

MAFLD vs. NAFLD: shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, placing an increasing burden on human health. NAFLD is a complex multifactorial disease involving genetic, metabolic, and environmental factors. It is closely associated with metabolic syndrome, obesity, and type 2 diabetes, of which insulin resistance is the main pathophysiological mechanism. Over the past few decades, investigation of the pathogenesis, diagnosis, and treatments has revealed different aspects of NAFLD, challenging the accuracy of definition and therapeutic strategy for the clinical practice. Recently, experts reach a consensus that NAFLD does not reflect the current knowledge, and metabolic (dysfunction) associated fatty liver disease (MAFLD) is suggested as a more appropriate term. The new definition puts increased emphasis on the important role of metabolic dysfunction in it. Herein, the shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy of the newly defined MAFLD, as compared with the formerly defined NAFLD, are reviewed for updating our understanding.

Keywords: Nonalcoholic fatty liver disease; Metabolic (dysfunction) associated fatty liver disease; Epidemiology; Pathophysiology; Diagnosis; Pharmacotherapy

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide.^[1] NAFLD is defined as the evidence of steatosis in >5% of hepatocytes detected by imaging techniques or histology, in the absence of known causes such as alcohol, viral hepatitis, hereditary liver diseases, or long-term use of steatogenic medication.^[2] It is an exclusive diagnosis, and for which liver biopsy is the golden standard. It is a spectrum of progressive liver disease from steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).^[3] NAFLD is strongly associated with metabolic syndrome, the components of which include hyperglycemia, hypertension, abdominal obesity, and dyslipidemia.^[4] Given the dramatically growing prevalence of NAFLD,^[5] the lack of clear nomenclature for nonalcohol-use-disorder fatty liver disease, alongside the absence of a properly defined “positive” diagnosis and lack of approved drugs for this disease, constitute urgent unmet needs in this field.

Recently, a consensus of international experts has proposed the disease name being changed from NAFLD to metabolic (dysfunction) associated fatty liver disease (MAFLD).^[6] The criteria are based on the evidence of hepatic steatosis, plus any of the following three conditions: overweight/obesity, presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation.^[7] In this review, we will discuss the shared features and potential differences between MAFLD and NAFLD in epidemiology, pathophysiology, diagnosis, and pharmacotherapy.

Epidemiology

Over the past two decades, NAFLD has become the most common chronic liver disease globally and it is estimated that 25.24% of the world's populations have NAFLD, with the highest prevalence rates in the Middle East and South America.^[8] The previous study has shown that diabetic individuals had an approximately three-fold higher risk of chronic liver disease, mainly associated with a non-virus and non-alcohol-related etiology which is largely attributable to NAFLD.^[9] Indeed, the prevalence of

Access this article online

Quick Response Code:



Website:

www.cmj.org

DOI:

10.1097/CM9.0000000000001263

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Chinese Medical Journal 2021;134(1)

Received: 31-07-2020 Edited by: Li-Shao Guo

NAFLD in patients with T2DM is more than two-fold higher than in the general population, occurring in up to 55.5%.^[10] A recent meta-analysis of NAFLD in China has reported an overall NAFLD prevalence is 29.88%, of which the prevalence is higher in participants with T2DM (51.83% in diabetic *vs.* 30.76% in nondiabetic) and those with obesity (66.21% in obese *vs.* 11.72% in lean).^[11] The prevalence of NAFLD is paralleled with the rising trend of obesity in China (the prevalence from approximately 2% in 2000 to 7% in 2014).^[12] Moreover, T2DM and obesity also increase the risk of progression from simple steatosis to NASH, cirrhosis, and HCC.^[13,14] Notably, in Asia, China has the highest prevalence, incidence, and annual NAFLD-related mortality rate.^[15] The growing epidemic of T2DM and obesity will fuel an increasing prevalence of MAFLD worldwide.

The new definition, MAFLD, puts more emphasis on the role of metabolic dysfunction in it, and the exclusion of significant alcohol intake or other chronic liver disease is not required for the diagnosis anymore.^[6] Indeed, the prevalence of obesity and metabolic syndrome in alcoholic liver disease (ALD) patients in the Third National Health and Nutrition Examination Survey (NHANES III) cohort are as high as 44.5% and 32.4%, respectively.^[16] Obesity and metabolic syndrome even exacerbate the progression of ALD.^[17] In clinical practice, NAFLD is recognized to coexist frequently with other conditions such as viral hepatitis.^[18,19] Concomitant MAFLD with other liver diseases is now defined as dual (or more) etiology fatty liver disease. All together will increase the prevalence of MAFLD further.^[20]

