Metabolic-Associated Fatty Liver Disease and Diabetes

A Double Whammy

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KEYWORDS

• Metabolic-associated fatty liver disease • Metabolic syndrome • Fatty liver
• Type 2 diabetes mellitus • Obesity

KEY POINTS

- Metabolic-associated fatty liver disease (MAFLD) and type 2 diabetes mellitus frequently tend to coexist, potentiating adverse outcomes and individual progression of both disorders.
- MAFLD is the most common cause of chronic liver disease in children and adolescents but can be effectively prevented with lifestyle modifications.
- Several biomarkers like SteatoTest/fatty liver index can be used in clinical practice to suspect MAFLD even in resource-limited settings.
- In addition to lifestyle modifications, pharmacologic interventions including certain antidiabetic agents, antihyperlipidaemic drugs, and some novel targeted agents in addition to bariatric procedures have been successful in the management of MAFLD.

INTRODUCTION

Fatty liver (FL) disease is a widely prevalent disorder first described in 1980s,[1] but more recently, the prevalence has increased several fold affecting almost a quarter of the global population. Initially referred to as nonalcoholic FL disease (NAFLD) over the years, with a better understanding of the disease process, the nomenclature has been changed and is more appropriately referred to as metabolic (dysfunction)-associated FL disease (MAFLD).[2] This is more relevant when investigated in the presence of

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diabetes mellitus. Although there are subtle differences between the two diagnoses, MAFLD seems to be a more appropriate term encompassing its heterogeneous pathogenesis and appropriate stratification of patients from a management standpoint.[3]

The two most significant differences in the diagnostic criteria between MAFLD and NAFLD are that MAFLD diagnosis does not require exclusion of patients with alcohol intake or other chronic liver disorders such as viral hepatitis. Furthermore, the presence of a metabolic abnormality (eg, type 2 diabetes mellitus [T2DM]) is necessary for diagnosis of MAFLD.[4] The diagnostic criteria for MAFLD are summarized in **Table 1** and are considered as the hepatic manifestation of metabolic syndrome.[5]

MAFLD encompasses a disease spectrum from hepatic steatosis to hepatitis, fibrosis, cirrhosis, and at times even malignancy (**Fig. 1**).[5]

Hepatic steatosis is an abnormal liver fat that exceeds 5% of the total liver weight or 5% of hepatocytes are laden with fat. Although ideal to diagnose this stage on histopathology, both imaging techniques and noninvasive biological scores are able to predict this with fair amount of accuracy. Nonalcoholic steatohepatitis (NASH) is defined by the histological presence of three components in the liver including steatosis, hepatocyte ballooning, and hepatocellular inflammation. Similarly, even fibrosis ideally requires histopathological examination but can be well predicted by using clinical-bio markers and/or imaging techniques using age-appropriate cutoffs. Cirrhosis is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa associated with pronounced distortion of hepatic vascular architecture. Cirrhosis remains asymptomatic until decompensation occurs due to portal hypertension or is detected during routine master health check. Furthermore, hepatocellular carcinoma could occur after cirrhosis or even bypassing the stage of cirrhosis directly after the stage of NASH.

PROBLEM STATEMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE AND DIABETES

MAFLD is the most common liver disease globally. Its prevalence has been rapidly increasing in parallel to the epidemics of diabetes and obesity. A meta-analysis by Younossi and colleagues,[6] on the prevalence of NAFLD in patients with T2DM, suggested the global prevalence to be about 55%, of whom 37.3% had NASH and approximately 4.8% had advanced fibrosis. The investigators in yet another study projected that about 18.2 million people in United States had both T2DM and MAFLD.[7] Over the next two decades, it is estimated that NASH with T2DM would account for 1.37 million cardiovascular deaths and 81,200 liver-related deaths. Similar estimates have been made from other countries as well.[8] In a recently published cohort study, it was shown that individuals with MAFLD had a 14% higher risk of cardiovascular mortality than non-MAFLD individuals.[9]

A meta-analysis on global prevalence by Lim and colleagues[10] reported a pooled prevalence of MAFLD in 39.2%, with the highest prevalence in Europe and Asia followed by North America. The MAFLD prevalence accounted for 81.59% of all individuals having NAFLD. MAFLD was found to be significantly associated with male sex,

Table 1
Diagnostic criteria for metabolic-associated fatty liver disease

1	Evidence of hepatic steatosis based on clinical/laboratory parameters and/or liver histology
2	Presence of a metabolic risk condition, for example, overweight/obesity and/or type 2 diabetes mellitus and/or any of the components of metabolic syndrome

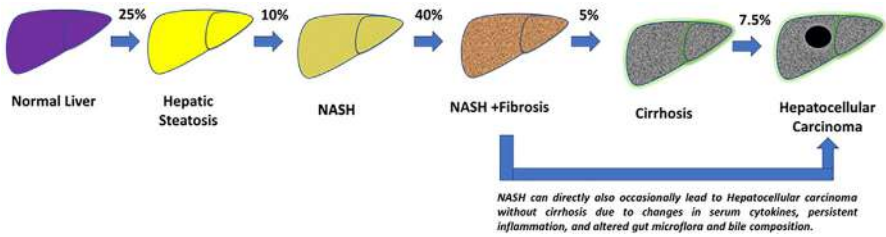

Fig. 1. The disease spectrum of metabolic-associated fatty liver disease (MAFLD). NASH, nonalcoholic steatohepatitis.

