatic fat. Studying various complications associated with pancreatic fat (such as pancreatitis, pancreatic cancer, T2DM, etc.) aids in understanding the progression of these diseases, laying the foundation for a comprehensive assessment of pancreatic health (56,88). Finally, changing the terminology from NAFPD to MAFPD is anticipated to avoid unsuitable language and unanticipated effects, including stigmatization, underestimation, and lack of knowledge about diagnosis and treatment. There is precedent for changing the terminology to lessen stigma, such as when "schizophrenia" was changed to "dissociative disorder", which has been shown to reduce

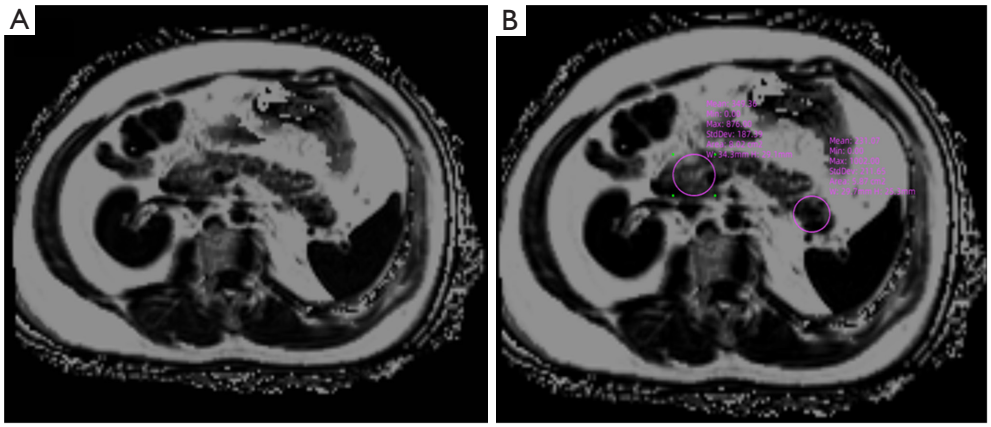

Figure 4 Magnetic resonance imaging shows the presence of fat infiltration in the pancreas. A patient with low (A) and high (B) amounts of pancreatic fat.

the stigma and increase the public's accurate understanding of the disease, and improve attitudes toward patients (103).

Future perspectives

Develop specific diagnostic criteria

It is important to underline that renaming NAFPD as MAFPD is just a starting point. Developing new diagnostic criteria is a complex procedure requiring, amongst other factors, in-depth research and professional consensus. This process requires reliable statistical methodologies and rigorous clinical validation to guarantee precision and practical applicability. Therefore, a comprehensive literature review is essential in subsequent work to determine key features, pathology, clinical manifestations, laboratory tests, and imaging presentations needed for the new criteria. The objective should be to create precise and actionable diagnostic standards by leveraging existing criteria and recent research developments.

Moreover, the diagnosis of MAFPD in the primary care setting is challenging due to the complex diagnostic criteria, overlap with other metabolic conditions, limitations of diagnostic tools, and challenges in multidisciplinary management. Therefore, for primary care physicians, comprehending and addressing pertinent risk factors for MAFPD (such as obesity, T2DM, sedentary lifestyle, smoking, alcohol use, and dyslipidemia) can assist them in promptly identifying and managing high-risk patients.

Clinical validation study

Upon establishing the diagnostic criteria, conducting extensive clinical validation studies becomes imperative to assess the practical applicability of the new standards within real patient populations. The task encompasses comparing and validating the updated standards against established criteria. Vital steps involve collecting data, conducting statistical analyses, and assessing the accuracy, reproducibility, and clinical applicability of these new standards. Additionally, conducting multicenter and large-scale studies spanning diverse regions, populations, and medical institutions is imperative to guarantee the universality and reliability of the new standards across various backgrounds and patient cohorts. Furthermore, extended monitoring through long-term follow-up studies is essential to evaluate the stability and durability of the new standards over time. More specific diagnostic criteria can be gradually established through these steps, validating their clinical application value and providing essential scientific foundations for diagnosing and treating this condition.

Improvement of diagnosis and evaluation methods

The validation of the newly proposed diagnostic criteria for MAFPD requires large-scale epidemiological investigations with long-term follow-ups to ensure their practicality. Furthermore, considering the increasing high prevalence of obesity worldwide, assessing pancreatic fat content

might also become a routine examination to evaluate the patient's physical condition in the future. Therefore, precise, convenient, and practical detection methods are crucial in diagnosing and promoting awareness of MAFPD. However, there are difficulties in diagnosing pancreatic fat content, and currently, there are no robust biological markers for diagnosing MAFPD. MAFPD detection mainly relies on imaging techniques. Imaging techniques may assess the fat buildup in the entire pancreatic organ; however, this technique is not easy. The pancreas has a lobular shape and is situated amid the gastrointestinal and intra-abdominal fatty tissues, making it challenging for imaging to differentiate it from neighboring tissues. This poses difficulties in diagnosing the disease (44). Therefore, in future research, a need exists to investigate new biomarkers, imaging techniques, and non-invasive detection methods for an early diagnosis and intervention of MAFPD in clinical practice.

Development of individualized diagnosis and treatments

Future research must also focus on developing and validating individualized diagnosis and treatment strategies for MAFPD. By integrating genomics, epigenomics, metabolomics and clinical data, models can be established to predict MAFPD risk, prognosis, and treatment response. Moreover, while the current treatment for MAFPD relies primarily on lifestyle interventions, the close interconnection between MAFLD and MAFPD suggests that future research could explore the efficacy of medications tested for treating MAFLD (including peroxisome proliferator-activated receptor agonists, glucose-dependent insulinotropic polypeptide agonists, glucagon receptor agonists and glucagon-like peptide-1 receptor agonists) in managing MAFPD.

Strengthening multidisciplinary collaboration

Research on MAFPD requires multidisciplinary collaboration, including endocrinology, metabolism, genetics, nutrition, biology, and computer science experts. Strengthening multidisciplinary cooperation can promote a better understanding of the complexity of MAFPD, facilitate the development of new research methods and technologies, and accelerate the transformation of research results into clinical practice.

Conclusions

MAFPD is a relatively common but often overlooked condition worldwide. Most studies have reported a significant increase in the prevalence of MAFPD in the context of obesity and metabolic disorders. Current evidence indicates that pancreatic fat accumulation may impair pancreatic functions, leading to a "vicious cycle" of further lipid dysmetabolism and progressive beta cell functional decline or necrosis. We propose that renaming NAFPD to MAFPD will better reflect current knowledge of the disease of pancreatic fat accumulation coupled with metabolic dysfunction. Further epidemiological studies are certainly required to validate our proposed diagnostic criteria for MAFPD and to assess the impact of (its) renaming alongside important clinical associations with other pancreatic and extra-pancreatic conditions.

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Footnote

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