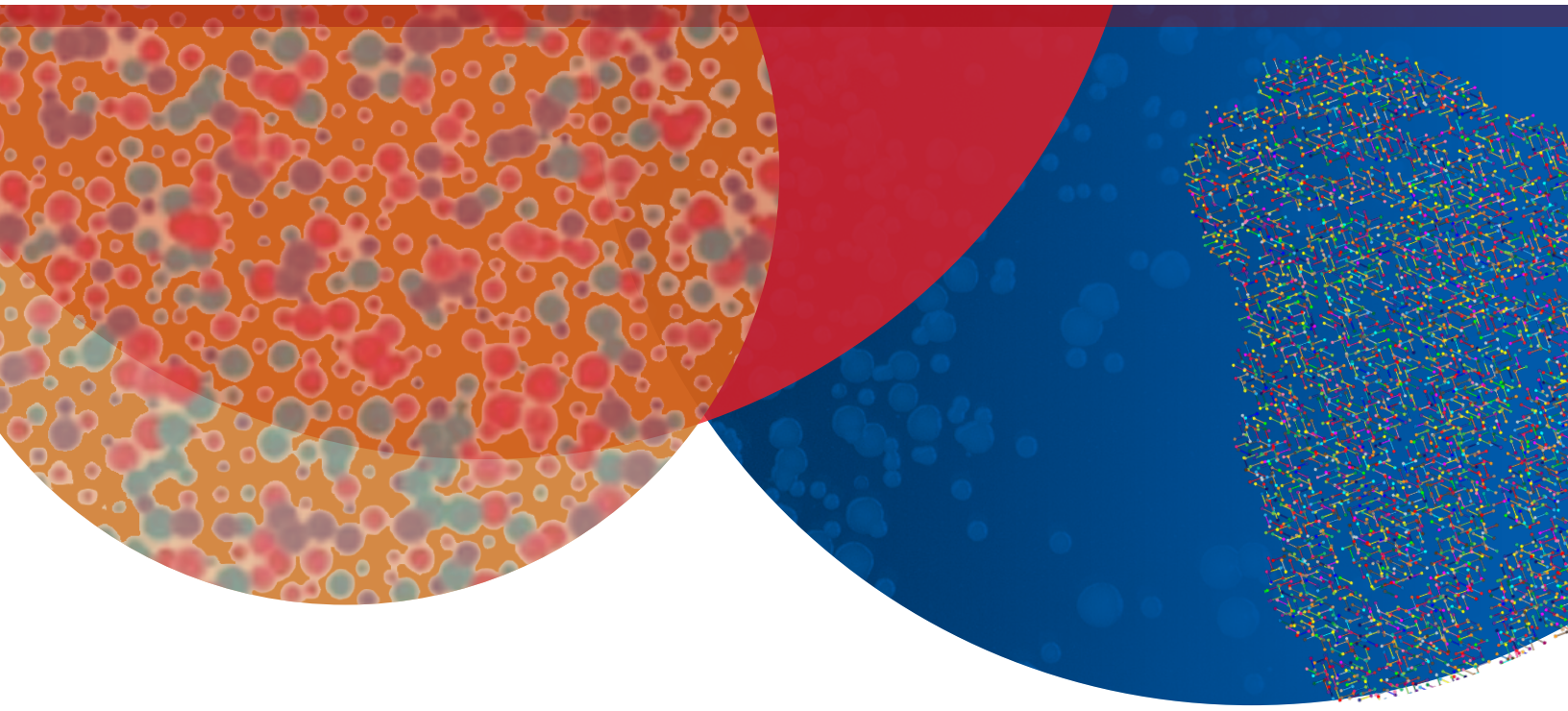
International Journal of

ATHEROGENIC DIABETIC DYSLIPIDEMIA



THIS ISSUE

Review Articles

Editor-in-Chief

Dr. Prof. Subhankar Chowdhury

VOLUME 5
ISSUE 2

Salubris

International Journal of

ATHEROGENIC DIABETIC DYSLIPIDEMIA

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VOLUME 5
ISSUE 2

Salubris

International Journal of ATHEROGENIC DIABETIC DYSLIPIDEMIA

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About the Journal

Atherogenic dyslipidemia, characterized by elevated triglycerides (TGs), raised small dense LDL (low-density lipoprotein) levels and decreased HDL (high-density lipoprotein) cholesterol levels, is the most common pattern of dyslipidemia in type 2 diabetic patients. It is characteristically seen in patients with obesity, metabolic syndrome, insulin resistance, and T2DM and has emerged as an essential marker for the increased CVD risk observed in these populations. In fact, the combined presence of dyslipidemia and diabetes escalates the CV risk by 3–4 times.

Dyslipidemia, diabetes and hypertension are all a part of the cluster that includes nonalcoholic fatty liver disease (NAFLD) too, another major CVD risk factor. As diabetic dyslipidemia is characterized by hypertriglyceridemia, the risk of pancreatitis is also high in these patients.

With the increasing burden of these conditions in the world, clinicians can struggle to keep themselves updated in the advances in research and therapy.