higher body mass index (BMI), presence of hypertension, diabetes, dyslipidemia, transaminitis, and greater fibrosis score compared with patients with NAFLD.[10]

LIVER PANCREAS CROSS TALK

There is a significant contribution of liver dysfunction in the development of T2DM. Although these mechanisms are not fully understood, hepatic fat accumulation leads to alterations in energy metabolism and inflammatory signals that contribute to insulin resistance. Moreover, chronic hyperinsulinemia as seen in patients with T2DM also leads to hepatic fat accretion. Lipotoxins, mitochondrial dysfunction, cytokines, and adipocytokines have been proposed to play a major role in the pathogenesis of both MAFLD and T2DM. Based on a recent review by Byrne and colleagues,[11] a diagrammatic representation of the risk of developing diabetes and MAFLD in the presence of each other is depicted in **Fig. 2**. A higher baseline FL index has been shown to be an independent predictor of developing new onset diabetes during a 10 year follow-up.

METABOLIC SYNDROME AND METABOLIC-ASSOCIATED FATTY LIVER DISEASE

Individual studies have shown that MAFLD has been associated with obesity, dyslipidemia, hypertension, and diabetes all of which have been individually associated with metabolic syndrome (MetS), such that it has been considered the hepatic manifestation of the MetS.[12] There is growing evidence that this relationship between MAFLD

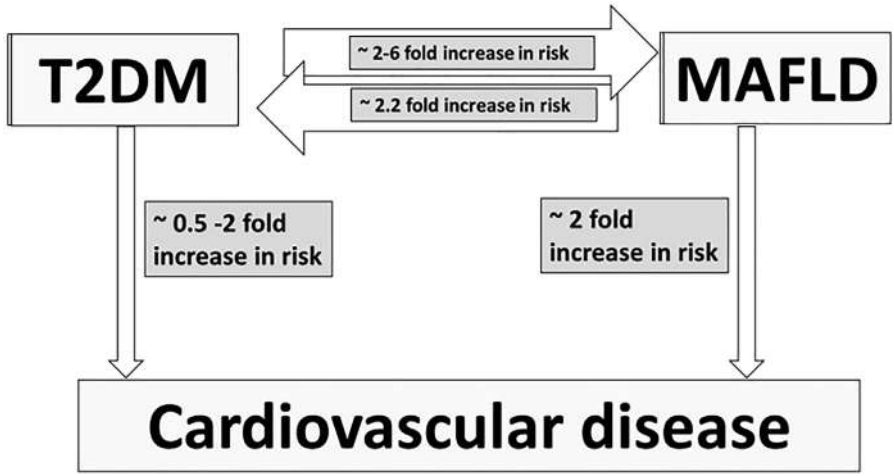

Fig. 2. The bidirectional risk of developing type 2 diabetes mellitus and MAFLD.

and MetS is bidirectional. MAFLD can predispose to different components of MetS, which can in turn exacerbate MAFLD. Although the relationship between MAFLD and MetS is considered bidirectional, recently there has been much interest in genotype/phenotype relationships where there is a disconnect between the liver disease and MetS features. This has been shown with genotypes such as patatin-like phospholipase domain-containing protein-3 (I148M) and transmembrane 6 superfamily member 2 protein (E167K).[13]

Evaluation of Metabolic (Dysfunction)-Associated Fatty Liver Disease in Presence of Diabetes

The following biochemical and radiological tools help to make a diagnosis of MAFLD. These investigations are used not only for diagnosis but also to follow-up and determine the severity in affected patients.

Serum Biomarkers

Even though at present there is no single ideal biomarker that can be used to diagnose MAFLD, there are certain noninvasive models that are proposed to help better prediction of steatosis. The most common biochemical parameter that raises a suspicion of underlying hepatic steatosis is the presence of elevated alanine aminotransferase. In a recent article by Zeng and colleagues,[14] several biomarkers that predict MAFLD have been described. Some of these are for clinical use, and others used as research tools have been described. These have been categorized as apoptosis biomarkers, fibrosis biomarkers, inflammatory biomarkers, adipokines and hepatokines, genomics, epigenomics, transcriptomics, and proteomics. Some clinically useful biomarkers have been described below.

SteatoTest: This is a logistic regression model comprising 12 clinical and biochemical parameters including age, sex, BMI, alanine aminotransferase, alpha-2 macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, gamma-glutamyl transferase, cholesterol, serum triglycerides, and blood glucose. In a study by Poynard and colleagues,[15] the SteatoTest had a sensitivity and specificity of 90% among 884 NAFLD subjects. The advantage of this tool is that it is noninvasive and uses easily available parameters in these patients.

Fatty liver index: This is based on a more simplified validated algorithm-based index derived from minimal indices including BMI, waist circumference, serum triglyceride levels, and gamma-glutamyl transferase. This index varies from 0 to 100 and a value of more than 60 is suggestive of FL disease. This has also been previously compared with the SteatoTest.