The presence of fatty liver with at least two metabolic risk abnormalities in lean or normal-weight individuals is also included in the diagnostic criterion of MAFLD. Lean or nonobese NAFLD is previously characterized as a unique phenotype,^[21] and its pathogenesis is still not entirely clear. Differences in metabolic adaptation between patients with lean and obese NAFLD, at least in part, explain the pathophysiology of lean NAFLD.^[22] A recent meta-analysis encompassing 93 studies from 24 countries or areas shows that in the general population, 5.1% of people have lean NAFLD and 12.1% have nonobese NAFLD.^[23] It is worth noting that NAFLD is not uncommon in lean adults even with normal waist circumference (12.9%).^[24] Thus, lean or normal-weight individuals but with metabolic abnormalities will constitute a certain proportion of MAFLD.

As mentioned above, the new definition of MAFLD and the new criteria incorporating other fatty liver diseases may result in a higher prevalence.

Pathophysiology of NAFLD/MAFLD

A “two-hit” theory was proposed in 1998 to describe the pathogenesis of NAFLD.^[25] It proposed that at the onset of disease, the “first hit” was represented by an increase in liver fat. Subsequently, the “second hit”, including inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress, was needed for the progression to NASH and advanced fibrosis.^[25] However,

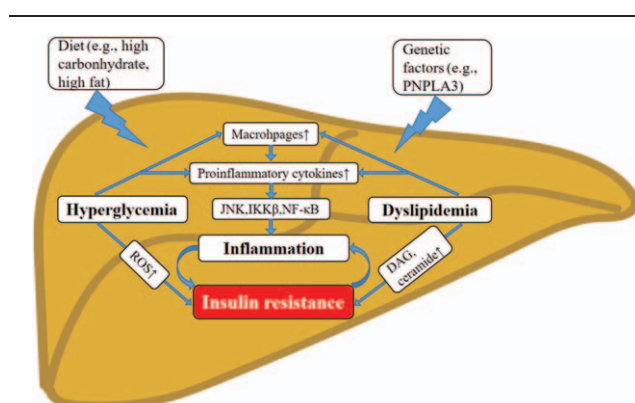


Figure 1: Pathophysiology of MAFLD involving genetic factors, glucotoxicity, and lipotoxicity. High-carbohydrate or high-fat diets contribute to the effect of glucotoxicity and lipotoxicity in the development of hepatic steatosis. Hyperglycemia and dyslipidemia induced hepatic insulin resistance and inflammation through different mechanisms in MAFLD. ROS: reactive oxygen species; IKK β : kinases I κ B kinase- β ; JNK: JUN N-terminal kinase; DAG: diacylglycerol; MAFLD: metabolic (dysfunction) associated fatty liver disease.

it was insufficient to include the various molecular and metabolic involvements in NAFLD-NASH-HCC progression since the pathogenic drivers of NAFLD are highly heterogeneous. A “multiple-hit” hypothesis, which incorporates various processes, such as insulin resistance, lipotoxicity, inflammation, imbalance of cytokines, activation of innate immunity, and microbiota, in the context of environmental and genetic factors, offers a more comprehensive delineation of the pathogenesis of NAFLD.^[26] In addition, the new terminology MAFLD proposes to define metabolic dysfunction as the corpus of the disease with these variable driving factors, resulting in further disease subtyping.^[27]

Nevertheless, fat accumulation in the liver caused by insulin resistance (IR) still represents the first and the core hit. In contrast to the high prevalence of NAFLD in patients with T2DM, the prevalence of NAFLD in patients with type 1 diabetes mellitus (T1DM) is relatively lower (8.8%).^[28] This finding further supports the hypothesis that insulin resistance, which is manifested in obesity and T2DM but rarely in T1DM, is the main contributing factor in the pathogenesis of NAFLD. Under conditions of IR, insulin is not capable of switching off hepatic glucose production anymore, but its ability to promote lipogenesis is retained.^[29] In this section, multiple factors contributing to the disease pathogenesis of NAFLD/MAFLD are reviewed [Figure 1].

Genetics

Findings from the genome-wide association study (GWAS) identified the main risk variants of the NAFLD population.^[30] Currently, at least five variants in different genes are robustly associated with the susceptibility to the progression of NAFLD. They are PNPLA3, TM6SF2, GSKR, MBOAT7, and HSD17B13.^[31-33] Of these genetic variants, some are associated with an increased risk of T2DM, including TM6SF2,^[34] TCFL2,^[35] and SREBF-2.^[36] Others are associated with the risk of developing obesity, such as ADIPOQ^[37] and SH2B1.^[38] These genes have been reported to be involved in IR, glucose, and lipid

homeostasis.^[39,40] The shared genes mentioned above indicate that NAFLD might have shared functional mechanisms that are involved in the pathogenesis of T2DM and obesity. They also support the diagnostic criteria of MAFLD in which the presence of metabolic dysfunction should be included.