With this journal, we aim to keep doctors updated in the current understanding, trends in therapy and new modalities of care. Our objective is:

- To be the knowledge partner for healthcare professionals by presenting contemporary research and novel treatment options in the field of atherogenic diabetic dyslipidemia.
- To raise awareness about the latest clinical practices, for better management of the condition, thus improving on the standards of overall disease management
- To provide researchers of the field with a medium to elicit like thought processes in their peers working on similar innovations or experiments
- To provide clinicians with a platform to showcase their case studies

International Journal of Atherogenic Diabetic Dyslipidemia will contain literature encompassing all the scientific and clinical aspects that address the cause and management of atherogenic dyslipidemia. The content of the journal shall include, but not limited to subject areas like atherogenic dyslipidemia, obesity, NAFLD, acute pancreatitis, hypertriglyceridemia, pharmacological management/therapeutic options for atherogenic dyslipidemia in type 2 diabetes and new strategies for management.

We hope to provide a platform to publish interesting and informative articles on topics connected with the management of atherogenic diabetic dyslipidemia as well as encourage correspondence and participation from our readers.

Editorial Board

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Review

Non-invasive Diagnosis of MASLD

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Abstract

Background: Non-invasive fibrosis tests (NITs) have significantly impacted clinical practice in hepatology over the past 15 years. MASLD, formerly known as non-alcoholic fatty liver disease (NAFLD), is the most prevalent liver disease in Western countries, affecting up to a third of the unselected adult population. In India, Chalmer et al estimated MASLD prevalence of 51.5% in 2016 while previous studies conducted earlier reported significantly lower prevalence rates.[1] NITs are used in diagnosing steatosis, steatohepatitis, and fibrosis, offering various approaches like serum markers, imaging techniques, and combined scores. These tests also serve as valuable prognostic tools, enabling better risk assessment and patient management, particularly in predicting liver-related events and overall mortality.[2]

Materials and Method: Review and extracting data from articles which have published data related to non-invasive detection of MASLD.

Results and Conclusion: Various studies reported biomarkers as the most commonly utilized method for non-invasive detection of MASLD.

Keywords: MAFLD, metabolic, non-invasive, diagnosis, detection, biomarkers, NIT

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) can progress over time, causing inflammation in liver tissue, liver fibrosis, and ultimately liver cirrhosis. Early detection and management can prevent the progression to more severe liver fibrosis and improve overall liver health. Liver fibrosis is the most important prognostic factor for liver-related events in MASLD. Advanced fibrosis, also known as compensated advanced chronic liver disease (cACLD), is an independent risk factor for liver-related events and non-liver-related morbidity and mortality. Liver biopsy remains the gold standard for diagnosing MASH and staging liver fibrosis, but it has limitations such as invasiveness, risk of complications, sampling variability, and potential patient reluctance. A biopsy length of at least 25 mm is recommended for accurate staging, although this may not always be feasible.[2]

The rise in MASLD and limitations of liver biopsy have led to the development of non-invasive tests (NITs) for accurate staging and risk stratification, including diagnosing steatosis, steatohepatitis, and staging liver fibrosis. These NITs, initially designed for fibrosis, are now used to determine liver-related prognosis and can be categorized into serum tests, imaging techniques, and combined scores.[2]

Aim: The aim of this review was to gain more understanding about the non-invasive procedures for the diagnosis/detection of MASLD.

Methods: Several articles related to topic of discussion which included biomarkers are employed in the diagnosis of MASLD were reviewed and data was extracted from them.

Keywords used were metabolic, liver disease, MASLD, non-invasive, diagnostic methods, serum biomarkers, fibrosis, staging, FibroScan, MRE. Data from articles published in years, 2014, 2021 and 2024 were collected from various online scientific journals such as European Journal of Internal Medicine, Gastroenterol Hepatol (N Y), J Hepatol, World J Gastroenterol and Aliment Pharmacology & Therapeutics.

Results: FibroScan has been used in numerous studies to assess the diagnostic accuracy of fibrosis in various types of Chronic Liver Disease (CLD). A meta-analysis showed that FibroScan had a sensitivity and specificity of 0.70 and 0.84, respectively. In a large meta-analysis of 50 studies, the areas under the curve (AUCs) for fibrosis, significant fibrosis, severe fibrosis, and cirrhosis were 0.84, 0.89, and 0.94, respectively. In a prospective study of patients with MASLD, FibroScan showed similar diagnostic accuracy to FIB-4 index and NAFLD Fibrosis Score (NFS) in detecting advanced fibrosis.[3]

A meta-analysis of Multi-Resolution Endoscopy (MRE) for diagnosing advanced fibrosis and cirrhosis in patients with MASLD showed AUCs of 0.93 and 0.94, respectively. MRE had significantly higher diagnostic accuracy compared to Traditional Endoscopy (TE) with an AUC of 0.94. This was supported by a cross-sectional study of 142 patients with biopsy-proven MASLD, where the diagnosis of at least fibrosis score (F2) by TE had an AUC of 0.82, while the AUC with MRE was 0.91.[3]

Non-invasive testing and risk stratification are crucial in addressing hepatic steatosis (MASLD) in patients. These methods, including non-invasive liver imaging techniques (FibroScan® and MRE), offer accurate diagnoses and risk assessments without invasive liver biopsies.