Imaging Modalities

Ultrasonography: This is a widely used technique for screening individuals who are suspected to have MAFLD. The underlying principle is that in the presence of excessive fat, there is an increased echogenicity of the liver, which in turn makes it appear brighter as compared with the renal cortex.[16]

Several studies have shown a sensitivity varying from 91% to 100%, which makes ultrasound a good screening tool.[17–19] It is preferred because it is noninvasive, relatively less expensive, and widely available. The major limiting factors include its operator dependence, inability to differentiate diffuse fibrosis versus diffuse hepatic steatosis and to precisely quantify the amount of fat at baseline and follow-up.[20] It is often difficult to interpret in obesity, which is often the case with MAFLD.[21]

A more objective method on sonography to detect FL is a hepato-renal ratio (HRR). This is based on the principle that in normal circumstances, the liver and kidney have a

similar echogenicity. In the presence of FL, the liver will appear brighter than the renal parenchyma. HRR has shown to have 100% sensitivity and 91% specificity for the diagnosis of hepatic steatosis.[22]

Vibration controlled transient elastography (VCTE)/fibroscan: Transient elastography is a noninvasive technique to measure the hepatic tissue elasticity and thereby predict the degree of fibrosis (liver stiffness). Although the liver stiffness was initially proposed as a reliable tool to identify fibrosis and cirrhosis in patients with hepatitis C, now data are also evident for its use in MAFLD.[23] The only major limiting factor in its use in patients with MAFLD is the usually high BMI associated in these patients which may underestimate the disease burden due to the attenuation of the ultrasound waves. Controlled attenuation parameter is a similar tool based on liver stiffness measurement that has been developed to use with a fibroscan. Its value may range from 100 to 400 decibels per meter (Db/M). A cutoff value more than 283 Db/M has shown to have a sensitivity of 76% and a specificity of 79% to detect steatosis.[24] The use of ultrasound elastography is a promising tool in most types of liver disease as in MAFLD; however, it has its own limitations especially in individuals with obesity, which may lead to underdiagnosis and thereby underestimation of primary MAFLD rates.

Computed tomography scan: Computed tomography (CT) scan provides a vivid assessment of the entire liver making it possible for even small amounts of focal infiltrations to be picked up in addition to diffuse involvement. Unlike the ultrasound, the CT scan measures the attenuation difference in contrast to spleen and not the kidney in terms of Hounsfield units.[25] This is best visualized in the non-contrast images where hepatic fat appears as hypodense areas on the liver. It has been shown to have a sensitivity of 73% to 100% and a specificity of 95% to 100% to detect moderate to severe steatosis.[26] However, despite a good pick-up rate, its role in practice for diagnosis of FL is limited by its cost and radiation exposure both of which make it difficult to use it even during follow-up.

Magnetic resonance imaging scan: Several studies have demonstrated that two-dimensional magnetic resonance (MR) elastography may be a promising biomarker in the noninvasive diagnosis of advanced fibrosis in MAFLD, with modest success in the diagnosis of NASH.[27] However, despite its good sensitivity and specificity, its cost and limited availability is a major limiting factor. MRE and vibration-controlled transient elastography have been shown to have an excellent diagnostic performance for assessing hepatic fibrosis in patients with morbid obesity.[28] In a study by Chen and colleagues,[28] MRE has been shown to be technically more reliable than vibration-controlled transient elastography (VCTE).

Magnetic resonance spectroscopy: This is another tool that has been validated to assess the hepatic fat content in individuals with MetS. Although magnetic resonance spectroscopy (MRS) was initially designed for cranial imaging, the proton-based 1H MRS is currently being used in the research setting to reliably asses the hepatic fat content.[29]

Liver biopsy: Liver biopsy remains the gold standard for the diagnosis and staging of NASH and to capture the degree of fibrosis due to the lack of many precise noninvasive measures to do that. NASH is characterized by ballooning of hepatocytes and lobular inflammation with or without perisinusoidal fibrosis in the background of steatosis. Although liver biopsy is not warranted in all patients with NASH due to its cost, invasive nature, and associated risks, the physician's discretion is required to balance between the risks and benefits in any given patient.[30] Liver biopsy may also rule out other associated causes (sero-negative autoimmune hepatitis, chronic hepatitis B or C virus infection, Wilson disease, drug-induced liver injury, and alpha-1-antitrypsin deficiency) of chronic liver disease in MAFLD.

Management of Metabolic-Associated Fatty Liver Disease with Type 2 Diabetes Mellitus

Lifestyle interventions

Lifestyle modification is the first-line of treatment of all patients with MAFLD. It often is the only intervention needed for a majority of these patients. Moreover, it needs to be continued even when other modalities of treatment are added.[31] In a study by Gomez and colleagues, where the impact of lifestyle intervention was studied prospectively in 293 patients after a year of weight loss, 25% achieved resolution of steatohepatitis, 47% had reductions in NAFLD score, and about 20% had regression in fibrosis. The maximum reduction in MAFLD-related parameters was observed in patients who had a weight loss more than 10%.[32]

The impact of dietary interventions in patients with diabetes and metabolic-associated fatty liver disease