In addition, genetic studies have revealed shared inherited determinants of NAFLD and other liver diseases. NAFLD associated variants in PNPLA3, TM6SF2, and MBOAT7 have been identified as risk loci for alcoholic cirrhosis.^[41] PNPLA3 and MBOAT7 are also associated with hepatic steatosis in patients with viral hepatitis.^[42,43] These findings hint that NAFLD is genetically interrelated with other liver diseases, supporting the inclusion of dual or more etiology to define MAFLD. The list of common variants associated with NAFLD, which also play a role in the development of metabolic disorders and other liver diseases, are presented in Table 1.

However, some of the disease-predisposing variants conferred in NAFLD are associated with a decreased risk of other metabolic disorders. For example, the NAFLD susceptible variants, GCRK P446L variant,^[44] are reported to have protective roles in developing T2DM. NAFLD risk allele at PNPLA3 I148M^[45] and TM6SF2^[46] are inversely associated with the risk of cardiovascular disease (CVD). The opposite effect of these variants on NAFLD and metabolic disorders (*ie*, T2DM and CVD) might be attributed to their divergent metabolic effects. For example, GCKR P446L variant induces *de novo* lipogenesis and improves hepatic glucose metabolism, resulting in elevated triglycerides (TG) in the liver but decreased glucose level.^[31] Thus, the effect of risk genes on liver fat content and metabolic variables are complex. Carriers with PNPLA3 I148M variant, the first and the most

common variant of NAFLD, are associated with a small increase risk of T2DM,^[34] but not accompanied by IR.^[45]

It is still unclear why patients with “genetic NAFLD” accumulate hepatic fat, which might be influenced by gain or loss of function of the risk variant. The differences in disease risk indicated by these variants may help to explain why individuals without diabetes or obesity could suffer from liver steatosis. Investigation of the genetic architecture of MAFLD should better characterize the role of risk variants in the disease heritability and pathogenesis in the future.

Glucotoxicity

Epidemiological studies indicate a correlation between high-carbohydrate diets and NAFLD.^[47] Diet with high sugars, such as fructose or sucrose, increases the risk of NAFLD.^[48] The abundant carbohydrate consumption and the resultant increased levels of blood glucose exert deleterious effects on cells, a phenomenon termed glucotoxicity. This concept is intrinsically linked to IR in the liver manifested with increased gluconeogenesis and decreased glycogenesis, leading to hyperglycemia.^[49]

T2DM is a chronic condition of glucotoxicity with characteristics of impaired glucose metabolism and hyperglycemia.^[50] The relation between NAFLD and T2DM is bidirectional and mutually causal. Studies in T2DM population have demonstrated that plasma glucose level is positively correlated with the histological severity of NAFLD.^[51] Glycemic variability is an independent predictive factor for the progression of NAFLD.^[52] Baseline IR is a good predictor of NAFLD incidence in the general population.^[53] Studies in rodents indicate that exposure to high glucose induces hepatic IR,^[54] which

Table 1: Summary of gene variants associated with the presence and/or severity of NAFLD