Discussion

NITs for fibrosis assessment

Serum markers

Serum markers, including Fibrosis 4 (FIB-4) and NAFLD Fibrosis Score (NFS), are used to diagnose advanced fibrosis However, FIB-4 underestimates fibrosis in patients under 35 years old and has decreased diagnostic accuracy in those over 65 years.[2]

The Aspartate Aminotransferase to Platelet Ratio Index (APRI) and the AST/ALT ratio, presence of diabetes and BMI (BARD) score are simple markers used in primary care and diabetology clinics to identify patients at higher risk of advanced fibrosis who should be referred to secondary care/hepatology clinics, as other markers like these are not routinely used in clinical practice.[2]

The Enhanced Liver Fibrosis (ELF) test, based on serum biomarkers related to fibrogenic process and extracellular matrix turnover, has been validated for liver fibrosis staging. The test measures tissue inhibitor of metalloproteinase-1, hyaluronic acid, and N-terminal procollagen III peptide, which has good diagnostic performance for advanced fibrosis, with a cut-off of >9.8, but could be sensitive to extra-hepatic inflammatory or fibrotic diseases.[2]

ELF, a widely available test in Western countries, is expensive for the general population. A two-step FIB-4 followed by ELF approach reduces costs and improves patient selection for secondary care referral by using the test only in populations with indeterminate results.[2]

The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines suggest that patients at risk of MASLD with high FIB-4 or NFS and intermediate FIB-4 or NFS and high FibroScan® or ELF should be referred to secondary care for further evaluation. Pro-C3, a direct biomarker of type-III collagen formation, has been proposed and validated as a non-invasive test for liver fibrosis assessment. In a recent multicentric study, it showed good performance in diagnosing advanced fibrosis in patients with MASLD.[2]

Serum biomarkers (Table 1) predicting advanced fibrosis can be classified as indirect or direct, reflecting changes in hepatic function but not extracellular matrix (ECM) metabolism. Indirect tests include aminotransferases, total bilirubin, gamma-glutamyl transpeptidase, platelet count, coagulation parameters, and α_2-macroglobulin.[3]

Direct tests reveal ECM deposition and degradation through markers like procollagen peptides, collagen, hyaluronic acid, inflammatory glycoprotein, metalloproteinases, and tissue inhibitors of metalloproteinases. Cytokines/chemokines associated with hepatic fibrosis, such as TGF-α and TGF-β, are also direct indicators of fibrosis.[3]

Table 1. Serologic Tests Used in the Evaluation of Hepatic Fibrosis.[3]

Biomarker (with abbreviation)	Components	Chronic liver disease(s)
AST to Platelet Ratio Index (APRI)	(AST/AST upper limit of normal)/(platelet count [10^9/L]) × 100	HCV, HBV, alcohol-associated liver disease, MASLD
Fibrosis-4 (FIB-4) index	(Age [years] × AST [U/L])/([platelet count (10^9/L)] × $\sqrt{\text{ALT}}$ [U/L])	HCV, HBV, alcohol-associated liver disease, MASLD
NAFLD Fibrosis Score (NFS)	1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (10^9/L) − 0.66 × albumin (g/dL)	MASLD
FibroTest	Serum 2-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and GGT, adjusted for age and sex	MASLD, HCV, HBV, alcohol-associated liver disease
Enhanced Liver Fibrosis (ELF) test	Type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1	MASLD/MASH

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; IFG, impaired fasting glucose; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease.

Liver Elastography

Liver fibrosis/liver stiffness measure (LSM) is closely linked to serum biomarkers and scoring systems and can be determined using ultrasound (US) and MRE techniques. US elastography methods include vibration-controlled transient elastography (VCTE), acoustic radiation force impulse (ARFI), point shear wave elastography (p-SWE), and two-dimensional shear wave elastography (2D-SWE).. However, liver tissue stiffness can be influenced by factors like steatosis, necro-inflammation, postprandial hepatic hyperemia, subcutaneous tissue thickness, cholestasis, and increased central venous pressure, which can limit the diagnostic accuracy of elastography.[2]

VCTE is a widely used US-based elastography method that measures liver stiffness by assessing shear wave propagation through hepatic tissue. Recent meta-analyses show excellent diagnostic accuracy for advanced fibrosis and cirrhosis in MASLD patients with AUROCs close to 0.90. However, VCTE and other US elastography methods are less accurate in diagnosing significant or lesser degrees of fibrosis. Steatosis can increase liver stiffness values, but this was not confirmed in a prospective study.[2]

The VCTE has a limitation as it lacks established cut-offs for diagnosing advanced fibrosis and cirrhosis. A single cut-off is better for excluding these stages due to their low prevalence.[2]

Studies comparing US elastography techniques for diagnosing fibrosis found no significant differences, but VCTE remains the most validated technique and recommended by international guidelines, despite no significant differences.[2]