Over the years, dietary interventions for managing noncommunicable disorders have evolved from a general disease-related advice to a patient-centric, customized dietary plan.[33] Several studies have tested which diet would work better for the management of MAFLD. A recent systematic review by Varkaneh and colleagues compared the efficacy of low carbohydrate versus low-fat interventions. The investigators concluded that the use of low-calorie diet, irrespective of fat and carbohydrate content, resulted in similar outcomes. Although both reduced body weight and liver fat content, low-fat diet was more successful in reducing the transaminase levels.[34] Similar results have also been shown with other diets including the Mediterranean diet, intermittent fasting, and other very low-calorie diets.[35–38] However, further studies that robustly evaluate the impact of these diets along with their acceptability, sustainability, and the effect on the patients' health-related quality of life are needed.[39]

EXERCISE-RELATED INTERVENTIONS FOR THE MANAGEMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE WITH DIABETES

Different exercise-related interventions have been tried in patients with MAFLD. Those that result in high-intensity energy expenditure and contribute to significant weight loss have been more beneficial. In a meta-analysis by Zhou and colleagues,[40] analyzing 17 studies with 1627 patients found that a combination of aerobic with resistance exercise followed by high-intensity interval training was most efficient in improving liver-related parameters. Another study by Hong and colleagues,[41] which demonstrated the beneficial effects of exercise training in patients with NAFLD, showed that the benefits were more marked in younger individuals than older patients. The key differences in the use of lifestyle interventions in patients with MAFLD with diabetes as compared with those without diabetes is that the intensity of interventions required for patients with MAFLD would often be twice as intense (5% weight loss for patients with diabetes versus 10% weight loss for MAFLD).

PHARMACOTHERAPY FOR THE MANAGEMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

The Utility of Antidiabetic Agents in the Management of Metabolic-Associated Fatty Liver Disease

A brief summary on the current evidence on the utility of commonly used management strategies of managing MAFLD in patients with diabetes mellitus are summarized in **Table 2**.

Table 2
Summary of the current evidence of different management strategies commonly used in patients with diabetes to address metabolic-associated fatty liver disease

Management Strategy	Current Evidence	Recommendation
Lifestyle interventions		
Dietary modifications	• Low-calorie diet irrespective of the macronutrient proportions that results in more than 10% weight loss is helpful in improving MAFLD-related parameters in patients with diabetes	• More studies needed to evaluate the impact of these diets along with their acceptability, sustainability, and the effect on health-related quality of life.
Exercise interventions	• Helpful in patients with MAFLD when coupled with a hypocaloric diet especially in younger adults; follow-up studies of 24 months.	• Long-term follow-up is needed to derive more meaningful conclusions.
Pharmacotherapy		
Pioglitazone	• Pioglitazone is recommended for treatment of MAFLD when there is evidence of nonalcoholic steatohepatitis (NASH) especially in the presence of T2DM.	• Side effects are problems including water retention, and increased risk of fragility fracture. Contraindications: Significant stages of congestive cardiac failure and wet maculopathy
Metformin (also recommended in non-MAFLD)	• Improves insulin resistance, hepatic enzymes, and body weight	• Not primarily recommended for patients with NASH though considered in treatment of diabetes with MAFLD and NASH
Dipeptidyl peptidase-IV (DPP-IV) inhibitors	• No significant improvement in MAFLD-related parameters • Not recommended to use in patients for management of MAFLD • No improvement in liver histology	• Not primarily recommended for patients with NASH though considered in treatment of diabetes with MAFLD and NASH
Glucagon-like peptide-1 analogs	• Improvement in MAFLD-related parameters likely due to associated weight loss.	• Recommended for the management of NASH, but to also explain the patient about the gastrointestinal(GI) side effects and high cost

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Table 2
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Management Strategy	Current Evidence	Recommendation
		• Very useful in type 2 diabetes management
Sodium–glucose cotransporter-2 (SGLT2) inhibitors	• Significant reduction in transaminitis and fibrosis-4 score(FIB-4) index	• Need for long-term studies to prove its sustained benefit.
Insulin	• No evidence to support improvement in MAFLD-related parameters	• Used for control of diabetes
Alpha-glucosidase inhibitors	• No evidence to support improvement in MAFLD-related parameters	• Can be used for the management of diabetes as needed
Sulphonylureas	• No evidence to support improvement in MAFLD-related parameters	• To be used with caution in patients with liver disease as most of these drugs are metabolized in the liver

Pioglitazone

The peroxisome proliferator-activated receptors gamma agonists are insulin sensitizers used in the management of T2DM. Pioglitazone is the only drug in this class of thiazolidinediones widely available. A recently published systematic review and meta-analysis by Kovalic and colleagues, summarizing 40 randomized clinical trials, reported that the relative risk of 45 mg pioglitazone in reducing a two-point improvement in NAFLD activity score was 3.29 (95% CI 1.74–6,22) and 2.65 (95% CI 1.36–5.12) for NASH resolution without worsening fibrosis. Currently, pioglitazone is recommended for treatment of MAFLD when there is evidence of NASH especially in the presence of T2DM.[42] However, its known adverse effects of water retention, limited use in patients with significant congestive cardiac failure and increased risk of osteoporosis have to be kept in mind before its rampant use.