Gene name	Variant	In NAFLD	In metabolic disorders	In other liver diseases	Effects of the variant
PNPLA3	rs738409 (I148M)	Increase susceptibility to the whole spectrum of NAFLD. ^[45]	1. Increase risk of T2DM. ^[34] 2. Reduce risk of T2DM. ^[46]	A risk loci for ALD, ^[41] viral hepatitis. ^[147,148]	1. Gain of function: overexpression causes hepatic triacylglycerol accumulation. ^[149] 2. Loss of function: reduce the lipitation of VLDL. ^[150] 3. No function: deficiency in mice showed no hepatic steatosis. ^[151]
TM6SF2	rs58542926 (E167K)	Associated with risk of NAFLD. ^[46]	1. Increase risk of T2DM. ^[34] 2. Protect against CVD. ^[152,153]	Associated with ALD. ^[41]	Loss of function: favoring lipid accumulation into the liver. ^[46]
GCKR	rs1260326 (P446L)	Associated with predisposition to NAFLD. ^[31]	Protect against T2DM. ^[44]	NA	Loss of function: Elevate hepatic glucose uptake and boost lipogenesis by increasing active cytosolic GCK. ^[12]
MBOAT7	rs641738 (G17E)	Associated with risk of NAFLD. ^[43]	NA	A risk factor for ALD ^[41] and viral hepatitis. ^[154,155]	Reduced expression. ^[158]
HSD17B13	rs72613567 (TA)	Reduce risk of NASH, but not steatosis. ^[33]	NA	Protect against advanced ALD. ^[156-158]	Loss-of-function ^[33] ; result in an unstable and truncated protein with reduced enzymatic activity. ^[159]
TCF7L2	rs7903146 (CT/TT)	Increase risk of NAFLD. ^[31]	Increase risk of T2DM. ^[35]	NA	Loss of function in T2DM: associated with beta-cell dysfunction. ^[35]
SREBF-2	rs133291 (CT/TT) ^[36]	Predicts incident NAFLD	Predicts risk of T2DM.	NA	Gain of function
ADIPOQ	G45T and G276T	Associated with predisposition to develop NAFLD. ^[37]	Predict risk of T2DM and obesity. ^[40]	NA	NA
SH2B1	rs7359397 ^[38]	A higher risk of developing NASH	A higher risk of developing obesity	NA	NA

ALD: alcoholic liver disease (ALD); CVD: cardiovascular disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NA: not applicable; T2DM: type 2 diabetes mellitus; VLDL: very low-density lipoproteins.

could be a consequence of suppressed insulin receptor signaling.^[55,56] IR is also an independent risk factor associated with liver fibrosis in patients with T2DM.^[57] Given the strong correlation between T2DM and fatty liver, it will be of great interest to investigate the cause and effect interaction among glucotoxicity, IR, and MAFLD.

The chronic low-degree inflammation, which could be provoked by glucotoxicity and leads to IR,^[58] is also a shared pathological feature of NAFLD and T2DM.^[59] The process of NAFLD inflammation is induced by two classical pathways: kinases I κ B kinase- β (IKK β) pathway and JUN N-terminal kinase (JNK) pathway.^[60] In serum of patients with T2DM, levels of interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor (TNF)-alpha, and C-reactive protein (CRP) are higher than those without T2DM.^[61] These inflammatory regulators activate IKK β and JNK pathway and thus promote IR in the liver.^[60] The down-stream transcription factor nuclear factor- κ B (NF- κ B) of these two inflammatory pathways amplifies the expression of the aforementioned pro-inflammatory cytokines.^[62] Besides, the increasing oxidative stress in hepatocytes also accounts for the glucotoxicity-related inflammation.^[63] In mice exposed to glucose fluctuation, liver inflammation is enhanced by the mitochondrial permeability transition and dysfunction.^[64]

To sum up, glucotoxicity-related systematic IR and chronic inflammation act as shared mechanisms in the progression of hepatic steatosis and T2DM. It supports the new definition of MAFLD with the involvement of glucotoxicity in the pathogenesis. Future study is required to investigate the mechanism by which glucotoxicity induces hepatic IR and the therapeutic options that could block this process.

Lipotoxicity

Hepatic steatosis develops within days of a high-fat diet (HFD) feeding in both human beings and rodents.^[65,66] A recent study found that a diet enriched in saturated fat was more harmful for elevating intrahepatic TG content than a diet enriched in free sugars in overweight males.^[67] These findings support the predominant role of lipotoxicity in NAFLD. Tracer studies in individuals with obesity have demonstrated that ~60% of liver TG content is derived from free fatty acids (FFAs) from adipose tissue.^[68] Obese individuals have increased visceral adipose tissue that could lead to IR and hyperinsulinemia, which will enhance adipose tissue lipolysis.^[3] Rodent models have shown that decreasing hepatic TG content could improve insulin sensitivity,^[69,70] suggesting a strong link between lipotoxicity and hepatic IR.^[71]

The potential lipids in inducing hepatic IR consist of two major classes of lipid intermediates: diacylglycerol (DAG) and ceramide.^[72] In obese, nondiabetic patients, hepatic DAG content is the best predictor of NAFLD-related IR.^[73] Later research verifies that the development of hepatic IR is ascribed to hepatic DAG-induced PKC ϵ activation in NAFLD.^[74] In mice, hepatocyte deletion of DAG acyltransferase 2 successfully reduces diet-induced hepatic steatosis.^[75] Intracellular DAG near the membrane

results in PKC activation, which in turn inhibits insulin signaling.^[76] Besides, studies in rats show that the hepatic ceramide level is increased in HFD induced hepatic steatosis and IR,^[77] and inhibiting ceramide synthesis could attenuate hepatic steatosis and IR.^[78] Thus, lipid metabolites act as inter-mediators in the causal link between lipotoxicity and IR, which both contribute to the development of NAFLD/MAFLD.