MRE is a method that studies shear waves in liver tissue, converting wavelength information into tissue stiffness maps. It offers a panoramic assessment of fibrosis and superior spatial resolution, exhibiting superior performance in stratifying intermediate stages of fibrosis. However, its high cost and low availability limit its practical application primarily to research purposes.[2]

MRE is reliable for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis, and is not affected by gender, BMI, steatosis, or inflammation grade. Proposed cut-offs are 3.66 kPa for significant fibrosis, 4.11 kPa for advanced fibrosis, and 4.71 kPa for liver cirrhosis.[2]

Elastography Scores

The increasing availability of elastography in secondary care settings, particularly FibroScan®, has highlighted limitations in its reliability due to factors like age, obesity, liver congestion, and elevated liver enzymes. To overcome these limitations, scores combining clinical, laboratory, and elastography variables have been proposed to identify patients with advanced fibrosis or cirrhosis in MASLD accurately.[2]

Sanyal et al.'s Agile 3+ score, which considers LSM, platelets, AST, ALT, diabetes diagnosis, age, and sex, demonstrated excellent diagnostic performance for advanced fibrosis in European and US validation courts with an Area under the Receiver Operating Characteristic Curve (AUROC)>0.85, significantly higher than LSM alone, FIB4, and NFS. However, Agile3+'s superiority compared to LSM alone is not confirmed in diabetic populations, raising questions about its net benefit.[2]

The proposed cutoff for exclusion of advanced fibrosis showed a sensitivity >80% in both European and US cohorts, while the cutoff for compensated advanced chronic liver disease (**cACLD)** diagnosis showed a specificity >85%. The percentage of patients falling into the grey area is small compared to other NITs, with 8–20% in both European and American validation cohorts. In Asian cohorts, Agile 3+'s AUROC for diagnosis of advanced fibrosis was 0.82, equal to LSM alone.[2]

Agile 4 is a diagnostic tool for cirrhosis, assessing variables like LSM, platelets, ALT, AST, gender, and T2DM status. It demonstrated high diagnostic performance in European and North American validation cohorts, with an AUC of 0.89 and 0.85, respectively. The dual cutoff strategy, 0.251 as a rule-out and 0.565 as a rule-in resulted in a low percentage of patients falling in the gray zone in European cohorts.[2]

Jung et al. found that combining MRE with FIB-4 (MEFIB score) can accurately identify patients with significant fibrosis. The combination yielded a clinical prediction rule with a 97.1% PPV, validating in the "Japan-NAFLD" cohort. The MEFIB score had an AUROC of 0.84, indicating its potential as a non-invasive tool for metabolic dysfunction-associated steatohepatitis (MASH) patients.[2]

NITs for Assessment of Prognosis in MASLD Patients

Liver fibrosis is a crucial prognostic factor in patients with MASH, influencing risk of liver cancer, cardiovascular events, liver transplant, and death. However, histopathological staging is limited due to the cost and invasive nature of liver biopsy. Non-invasive tests are being used as prognostic factors to guide clinical and therapeutic choices, overcoming this limitation and being encouraged by major scientific societies worldwide.[2]

NFS and FIB-4 performed well in predicting liver-related events, HCC, and overall mortality, but showed a lower association with the risk of cardiovascular events and extrahepatic cancers, respectively).[2]

A meta-analysis found that NFS and FIB-4 are the best predictors of all-cause mortality compared to other indirect NITs (APRI and BARD), with HR>3. NFS also predicts cardiovascular-related mortality (HR 3.09), possibly due to its inclusion of known cardiovascular risk factors like T2DM and BMI. Changes in NFS and FIB-4 are significantly associated with fibrosis progression, with a mean progression of 0.26 and 0.19 stages for every unit change in either.[2]

ELF has been shown to have a prognostic role in MASLD patients, with patients with ELF>11.3 having a 5-fold higher risk of liver-related events.[2]

LSM is a reliable prognostic factor in MASLD patients, with studies showing that baseline LSM can stratify overall survival and risk of liver-related events. LSM values above 10–12 kPa are associated with a higher risk of events and lower overall survival, confirming advanced fibrosis as a main prognostic factor. A recent meta-analysis by Mozes et al. showed that LSM-based prognostic stratification performed as well as histologically assessed fibrosis. Patients with LSM>20 kPa and LSM between 10–20 kPa had a 10-fold and 3-fold higher risk of liver-related events, HCC occurrence, and overall mortality compared to those with LSM<10 kPa.[2]

Agile3+ is a prognostic factor in MASH patients, particularly for predicting liver-related events. Pennisi et al. found that Agile3+ and LSM perform well at 3, 5, and 8 years, with Agile 3+ slightly superior to LSM.[2]

Serra-Burriel et al. developed the LiverRisk score, a tool based on age, sex, and six laboratory variables, to identify patients at risk for liver-related complications. The score, derived from a large international cohort study, was validated in two general population cohorts. It showed high accuracy in predicting liver stiffness and effectively stratified individuals into

different risk groups for liver-related outcomes. This score can help identify individuals at risk for liver-related complications, potentially enabling more targeted and timely preventative care.[2]