Metformin

Metformin, a biguanide is one of the most widely prescribed drugs for the management of T2DM. Given its euglycemic nature, associated weight loss, efficient glycemic control, lower cost, and a beta cell sparing action makes it one of the most ideal antidiabetic agents available today. However, in the setting of MAFLD, it has only shown to improve liver function, insulin sensitivity, and body weight. There has been no histological improvement in patients with NASH and T2DM and hence not recommended for specifically treating MAFLD.[42]

Dipeptidyl Peptidase-IV Inhibitors

Although incretin physiology has been known for several years, its pharmacologic manipulation has been an area of great research in the past few decades. The endogenously secreted incretin hormones are degraded by the enzyme dipeptidyl peptidase-IV (DPP-IV), and thereby by inhibiting this enzyme, the physiological action of the endogenously produced glucagon-like peptide-1 (GLP-1) can be enhanced. Although DPP-IVi has several advantages for use in patients with T2DM including weight neutrality, less incidence of hypoglycemia, and low cost, they have not been found to be very beneficial in patients with MAFLD. In a recently published meta-analysis including 40 randomized clinical trials, it was found that DDP-IVi did not show significant improvements in MAFLD-related parameters in patients with T2DM and hence not recommended for use in this setting.[43]

Glucagon-like peptide-1 analogs

GLP-1 analogs are currently the most effective noninsulin antidiabetic agents that in addition to control blood glucose, also help attaining significant weight loss.[44,45] They work by enhancing the incretin physiology and have been studied extensively for their utility in patients with MAFLD. Significant weight reduction caused by GLP-1 analogs is said to be one of the main reasons for improvements in MAFLD. A recent meta-analysis composing of 40 randomized clinical trials showed a significant reduction in liver enzymes and FIB-4 index unlike DPP-IVi.[43]

As per the recent AACE guidelines, these drugs are recommended for the management of NASH, moreover they also provide good glycemic control, modest weight loss, and other cardiometabolic benefits. However, cost is still a limiting factor especially in the developing world.[46] Moreover, gastrointestinal side effects along with other side effects may result in a discontinuation rate of about 5 to 10% during the course of treatment.[42]

Sodium–Glucose Cotransporter-2 Inhibitors

SGLT-2is are antidiabetic agents that in addition to reduction in glucose provide cardio-renal protection and also promote mild weight loss in a non-islet cell-dependent manner.[47] A recent meta-analysis comparing the efficacy of newer antidiabetic agents in improvement of MAFLD has shown remarkable reduction in transaminitis and FIB-4 index with the use of sodium–glucose cotransporter-2 inhibitors. Although preliminary studies seem promising, long-term data are warranted to prove their sustained efficacy in MAFLD despite only a modest weight loss.[43]

Summarizing, SGLT2-inhibitors are likely to control diabetes and also benefit MAFLD.

THE UTILITY OF OTHER DRUGS (NOT ANTIDIABETIC AGENTS) IN THE MANAGEMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE

Although management of MAFLD in patients with diabetes requires the optimal choice of antidiabetic agents, certain other agents have also been tried. **Table 3** summaries the current evidence for the utility of these drugs in clinical practice to manage MAFLD in the presence of diabetes.[42]

BARIATRIC SURGERY AND INTRAGASTRIC PROCEDURES

Currently, bariatric procedures are the most effective methods to reduce weight in patients with severe obesity. The drastic weight reduction after these procedures helps in remission of several metabolic disorders such as, T2DM dyslipidemia, obstructive sleep apnea, and even MAFLD.

The two common bariatric surgery procedures include the Roux-en-Y gastric bypass and sleeve gastrectomy (SG). However, these are indicated for specific obesity status and not for MAFLD.[51]

Similarly, less invasive endoscopic bariatric procedures such as intragastric balloon are increasingly performed worldwide.[52] These have fewer surgical side effects and help to attain a significant weight loss. Although long-term data on outcomes of MAFLD-related parameters for them are still not available, short-term data seem promising for patients in whom these are indicated otherwise.

MANAGEMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE AMONG PATIENTS WITH DIABETES IN SPECIAL SITUATIONS

Gestational Diabetes and Metabolic-Associated Fatty Liver Disease

Gestational diabetes has a significant impact on both the mother and the fetus. The presence of MAFLD is associated with a further increase in the risk of developing pregnancy-induced hypertension, postpartum hemorrhage, and premature delivery due to the underlying insulin resistance parameters. In a study by Lee and colleagues,[53] it was found that about one in five women in pregnancy had MAFLD and its presence was found to be an independent risk factor for the presence of gestational diabetes. Moreover, in another study by Mosca and colleagues,[54] it was shown that fetus exposed to MAFLD in the mother had a greater risk of developing obesity and MAFLD in early childhood.

Type 1 Diabetes and Metabolic-Associated Fatty Liver Disease

Although MAFLD is largely considered as a hepatic manifestation of MetS, it has also been reported in patients with type 1 diabetes mellitus (T1DM).[55–57] About a third of patients with T1DM have MAFLD, but the prevalence varies largely depending on

Table 3
Summary of the current evidence of nondiabetic agents in the treatment of metabolic-associated fatty liver disease