Lipotoxicity related chronic low-grade inflammation is involved in the development of NAFLD.^[79] In obese individuals, the degree of inflammation indicated by IL-6 and TNF- α were in a dose-dependent manner correlated with the severity of NAFLD.^[80] The production of pro-inflammatory mediators further activates the key transcriptional factors such as JNK and NF- κ B,^[81] leading to steatohepatitis. At the same time, the impaired release of anti-inflammatory adipokines (*eg*, adiponectin) also diminishes insulin sensitivity.^[82] Apart from inflammatory molecules, the recruitment of macrophages in the liver is associated with IR and steatohepatitis.^[83]

From the above, lipotoxicity-related IR and inflammation contribute to the pathogenesis of fatty liver. As obesity and dyslipidemia are implicated in the new definition of MAFLD, further research is needed to clarify the mechanisms of lipotoxicity induced MAFLD.

Diagnosis

The proposed criteria for the diagnosis of MAFLD rely on the evidence of hepatic steatosis, which could be detected either by imaging techniques, blood biomarkers, or liver histology. Several noninvasive screening and diagnostic assessments have been developed in recent years for liver steatosis evaluation.^[84] Here, we summarize the current status of noninvasive (imaging, biomarkers) and invasive (liver biopsy) methods available for the diagnosis of NAFLD/MAFLD.

Imaging techniques

Owing to the asymptomatic features of NAFLD, hepatic steatosis is often incidentally diagnosed on imaging checks such as abdominal ultrasound, CT scan, or magnetic resonance imaging (MRI). The most common imaging method for diagnosis is an abdominal ultrasound which is easily accessible and can sonographically demonstrate the fat infiltration of the liver.^[85] However, when steatosis is less than 30%, the sensitivity reduces significantly.^[86,87] Although the diagnostic accuracy of CT is much more precise than ultrasound for grading moderate to severe steatosis, its capability is also limited for mild steatosis. Moreover, the radiation exposure limits its use as a screening or early diagnostic tool.^[88] An alternative diagnostic method is MRI, which is highly sensitive for small amounts of isolated steatosis. But this modality is not readily available or cost-effective.^[89]

More recently, transient elastography (TE, FibroScan) performed with ultrasound has gained attraction due to the allowance of rapid measurements of liver stiffness, an indicator that is strongly related to the stage of liver

fibrosis.^[90] Controlled attenuation parameter (CAP) has been developed to assess the quantification of hepatic steatosis and fibrosis simultaneously, based on the properties of ultrasonic signals through the TE in patients with T2DM.^[91] Screening for NAFLD in T2DM individuals using FibroScan/CAP is recommended in the latest Asia-Pacific Working Party on Non-Alcoholic Liver Disease guidelines.^[92] Studies using FibroScan/CAP has found a high prevalence of NAFLD (ranging from 60.7% to 70.4%) in patients with T2DM.^[93,94] This range is in agreement with the prevalence of NAFLD (47.26%–63.67%) in T2DM.^[10] It will be plausible to optimize its use in screening fatty liver in patients manifested with metabolic dysfunction.

Blood biomarkers

Intensive efforts have been exerted to develop non-invasive biomarkers for the detection of fibrosis in patients with NAFLD.^[95] In clinical practice, NAFLD fibrosis score (NFS) and fibrosis-4 index (FIB-4) scoring systems work well to exclude advanced fibrosis-cirrhosis (with negative predictive values >90%); therefore, they could be used as a first-line classification to identify patients with low risk of advanced fibrosis.^[96] However, it may be late to take action in reversing the fibrosis stage. The ability to detect simple steatosis and steatohepatitis early and noninvasively in patients with fatty liver is crucial for preventing disease progression. Previous studies demonstrated that the biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin A1c, and homeostatic model assessment (HOMA)-IR could provide good prediction indices of NAFLD in patients with metabolic syndrome^[97,98] or even in the general population.^[99] The advances in novel serum markers, including cytokeratin 18 fragment (CK18-F) and insulin-like growth factor-1 (IGF-1), have shown desirable performance in routine screening for NAFLD.^[100] Besides, the serum miRNAs test exhibits robust diagnostic efficacy for NASH in obese subjects.^[101]

Nevertheless, a recent study shows that the well-validated biomarker panels for the diagnosis of different stages of NAFLD such as simple steatosis, steatohepatitis, and advanced fibrosis may underperform in patients with T2DM.^[97] It suggests that patients with T2DM may require predictive models that have been specifically developed for them.