Role of NITs in Evaluating Response to Treatment

A study by Rinella et al. used non-invasive tests to evaluate the therapeutic response to obeticholic acid (OCA) in 931 patients with non-alcoholic steatohepatitis (NASH) and fibrosis stage F2 or F3. The study found a reduction in aminotransferases, fibrosis scores, and vibration-controlled transient elastography (VCTE) in OCA-treated patients compared to placebo-treated patients. The reduction was most evident in patients with an improvement in fibrosis >−1 stage. Aminotransferase levels also improved in OCA-treated patients without any change or worsening in the fibrosis stage, suggesting these changes are unrelated to fibrosis.[4]

Limitation of Study:

This review is limited to the information available in published articles or studies.

Conclusion

Non-invasive testing and risk stratification are crucial in addressing hepatic steatosis (MASLD) in patients. These methods, including non-invasive liver imaging techniques (FibroScan® and MRE), offer accurate diagnoses and risk assessments without the need for invasive liver biopsies. They include serum markers, imaging techniques, and combined scores. These tests also serve as valuable prognostic tools, enabling better risk assessment and patient management, particularly in predicting liver-related events and overall mortality. As the field evolves, these methods will revolutionize diagnostics and improve patient outcomes.[2]

Conflict of Interest

No conflict of interest.

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Review

Cardiovascular and Endocrine Risk associated with MASLD

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ABSTRACT

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is the most prevalent chronic liver condition worldwide, affecting approximately one-third of the population. In certain individuals, it can progress to more severe forms, including MASH, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The pathogenesis of MASLD is closely associated with obesity, dyslipidemia, and type 2 diabetes mellitus (T2DM), emphasizing the importance of nutritional and lifestyle interventions in mitigating the risk of HCC progression and influencing disease outcomes.[1]

Cardiovascular disease (CVD) is the primary cause of mortality in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD), which is recognized as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD).[2] While obesity and insulin resistance are key contributors, the interplay between the liver and various endocrine systems also plays a significant role. Endocrine imbalances, such as reduced levels of growth hormone, sex hormones, and thyroid hormone, drive the onset and progression of MASLD.[3]

Materials and Method: Review and extracting data from articles which have published data related to risk factors (cardiovascular and endocrine) associated with MASLD.

Results and Conclusion: Various studies reviewed reported CVD disease is the leading cause of death in MASLD patients. Endocrine dysregulation promotes the development and progression of MASLD.[3]

Keywords: MASLD, risk factor, cardiovascular, endocrine, diabetes, disease

Introduction

Aim: The aim of this review was to gain more understanding about the cardiovascular and endocrine risk as reported in patients with MASLD.

Methods: Several articles discussing the pathophysiology of MASLD, the risk factors such as cardiovascular and endocrine which could possibly increase the occurrence of MASLD were reviewed and relevant data was extracted from them.

Results: Research indicates that cardiovascular disease (CVD) is the leading cause of death in individuals with MASLD. Endocrine dysregulation plays a significant role in the development and progression of MASLD.[3]

However, the complex relationship between endocrine dysregulation and CVD in MASLD patients requires further investigation. The limited understanding of the disease's natural history and the lack of approved pharmaceutical treatments complicate clinical decision-making. Nevertheless, targeted management of metabolic syndrome (MetS) components, including obesity, dyslipidemia, and hypertension, can help prevent diabetes and cardiovascular complications.[4]

Discussion

Cardiovascular Disease Risk associated with MASLD

Cardiovascular disease (CVD) is the leading cause of mortality in individuals with MASLD, which is recognized as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD). While factors such as type 2 diabetes mellitus (T2DM) and abdominal obesity contribute to this risk, additional influences include insulin resistance, pro-inflammatory mediators, pro-atherogenic dyslipidemia, oxidative stress, and hepatokines.[5]

Given the shared risk factors between MASLD and CVD—such as obesity, insulin resistance, hypertension, and dyslipidemia—MASLD is increasingly regarded as a potential independent risk factor for CVD. Although the exact mechanisms linking MASLD to CVD remain unclear, they likely involve interconnected metabolic, inflammatory, and vascular pathways.[6]

Individuals with MASLD often exhibit T2DM, severe dyslipidemia, insulin resistance, and heightened subclinical inflammation, along with the potential for cardiac lipotoxicity.[4]

A systematic review and meta-analysis of 20 studies revealed that MASLD is associated with a higher risk of myocardial infarction, ischemic stroke, atrial fibrillation, and heart failure compared to individuals without MASLD.[7]

Another meta-analysis of 11 longitudinal cohort studies found that MASLD increases the long-term risk of new-onset heart failure by 1.5 times, independent of diabetes, hypertension, and other common cardiovascular risk factors. Many MASLD patients also have additional cardiovascular risk factors, including comorbid type 2 diabetes mellitus (T2DM), which shares underlying contributors such as insulin resistance and obesity.[7]