Management Strategy	Key Points Summarizing the Current Evidence	Recommendations
Statins and other antihyperlipidemic drugs	• Improves steatosis grade and NAFLD activity score[48]	• Should be considered in all patients except those with transaminitis (>3 times the upper limit of normal) • More evidence is needed for other antihyperlipidemic drugs such as fenofibrate and pro-protein convertase subtilisin/kexin type 9 inhibitors
Vitamin E/alpha-tocopherol	• Associated with worsening of insulin resistance[49]	• Not recommended in patients with diabetes[46]
Orlistat	• Conflicting results in favor and against its use[50]	• Encouraging data from basic science and animal experiments suggest further testing in long-term clinical trials.
Obeticholic acid	• Bile acid mimic shows encouraging results in short-term studies • Could be a potential treatment option in future for patients with MAFLD, considering that it reduces fatty liver and liver fibrosis	• No role in control of DM
Aldafermin (FGF-19 analog)	• Activates farnesoid X receptor (FXR) receptors and simulates actions like fibroblast growth factor 19 (FGF19)	• Short-term initial studies look promising for its future use (for MAFLD?)

the age and BMI of the study cohort.[58,59] Although increasing insulin resistance in relatively older patients with T1DM is described as an important risk factor for the development of MAFLD, even oxidative stress, poor glycemic control, genetic predisposition, and exogenous insulin administration also play a role. An entity called glycogenic hepatopathy (liver dysfunction in poorly controlled T1DM) is a close differential diagnosis in such patients. The evaluation and management of MAFLD in patients with T1DM is similar to those with T2DM.[60]

OUTCOMES OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE IN PATIENTS WITH DIABETES AS COMPARED WITH THOSE WITHOUT DIABETES

Multiple studies have shown that the prevalence of MAFLD is two to three-fold more common in patients with diabetes as compared with those without diabetes. In a recent study by Ajmera and colleagues,[61] about 65% of individuals were found to be affected using the MRI-based assessment of liver fat. Furthermore, several studies have demonstrated that the MAFLD-associated severity, morbidity, progression, and liver-related mortality are much higher in patients with diabetes.[61–63]

Lean Metabolic-Associated Fatty Liver Disease and Diabetes

Although MAFLD is conventionally described in people with obesity, it may less often also be associated in individuals with an apparently lean phenotype.[64] This is especially peculiar in the south Asian phenotype, wherein individuals may have high body fat despite a normal BMI.[65] The body fat percentage in these individuals is significantly high and is often deposited in ectopic sites such as the liver, muscle, heart, omentum, and kidney.[66] The response to lifestyle interventions in such individuals is often more difficult.[67,68]

SUMMARY

MAFLD is a major public health issue especially in patients with diabetes. It is essential to screen and evaluate patients with diabetes, even in cost-restrained settings using simple screening tools such as ultrasound or fibroscan and biomarkers. The more recently available antidiabetic agents including GLP-1 analogs and SGLT-2is have been shown to be effective in both diabetes and MAFLD. Beyond antidiabetic agents, newer drugs such as FGF-19 analogs and bariatric/endoscopic procedures for obesity have also been shown effective in reduction of MAFLD-related parameters in DM. Long-term studies are needed to determine their efficacy and safety for routine clinical use.

CLINICS CARE POINTS

- The prevalence of metabolic-associated fatty liver disease (MAFLD) is approximately 55% in patients with type 2 diabetes mellitus and represents a spectrum of disorders ranging from hepatic steatosis to hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.
- All patients with diabetes should be screened for MAFLD and vice versa. Several serum biomarkers and radiological modalities have been suggested for screening, depending on the clinical setting.
- Antidiabetic agents such as pioglitazone, glucagon-like peptide-1 analogs, and sodium–glucose cotransporter-2 inhibitors have shown significant improvement in MAFLD-related parameters in patients with diabetes. Newer drugs and endoscopic/bariatric procedures also have shown to be helpful in short-term studies.

REFERENCES

1. Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55(7):434–8.
2. Eslam M, Sanyal AJ, George J. MAFLD: a consensus-driven proposed nomenclature for metabolic-associated fatty liver disease. Gastroenterology 2020;158(7): 1999–2014.e1991.
3. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int 2020;40(9):2082–9.
4. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73(1):202–9.
5. Binet Q, Loumaye A, Preumont V, et al. Non-invasive screening, staging and management of metabolic dysfunction-associated fatty liver disease (MAFLD) in type 2 diabetes mellitus patients: what do we know so far. Acta Gastroenterol Belg 2022;85(2):346–57.
6. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol 2019;71(4):793–801.
7. Younossi ZM, Tampi RP, Racila A, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the U.S. Diabetes Care 2020;43(2):283–9.
8. Vandekerckhove P, Van Damme B, Annemans L. How will the welfare state cope with welfare diseases such as NASH? Acta Gastroenterol Belg 2019;82(4):548–9.
9. Yoo TK, Lee MY, Kim SH, et al. Comparison of cardiovascular mortality between MAFLD and NAFLD: a cohort study. Nutr Metab Cardiovasc Dis 2023;00024–8.
10. Lim GEH, Tang A, Ng CH, et al. An observational data meta-analysis on the differences in prevalence and risk factors between MAFLD vs NAFLD. Clin Gastroenterol Hepatol 2021;00024–8.
11. Byrne CD. Banting memorial lecture 2022: 'type 2 diabetes and nonalcoholic fatty liver disease: partners in crime'. Diabet Med 2022;39(10):e14912.
12. Godoy-Matos AF, Silva Júnior WS, Valerio CM. NAFLD as a continuum: from obesity to metabolic syndrome and diabetes. Diabetol Metab Syndrome 2020; 12:60.
13. Wainwright P, Byrne CD. Bidirectional relationships and disconnects between NAFLD and features of the metabolic syndrome. Int J Mol Sci 2016;17(3):367.
14. Zeng Y, He H, An Z. Advance of serum biomarkers and combined diagnostic panels in nonalcoholic fatty liver disease. Dis Markers 2022;2022:1254014.
15. Poynard T, Peta V, Deckmyn O, et al. Performance of liver biomarkers, in patients at risk of nonalcoholic steato-hepatitis, according to presence of type-2 diabetes. Eur J Gastroenterol Hepatol 2020;32(8):998–1007.
16. Quinn SF, Gosink BB. Characteristic sonographic signs of hepatic fatty infiltration. AJR Am J Roentgenol 1985;145(4):753–5.
17. Jimba S, Nakagami T, Takahashi M, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med 2005;22(9):1141–5.
18. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123(3):745–50.