Histological biopsy

Liver biopsy remains the golden standard for the diagnosis of NAFLD, especially for the diagnosis of NASH.^[102] However, limitations of liver biopsy should be noted. For instance, a biopsy procedure is an invasive test with interobserver variability that could produce complications, and the mortality percentage of biopsy is about 0.05%.^[103] In addition to technical problems, liver biopsy is a costly procedure that requires operators and pathologists trained to obtain adequate and representative results, which limits its use for mass screening.^[96] The accuracy of liver biopsy to evaluate fibrosis has been questioned, mainly due to the sampling errors and intra-

and inter-observer variability, which can lead to an over or underestimation of the hepatic fibrosis stage.^[104] For these reasons, noninvasive methods might be preferred as the first choice to detect NAFLD/MAFLD. Liver biopsy is reserved for the patients in whom the etiology of the liver disease needs to be clarified, or when NASH and the degree of liver fibrosis cannot be ascertained with noninvasive measures.^[105]

Pharmacotherapy

No specific pharmaceuticals are currently FDA approved for NASH. Drugs that target inflammation and fibrogenesis are under investigation,^[106] but with limited clinical success. The likely cause of failures of phase 2 and phase 3 studies involving the anti-apoptosis and anti-fibrosis treatment^[107] may be that the drug targets a later stage in the development of NASH. In addition, the American Association for the Study of Liver Diseases (AASLD) guidance suggests that drugs should be limited to patients with NASH and fibrosis,^[2] leaving a gap in pharmacotherapy for earlier stage of NAFLD. The new criteria for the diagnosis of MAFLD will promisingly encourage the initiation of drugs in the early stage.

Since T2DM and obesity shared the common pathophysiological factors with NAFLD/MAFLD, anti-obesity and anti-hyperglycemic drugs may exert efficacy in improving liver histology and clinical outcomes in NAFLD/MAFLD. Particularly, CVD is the leading cause of death in patients with NAFLD and NASH.^[108] Drugs that have beneficial CVD outcomes in T2DM, such as glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors, might also reduce the risk of cardiovascular mortality in patients with NAFLD/MAFLD. A composite of current glucose and lipid-lowering drugs with trials undergoing in NAFLD is listed in Table 2.

Insulin sensitizers and vitamin E

As mentioned previously, IR and oxidative stress contribute to the process of liver lipid accumulation. Pioglitazone, a peroxisome proliferator-activated receptor (PPAR)- γ agonist that belongs to thiazolidinediones (TZDs), is approved for the treatment of T2DM by alleviating IR.^[109] Vitamin E is a potent antioxidant that may reduce oxidative stress in NAFLD. In the PIVENS (Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis) trial, both pioglitazone and vitamin E were associated with ameliorated hepatic steatosis in NASH patients without diabetes,^[110] with no benefit in fibrosis improvement. In patients with T2DM, pioglitazone has shown effects in alleviating IR with improvement in liver steatosis and inflammation compared to placebo.^[111] A recent proof-of-concept study has revealed that pioglitazone in combination with vitamin E is better than a placebo in improving liver histology in patients with NASH and T2DM.^[112] Based on these studies, pioglitazone and vitamin E are now recommended by guidelines as treatment options for biopsy-proven NASH patients with and without diabetes, respectively.^[2] However, the use of pioglitazone has been

Table 2: Summary of pharmacotherapy with currently undergoing clinical trials in NAFLD.

Class	Agents	Mechanism of action	Outcomes in treating NAFLD/NASH	Recommendation in AASLD 2018
Anti-oxidant agents	Vitamin E	Antioxidant effect	1. Improve steatosis, inflammation, and resolution of NASH. ^[110] 2. Significantly reduce serum hepatobiliary enzymes, hepatic steatosis, inflammation, and hepatocellular ballooning. ^[160]	Nondiabetic adults with biopsy-proven NASH
Insulin sensitizers	Pioglitazone	PPAR- γ agonism	1. Significantly improve hepatic steatosis and lobular inflammation in NASH with ^[110] and without T2DM with additional weight loss. ^[111] 2. Improved liver histology in combination with vitamin E. ^[112]	Patients with biopsy-proven NASH
	Metformin	IR alleviation	No effect of metformin on liver histology. ^[116]	Not recommended
GLP1 analogues	Liraglutide	GLP1 receptor agonism	Meet the primary endpoint of histological resolution of NASH with no worsening in fibrosis. ^[123]	Premature as a specific treatment for NASH
	Semaglutide		1. Reduce ALT and hypersensitive CRP. ^[126] 2. Resulted in a significantly higher percentage of patients with NASH resolution than placebo. ^[127]	
SGLT2 inhibitors	Empagliflozin	SGLT2 inhibition	Reduces liver fat, improves ALT levels in patients with T2DM and NAFLD. ^[131]	NA
Statins	Simvastatin	HMG-CoA reductase inhibitor	Reduce the risk of steatosis by 71% after 4 years of treatment in combination with vitamins C and E in patients with NAFLD. ^[161]	Can be used to treat dyslipidemia and should be avoided in decompensated cirrhosis.
FXR agonist	Obeticholic acid	FXR agonism	1. Reduce NAFLD activity ^[141] and improving fibrosis. ^[142] 2. Combination with statin mitigate OCA-induced increases in LDLc. ^[145]	Should not be used off-label to treat NASH.

AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase; CRP: C-reactive protein; FXR: farnesol X receptor; GLP1: glucagon-like peptide 1; HMG-CoA: hydroxymethylglutaryl-CoA; IR: insulin resistance; LDLc: low-density lipoprotein cholesterol; NA: not applicable; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; OCA: obeticholic acid; PPAR: peroxisome proliferator-activated receptor; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter 2; T2DM: type 2 diabetes mellitus.

restricted by the risk of congestive heart failure and postmenopausal bone loss.^[113] Long-term use of high-dose vitamin E has been reported to be associated with an increased incidence of hemorrhagic stroke.^[114] Thus, the benefits of these drugs must be balanced against the potential risks when the decision is made in clinical practice.

Apart from TZDs, metformin, another kind of insulin sensitizer, has been positioned as the first-line agent for T2DM for many years.^[115] Although there is a lack of evidence for metformin as an adequate treatment to improve liver histology of NAFLD,^[116] the weight loss-promoting and insulin-sensitizing properties of metformin are desirable.^[117] A recent study in T2DM patients with biopsy-proven NASH and fibrosis showed that long-term metformin use is associated with a lower risk of overall mortality, liver transplant, and HCC.^[118] These benefits together with its low cost and safe profile^[119] could make metformin an ideal candidate for the treatment of T2DM and NAFLD/MAFLD.

New antidiabetic agents

Over the past few decades, there have been efforts to study the effect of new antidiabetic agents, such as GLP-1 RAs, dipeptidyl-peptidase 4 (DPP-4) inhibitors, and SGLT2 inhibitors with the goal of reversing hepatic steatosis and preventing the progression to NASH with advanced fibrosis.^[120] GLP-1 RAs along with SGLT2 inhibitors become the first-line therapy for patients at high risk of major adverse cardiovascular events in T2DM.^[121] According to a recent meta-analysis of seven trials, GLP-1 RAs have beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with T2DM.^[122] The efficacy of liraglutide was reported in NASH patients in the Liraglutide Efficacy and Action in NASH (LEAN) study^[123] and Japanese studies (LEAN-J study).^[124] The phase 2 of the LEAN study showed that liraglutide met the primary endpoint of histological resolution of NASH with no worsening in fibrosis. Semaglutide, a novel GLP-1 RA, has been proved for glucose control and weight loss in patients with T2DM.^[125] In sub-analyses of the SUSTAIN-6 study, semaglutide has been shown to reduce ALT and

hypersensitive CRP.^[126] A recent phase 2 trial has shown that semaglutide treatment resulted in a significantly higher percentage of patients with NASH resolution and with no worsening of fibrosis than placebo (59% in the 0.4-mg group and 17% in the placebo group).^[127] Although DPP-4 inhibitors prolong the effect of endogenous GLP-1, it is not effective for patients with hepatic steatosis or steatohepatitis as shown by a recent systematic review.^[128] Therefore, GLP-1 RAs will be a promising incretin-based drug for the treatment of MAFLD, especially in patients with T2DM.