The relationship between T2DM and MASLD is considered bidirectional. T2DM accelerates the progression of MASLD to MASH and cirrhosis, increasing both all-cause and liver-related mortality, while MASLD exacerbates insulin resistance and impairs glycemic control. Other comorbidities, such as overweight/obesity and dyslipidemia, likely play a mediating role in the link between MASH and cardiovascular disease risk.[7]

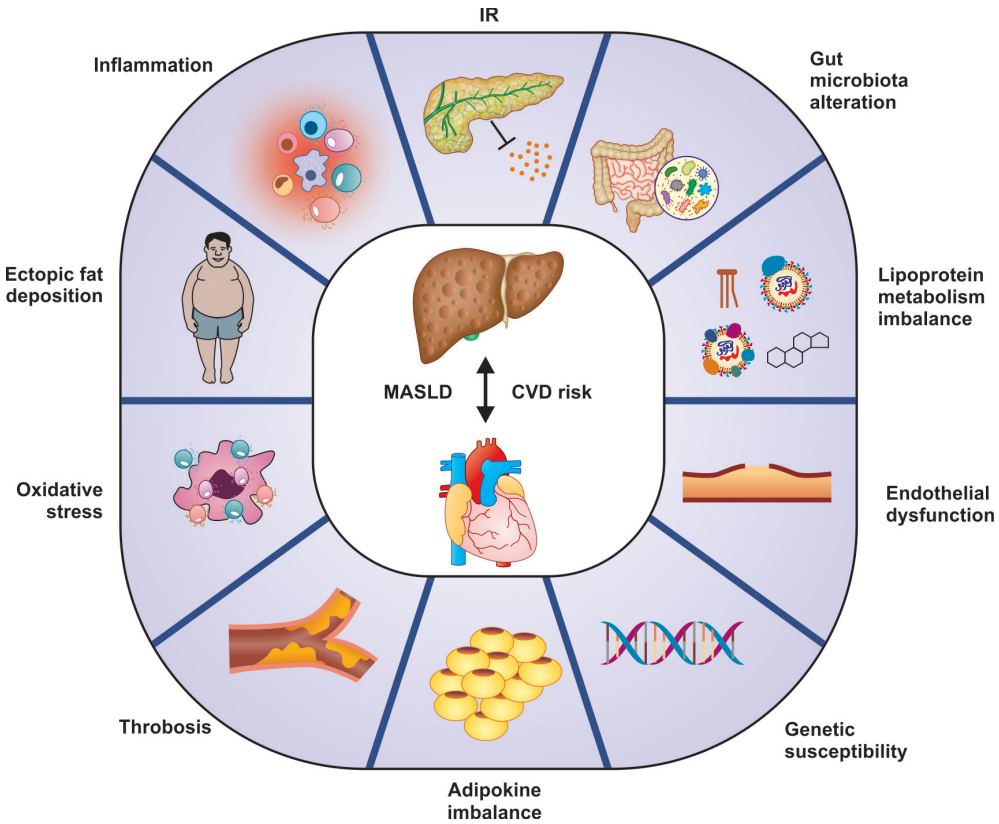

Fig 1. Pathophysiological mechanisms linking MASLD to CVD.[8]

Dyslipidemia in MASLD is characterized by increased secretion of very low-density lipoprotein (VLDL), resulting in elevated triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C). This condition is linked to the heightened atherogenicity of liver-secreted VLDL, impaired clearance by lipoprotein lipase, and postprandial lipemia. Hypertriglyceridemia in MASLD further contributes to atherogenesis risk. Patients with elevated alanine transaminase (ALT), high plasma triglycerides, and cholesterol are at greater risk of developing MASLD.[4]

Dysfunctional adipose tissue releases excessive free fatty acids (FFAs), causing ectopic fat deposition in tissues poorly suited for triglyceride accumulation. In middle-aged obese individuals with MASH, insulin resistance in adipose tissue is strongly associated with both metabolic and histological damage. Insulin resistance in the liver and steatosis are closely tied to adipose tissue insulin resistance. Dysfunctional adipocytes also release inflammatory cytokines, which impair insulin signaling in the liver and muscle, recruiting, and activating macrophages that exacerbate insulin resistance, elevate plasma FFA levels, and promote lipotoxicity.[4]

A chronic rise in plasma FFA levels adversely affects the heart and vascular systems, playing a key role in cardiovascular disease (CVD) development. Myocardial TG levels are elevated in individuals with glucose intolerance or type 2 diabetes mellitus (T2DM). MASLD patients are believed to have a higher prevalence of coronary, cerebrovascular, and peripheral vascular diseases. A modest elevation in plasma FFA levels, similar to those observed in T2DM, for 48–72 hours due to lipid infusion, can increase blood pressure and stimulate the production of systemic inflammatory markers.[4] This short-term rise in plasma FFA concentrations also elevates soluble E-Selectin, myeloperoxidase, and total plasminogen activator inhibitor-1 levels, indicating a procoagulant state and abnormal vascular reactivity.[4]