19. Wu J, You J, Yerian L, et al. Prevalence of liver steatosis and fibrosis and the diagnostic accuracy of ultrasound in bariatric surgery patients. Obes Surg 2012; 22(2):240–7.
20. Palmentieri B, de Sio I, La Mura V, et al. The role of bright liver echo pattern on ultrasound B-mode examination in the diagnosis of liver steatosis. Dig Liver Dis 2006;38(7):485–9.
21. Atri A, Jiwanmall SA, Nandyal MB, et al. The prevalence and predictors of non-alcoholic fatty liver disease in morbidly obese women - a cross-sectional study from Southern India. Eur Endocrinol 2020;16(2):152–5.
22. Borges VF, Diniz AL, Cotrim HP, et al. Sonographic hepatorenal ratio: a noninvasive method to diagnose nonalcoholic steatosis. J Clin Ultrasound 2013;41(1): 18–25.
23. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29(12):1705–13.
24. Myers RP, Pollett A, Kirsch R, et al. Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. Liver Int 2012;32(6):902–10.
25. Fierbinteanu-Braticevici C, Dina I, Petrisor A, et al. Noninvasive investigations for nonalcoholic fatty liver disease and liver fibrosis. World J Gastroenterol 2010; 16(38):4784–91.
26. Roldan-Valadez E, Favila R, Martínez-López M, et al. Imaging techniques for assessing hepatic fat content in nonalcoholic fatty liver disease. Ann Hepatol 2008; 7(3):212–20.
27. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology 2015; 61(4):1239–50.
28. Chen J, Yin M, Talwalkar JA, et al. Diagnostic performance of MR elastography and vibration-controlled transient elastography in the detection of hepatic fibrosis in patients with severe to morbid obesity. Radiology 2017;283(2):418–28.
29. Makhija N, Vikram NK, Srivastava DN, et al. Role of diffusion-weighted magnetic resonance imaging in the diagnosis and grading of hepatic steatosis in patients with non-alcoholic fatty liver disease: comparison with ultrasonography and magnetic resonance spectroscopy. J Clin Exp Hepatol 2021;11(6):654–60.
30. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41(6): 1313–21.
31. Kapoor N, Sahay R, Kalra S, et al. Consensus on medical nutrition therapy for diabesity (CoMeND) in adults: a South Asian perspective. Diabetes Metab Syndr Obes 2021;14:1703–28.
32. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2):367–78.e365 [quiz: e314-365]].
33. Kalra S, Kapoor N, Kota S, et al. Person-centred Obesity Care - Techniques, Thresholds, Tools and Targets. Eur Endocrinol 2020;16(1):11–3.
34. Varkaneh HK, Poursoleiman F, Al Masri MK, et al. Low fat diet versus low carbohydrate diet for management of non-alcohol fatty liver disease: a systematic review. Front Nutr 2022;9:987921.