SGLT2 inhibitors decrease blood glucose levels in patients with T2DM via the promotion of renal excretion of glucose.^[129] A meta-analysis of randomized controlled trials (RCTs) with the reported outcome up to October 1, 2019, has shown that SGLT2 inhibitors could significantly decrease ALT level, reduce liver fat content and body weight in patients with T2DM, which indicates a positive effect of SGLT2 inhibitor on improving fatty liver.^[130] In an open-label pilot study, empagliflozin (an SGLT2 inhibitor) has reduced liver steatosis, ballooning, and fibrosis in T2DM patients with liver-biopsy proven NASH.^[131] Robust clinical data has demonstrated that apart from renal protection, SGLT2 inhibitors improve cardiovascular outcomes in patients with T2DM.^[132] Given CVD being the most common cause of death in NAFLD, the effect of SGLT2 inhibitors on the reduction of cardiovascular death will be beneficial to the prognosis of NAFLD. Studies have shown that the combination of GLP-1 RAs and SGLT2 inhibitors results in significant improvements in glycemic control with acceptable tolerability in patients with T2DM.^[133,134] Based on the above evidence, GLP-1 RAs, SGLT2 inhibitors, the combination of them, or an add-on to each other might be useful in the treatment of MAFLD in the future. However, more clinical trials and evidence are urgently needed.

Statins

Statins, a class of lipid-lowering drugs, reduce the risk of cardiovascular morbidity and mortality in patients with NASH and dyslipidemia.^[135] Though no evidence proves the benefits of statins on liver histology in NASH patients,^[136] statins may reduce the risk of HCC in diabetic patients.^[137,138] The current guideline has pointed out that statins can be safely used to treat dyslipidemia and prevent CVD in patients with NAFLD/NASH.^[2] As lipid accumulation is closely associated with the progression and cardiovascular outcomes of NAFLD, statins are promising drugs for the treatment of MAFLD.

Farnesoid X receptor (FXR) agonists

FXR is a member of the nuclear receptor superfamily controlling a variety of genes involved in bile acid synthesis and transport, also in glucose and lipid metabolism.^[139] Obeticholic acid (OCA), an FXR agonist, is now waiting for the FDA decision to approve its marketing authorization application by June 2020. In phase 2 RCT, OCA improved IR and liver function tests better than placebo in patients with NAFLD and T2DM.^[140] Following the encouraging results of the “FLINT” trial which has shown

the superiority of OCA at reducing NAFLD activity score (NAS) by two points without fibrosis worsening in adults with NASH,^[141] a phase 3 trial called “REGENERATE” is currently underway. Its interim analysis has shown that OCA significantly improved fibrosis and NASH activity.^[142] Nevertheless, pruritus was reported to be the most common side effect of OCA treatment in this interim analysis,^[142] leading to discontinuation of treatment in some patients. In *post hoc* analyses of the phase 2b FLINT trial, OCA was associated with an increase in serum alkaline phosphatase, LDL cholesterol (LDLc), and hemoglobin A1c levels.^[143,144] Combination treatment of OCA with atorvastatin has subsequently been proven efficacious in preventing the LDLc increase present in OCA monotherapy.^[145] Novel candidate compounds for selective FXR modulation is in urgent demand to improve the tolerability in the treatment of NAFLD.

Since MAFLD is associated with disturbance in lipid and glucose metabolism, a combination of drugs targeting different pathogenic mechanisms will be the highly anticipated treatment.

Conclusion

A growing epidemic worldwide of T2DM and obesity, and the new definition of MAFLD may lead to a higher prevalence of MAFLD in the future. The pathophysiology of MAFLD is closely associated with metabolic syndrome, T2DM, and obesity. The complex interactions between genetics, glucotoxicity, and lipotoxicity make it difficult to distinguish the precise mechanisms underlying the increased risk of MAFLD in T2DM or obesity. There is thus an imperative need to clarify the epidemiological features and mechanisms that drive the development and progression of MAFLD. Rising the awareness of early screening for MAFLD is important for timely diagnosis and effective interventions. As the patient population is heterogeneous and the pathophysiology is complex, the area of drug development is particularly challenging. Drugs that target the advanced stage of NASH, including liver fibrosis and cirrhosis, are currently under investigation, but with limited clinical success. It suggests that interventions should be initiated at the early stage of NAFLD/MAFLD to obtain cardiovascular benefits and prevent the progression to the advanced stages. Pharmacological strategies aiming at improving metabolic dysfunctions will be promising for improving the clinical outcomes of NAFLD/MAFLD.

Funding

This study was supported by grants from the National Natural Science Foundation of China (Nos. 81670782 and 81970741), the Local Innovative and Research Teams Projects of Guangdong Pearl River Talents Program (No. 2017BT01S131), the Guangdong High-Level Talents Special Support Program (No. 2016TQ03R590), and the Pearl River S&T Nova Program of Guangzhou (No. 201610010175).

Conflicts of interest

None.

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How to cite this article: Xian YX, Weng JP, Xu F. MAFLD *vs.* NAFLD: shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy. *Chin Med J* 2021;134:8–19. doi: 10.1097/CM9.0000000000001263