Elevated free fatty acids (FFAs) can increase blood pressure (BP) by impairing endothelial vascular function (EDV) through reduced expression and activity of endothelial nitric oxide synthase (eNOS) mRNA. Oxidative stress further exacerbates this effect. High plasma FFA levels also induce insulin resistance (IR) by inhibiting glucose transport activity. Direct reductions in endothelial NO production and eNOS mRNA expression caused by elevated FFAs may contribute to increased BP.[9]

Patients with MASLD exhibit impaired flow-mediated vasodilation and increased carotid artery intima-media thickness, though these findings require validation through larger, controlled studies.[4]

Cardiovascular disease (CVD) is highly prevalent in individuals with metabolic dysfunction-associated steatohepatitis (MASH), particularly those with advanced liver disease, and is a significant contributor to mortality. Proactive management of cardiovascular risk factors is essential in this population. Future research will clarify whether the CVD burden in MASH arises directly from the disease or reflects broader cardiometabolic abnormalities. Treatment for MASLD primarily involves lifestyle interventions and aggressive management of cardiovascular risk factors.[4]

Endocrine aspects of MASLD: Beyond insulin resistance

Obesity and insulin resistance are closely associated with MASLD. However, its pathophysiology also involves complex interactions with various endocrine systems. Endocrine dysregulation, including reduced levels of thyroid hormones, sex hormones, and growth hormone, may aggravate MASLD severity. Additionally, the roles of adipokines and steroid hormones, such as cortisol and dehydroepiandrosterone, appear to be more nuanced.[3]

Determining causal relationships between endocrinopathies and MASLD remains challenging. Nonetheless, endocrine dysregulation is frequently associated with increased prevalence and severity of MASLD, indicating significant links that extend beyond the contributions of obesity and insulin resistance.[3]

A decrease in growth hormone (GH) levels contributes to intrahepatic fat accumulation, whereas excess GH does not significantly affect the risk of fatty liver. Individuals with GH deficiency are at an increased risk of developing MASLD. Thyroid dysregulation has been more strongly associated with MASLD development, including conditions such as hypothyroidism, autoimmune thyroiditis, lower T4 levels, higher TSH (thyroid-stimulating hormone) levels, and correlations with body mass index (BMI). Studies involving biopsy-proven MASLD or MASH consistently highlight a robust relationship between thyroid dysfunction and MASLD severity.[3]

Resmetirom, a liver-targeted thyroid hormone receptor beta (THR-β) selective agonist, has shown significant efficacy in reducing liver fat content, improving liver histology, and lowering LDL cholesterol levels. Phase 3 trials demonstrated its ability to enhance fibrosis without exacerbating the NAFLD Activity Score.[10]