35. Haigh L, Kirk C, El Gendy K, et al. The effectiveness and acceptability of mediterranean diet and calorie restriction in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. Clin Nutr 2022;41(9):1913–31.
36. Różański G, Pheby D, Newton JL, et al. Effect of different types of intermittent fasting on biochemical and anthropometric parameters among patients with metabolic-associated fatty liver disease (MAFLD)-a systematic review. Nutrients 2021;14(1):91.
37. Yin C, Li Z, Xiang Y, et al. Effect of intermittent fasting on non-alcoholic fatty liver disease: systematic review and meta-analysis. Front Nutr 2021;8:709683.
38. Scragg J, Avery L, Cassidy S, et al. Feasibility of a very low calorie diet to achieve a sustainable 10% weight loss in patients with nonalcoholic fatty liver disease. Clin Transl Gastroenterol 2020;11(9):e00231.
39. Ramasamy S, Joseph M, Jiwanmall SA, et al. obesity indicators and health-related quality of life - insights from a cohort of morbidly obese, middle-aged South Indian women. Eur Endocrinol 2020;16(2):148–51.
40. Zhou BJ, Huang G, Wang W, et al. Intervention effects of four exercise modalities on nonalcoholic fatty liver disease: a systematic review and Bayesian network meta-analysis. Eur Rev Med Pharmacol Sci 2021;25(24):7687–97.
41. Hong F, Liu Y, Lebaka VR, et al. Effect of exercise training on serum transaminases in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Front Physiol 2022;13:894044.
42. Jeeyavudeen MS, Khan SK, Fouda S, et al. Management of metabolic-associated fatty liver disease: the diabetology perspective. World J Gastroenterol 2023; 29(1):126–43.
43. Zafar Y, Rashid AM, Siddiqi AK, et al. Effect of novel glucose lowering agents on non-alcoholic fatty liver disease: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2022;46(7):101970.
44. Kalra S, Bhattacharya S, Kapoor N. Contemporary classification of glucagon-like peptide 1 receptor agonists (GLP1RAs). Diabetes Ther 2021;12(8):2133–47.
45. Kalra S, Arora S, Kapoor N. Classification of non-insulin glucose lowering drugs. J Pak Med Assoc 2022;72(1):181–2.
46. Cusi K, Isaacs S, Barb D, et al. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American association for the study of liver diseases (AASLD). Endocr Pract 2022;28(5):528–62.
47. Kalra S, Bhattacharya S, Kapoor N. Glucagon-like peptide 1 receptor agonists (GLP1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i): making a pragmatic choice in diabetes management. J Pak Med Assoc 2022;72(5): 989–90.
48. Boutari C, Pappas PD, Anastasilakis D, et al. Statins' efficacy in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Clin Nutr 2022; 41(10):2195–206.
49. Alcala M, Calderon-Dominguez M, Serra D, et al. Short-term vitamin E treatment impairs reactive oxygen species signaling required for adipose tissue expansion, resulting in fatty liver and insulin resistance in obese mice. PLoS One 2017; 12(10):e0186579.
50. Wang H, Wang L, Cheng Y, et al. Efficacy of orlistat in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Biomed Rep 2018;9(1):90–6.

51. Madhu SV, Kapoor N, Das S, et al. ESI clinical practice guidelines for the evaluation and management of obesity In India. Indian J Endocrinol Metab 2022;26(4):295–318.
52. Jaleel R, Kapoor N, Kalra S. Endoscopic intragastric balloon: a novel therapy for weight loss. J Pak Med Assoc 2022;72(7):1444–6.
53. Lee SM, Kwak SH, Koo JN, et al. Non-alcoholic fatty liver disease in the first trimester and subsequent development of gestational diabetes mellitus. Diabetologia 2019;62(2):238–48.
54. Mosca A, De Cosmi V, Parazzini F, et al. The role of genetic predisposition, programing during fetal life, family conditions, and post-natal diet in the development of pediatric fatty liver disease. J Pediatr 2019;211:72–7.e74.
55. Muzurović E, Rizzo M, Mikhailidis DP. Obesity and nonalcoholic fatty liver disease in type 1 diabetes mellitus patients. J Diabet Complications 2022;36(12):108359.
56. de Vries M, El-Morabit F, van Erpecum KJ, et al. Non-alcoholic fatty liver disease: identical etiologic factors in patients with type 1 and type 2 diabetes. Eur J Intern Med 2022;100:77–82.
57. de Vries M, Westerink J, El-Morabit F, et al. Prevalence of non-alcoholic fatty liver disease (NAFLD) and its association with surrogate markers of insulin resistance in patients with type 1 diabetes. Diabetes Res Clin Pract 2022;186:109827.
58. Barros BSV, Monteiro FC, Terra C, et al. Prevalence of non-alcoholic fatty liver disease and its associated factors in individuals with type 1 diabetes: a cross-sectional study in a tertiary care center in Brazil. Diabetol Metab Syndrome 2021;13(1):33.
59. Sae-Wong J, Chaopathomkul B, Phewplung T, et al. The Prevalence of Nonalcoholic Fatty Liver Disease and Its Risk Factors in Children and Young Adults with Type 1 Diabetes Mellitus. J Pediatr 2021;230:32–7.e31.
60. Memaj P, Jornayvaz FR. Non-alcoholic fatty liver disease in type 1 diabetes: prevalence and pathophysiology. Front Endocrinol 2022;13:1031633.
61. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol 2022;471–8.
62. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62(5):1148–55.
63. Simon TG, Roelstraete B, Sharma R, et al. Cancer risk in patients with biopsy-confirmed nonalcoholic fatty liver disease: a population-based cohort study. Hepatology 2021;74(5):2410–23.
64. Tang A, Ng CH, Phang PH, et al. Comparative burden of metabolic dysfunction in lean NAFLD vs Non-lean NAFLD - a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2022;00669–3.
65. Kapoor N, Lotfaliany M, Sathish T, et al. Prevalence of normal weight obesity and its associated cardio-metabolic risk factors - results from the baseline data of the Kerala diabetes prevention program (KDPP). PLoS One 2020;15(8):e0237974.
66. Kapoor N, Furler J, Paul TV, et al. Normal weight obesity: an underrecognized problem in individuals of South Asian descent. Clin Ther 2019;41(8):1638–42.
67. Kapoor N, Lotfaliany M, Sathish T, et al. Effect of a peer-led lifestyle intervention on individuals with normal weight obesity: insights from the Kerala diabetes prevention program. Clin Ther 2020;42(8):1618–24.
68. Xu R, Pan J, Zhou W, et al. Recent advances in lean NAFLD. Biomed Pharmacother 2022;153:113331.