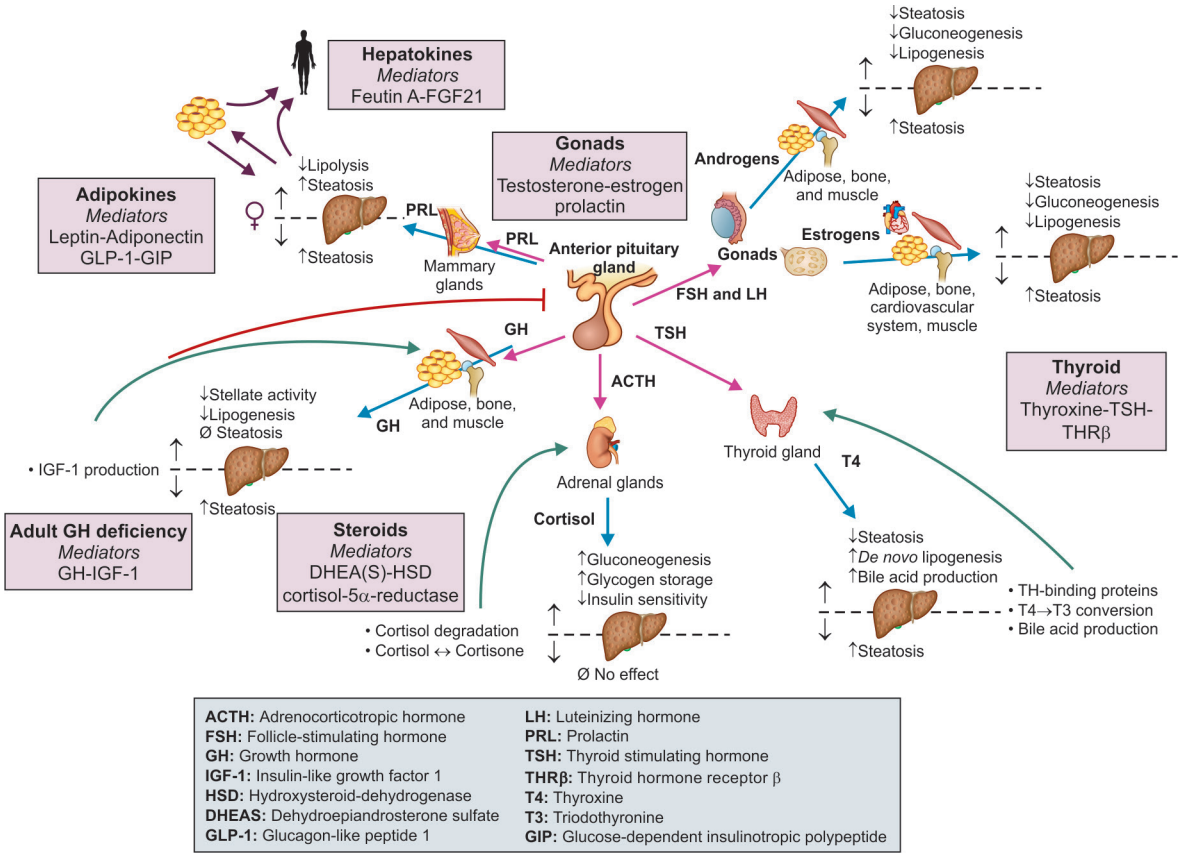

Fig 2. An overview of endocrine mediators, other than insulin resistance, of MASLD is shown.[3]

As the first FDA-approved medication for NASH, Resmetirom represents a major advancement in treatment, offering a targeted approach that minimizes systemic thyroid-related side effects. It shows promise in reducing liver fat, improving histological and metabolic parameters, and is particularly beneficial for patients with moderate to advanced fibrosis. However, further long-term studies are needed to assess its durability and overall impact on clinical outcomes. Resmetirom provides a novel and promising option for managing NASH.[10]

Glucocorticoids can exacerbate metabolic and histological features of MASLD, while androgen and oestrogen deficiency may promote MASLD. Sexual dimorphism is a major feature of MASLD, with evidence suggesting that androgens may be an important mediator of liver fat content. Testosterone deficiency in men promotes MASLD development, and oestrogen deficiency in post-menopausal women can exacerbate histological features of MASLD. Primary aldosteronism has a positive relationship with MASLD, with the severity of hypokalemia in primary aldosteronism relating to the severity of associated metabolic syndrome and the rate of MASLD.[3]

The liver plays a vital endocrine role, and MASH may be considered an endocrinopathy mediated by liver-produced hormone-like proteins (hepatokines) that affect extrahepatic metabolic regulation.[3]

Cardiometabolic factors, particularly obesity, are key drivers of metabolic dysfunction-associated steatotic liver disease (MASLD), with individuals having metabolic syndrome at higher risk. Around 70% of type 2 diabetes (T2DM) patients show symptoms of MASLD, and insulin resistance plays a central role in its development. MASLD also involves complex interactions with other endocrine systems, with low levels of growth hormone, sex hormones, and thyroid hormone contributing to its progression, while steroid hormones and adipokines have more variable effects. Effective management of MASLD requires evaluating non-insulin endocrine pathways, with emerging therapies targeting the fibroinflammatory cascade in MASH offering promising treatment options.[3,6]

Table 1. Link between MASLD and T2DM[7]

The majority of patients with type 2 diabetes (T2DM) have fatty liver, and up to 50% or more may develop MASH.
Elevated liver aminotransferases are a strong indicator of an increased risk of developing type 2 diabetes (T2DM).
Patients with T2DM and MASH experience more severe insulin resistance and the progression of liver disease.
The presence of fatty liver in patients with T2DM makes it harder to control diabetes and often necessitates higher insulin doses.

MASLD and diabetes are closely linked. For instance, rising liver aminotransferase levels in the general population are associated with an increased risk of developing type 2 diabetes (T2DM). Conversely, the majority of T2DM patients have fatty liver, and up to 50% may develop MASH. However, MASH is often overlooked in T2DM patients, and there are no specific guidelines to assist clinicians in screening for the condition. Elevated liver aminotransferases are a strong indicator of potential MASH and a higher likelihood of more advanced disease, highlighting the need for a more proactive diagnostic approach. Unfortunately, many diabetic patients have normal liver aminotransferases, leading clinicians to overlook the possibility of MASLD.[8]

Establishing causal relationships between specific endocrinopathies and MASLD is challenging, but endocrine dysregulation is often linked to higher prevalence and severity of the condition. The distinction between primary MASLD with coexisting endocrinopathies and secondary MASLD, where endocrinopathies are driving factors, may not be crucial. Healthcare providers should consider the potential role of both new and existing endocrinopathies in influencing the likelihood and severity of MASLD. Patients with overlapping endocrinopathies and MASLD may require more frequent monitoring for fibrosis progression.[6]

Conclusion

Managing patients with MASLD requires a comprehensive approach. Physicians should distinguish between fatty liver and MASH, as MASLD can lead to metabolic issues like insulin resistance and diabetes, while MASH indicates liver inflammation and necessitates a liver biopsy. Treatment decisions are complicated by the disease's unclear natural progression and the lack of approved pharmacological treatments. However, aggressive management of metabolic syndrome (MetS) components such as obesity, dyslipidemia, and hypertension can help prevent the onset of diabetes and cardiovascular disease (CVD).[8] As the first FDA-approved medication for NASH, Resmetirom marks a significant breakthrough, offering a targeted treatment that reduces systemic thyroid-related side effects.[10]

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