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Diagnosis and management of metabolic dysfunction- associated steatotic liver disease in South Asians- A clinical review

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed as nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of obesity and metabolic syndrome. It is mainly caused by insulin resistance. With the increased risk of visceral obesity in South Asians, the prevalence of MASLD is on the rise. The morbidity associated with MASLD and its complications, including hepatocellular carcinoma is projected to increase in this South Asian population.
Methods: In this narrative review we explore the diagnosis and management of MASLD in the South Asian population. We summarize the findings from the recent literature on the diagnostic methods and management options for MASLD in this population.
Results: Through our search we found no specific guidelines for the diagnosis and management of MASLD in the South Asian population. The existing general guidelines may not be applied to South Asian populations due to the differences in phenotype, genotype, social and cultural aspects. South Asian countries also have limited resources with the non-availability of newer pharmacotherapeutic agents.
Conclusion: The goal of this review is to guide obesity physicians and primary care providers to have a stepwise approach to treat patients at risk for MASLD with a main focus on interdisciplinary management most applicable to South Asian patients. More research is needed to formulate guidelines and algorithm that are specific for the South Asian population.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the term given to what was previously known as nonalcoholic fatty liver disease (NAFLD) until June 2023. MASLD includes patients who have hepatic steatosis and at least one of the following five cardiometabolic risk factors as shown in Figure-1 [1]. According to a meta-analysis study, the prevalence of MASLD in Asia is 29.62 % regardless of the diagnostic method that was used for diagnosis [2].

1.1. Classification of steatotic liver disease (SLD)

Steatotic liver disease (SLD) is a broader term which includes both alcoholic and nonalcoholic liver disease. The subclassification of SLD according to the Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) is illustrated in Figure-2.

1.2. MASLD – A multisystem disorder

MASLD is a multisystem disorder with an increased risk of

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development of hypertension, coronary heart disease, cardiomyopathy, and cardiac arrhythmias. In the majority of patients, MASLD is associated with metabolic comorbidities such as obesity, type 2 diabetes mellitus and dyslipidemia [3]. MASLD patients are also at a higher risk of neurological complications such as cognitive impairment due to a decrease in brain volume and the presence of white matter lesions. An increased risk of stroke is also noted [4]. Apart from liver related complications, other gastrointestinal conditions such as gastritis, ascites, and ulcerative colitis are also reported. MASLD is significantly associated with increased risk of developing GI cancers (esophagus, stomach, pancreas, or colorectal cancers), lung, breast, gynecological and urinary system cancers [5]. Studies suggest acute or chronic renal failure, iron deficiency anemia, and an increased risk of sepsis related complications in patients with MASLD [6,7].

1.3. Diagnostic criteria and tests for MASLD

MASLD is diagnosed when imaging confirms steatosis and if any one of the five cardiometabolic risk factors are present. If alcohol is the principal cause of liver injury, then it is termed as Metabolic associated, and alcohol associated liver disease MetALD [8]. The degree of fibrosis is further established with additional non-invasive testing and biopsy. Liver biopsy is the gold standard for diagnosing fibrosis [9]. Non-invasive testing for fibrosis includes calculation of Fibrosis-4 index (FIB-4) which is based on age, aspartate aminotransferase [AST], alanine aminotransferase [ALT] and platelet count. NAFLD fibrosis score (NFS), Steatosis-associated fibrosis estimator (SAFE), body mass index, AST/ALT ratio, diabetes (BARD) score are also used to diagnose fibrosis [10–12]. These tests are useful for ruling out advanced disease. The cut off points for high-risk fibrosis in each of these tests is as follows: FIB-4 $\geq$ 1.3, NFS $\geq$ - 1.455, SAFE score >100 and BARD >1 [12–15]. Enhanced Liver Fibrosis (ELF) panel blood work includes hyaluronic acid, tissue inhibitor of metalloproteinase (TIMP-1) and N-terminal procollagen III-peptide (PIINP) [16,17]. Imaging studies include magnetic imaging elastography (MRE) and vibration controlled transient elastography (VCTE) Fibroscan [18–22]. Recent studies have shown using MRI with proton density fat fraction (PDFF) is valuable in evaluating sarcopenia in Asian patients [23], and sarcopenic obesity is a risk factor for MASLD.

In a resource limited setting the use of FIB-4 index for screening fibrosis is recommended. It is an initial test to screen for advanced liver fibrosis [24–26]. The FIB-4 scoring system has very good negative predictive value for advanced liver fibrosis, but its positive predictive value is suboptimal. If a FIB-4 score is below 1.3, then this suggests a >90 % chance the patient does not have advanced fibrosis. According to latest clinical practice guidelines from European Associations for study of the Liver, Diabetes and Obesity, risk stratification is done based upon the FIB-4 score. If the score is less than 1.3, reassessment is done every 1–3 years. If the score is between 1.3 and 2.67, intensive management of comorbidities is recommended in addition to reassessment less than or equal to one year. If the score is above 2.67 referral to hepatologist is recommended. Patients with elevated FIB-4 should be followed up with Liver stiffness measurement (LSM) for further risk stratification using Fibroscans. If resources are available, then testing of additional markers for fibrosis and MRE imaging studies are recommended [19,27]. This is illustrated in Table-1 [28–32].

2. Discussion

2.1. MASLD and Sarcopenia

According to an Asian multicenter cohort study, the rate of Metabolic Associated Steatohepatitis (MASH) is higher in patients undergoing liver biopsy [33,34]. MASH has become one of the leading causes of adult liver transplantation worldwide [35–38]. Sarcopenic obesity is characterized by the combination of obesity, defined by high body fat percentage, and sarcopenia, defined as low skeletal muscle mass accompanied by low muscle function [39].

Studies indicate sarcopenic obesity is an independent risk factor for MASLD. Several studies indicate sarcopenia in addition to visceral fat obesity as a strong predictor of mortality and morbidity for MASLD, MASH, and cirrhosis [40–42]. A known phenotype of South Asian obesity is the 'thin-fat obesity' or 'sarcopenic obesity thus increasing the risk for complications associated with MASLD in them [43].

The severity of sarcopenia can be measured clinically by assessing how well patients can exercise or do simple tests like time to get up and go, or walk 400 m [44]. If resources are available, skeletal muscle mass can be evaluated by Dual-energy x-ray absorptiometry (DXA) and Bioelectrical impedance analysis body composition scales (BIA) as well as imaging studies such as Computed tomography or Magnetic resonance imaging. It is important to note that DXA and BIA are potentially less accurate than CT or MRI in assessing skeletal muscle.

Asian Working Group for Sarcopenia (AWGS) recommends specific

- **At least 1 out of the following 5 must be present:**
- **1. Body mass index (BMI) / Waist circumference (WC)**
- Body mass index (BMI) of at least 25 kg/m2, or waist circumference (WC) of more than 90 cm for men and 80 cm for women
- **2. Glucose/Hemoglobin A1c (Hb A1c)**
- Fasting serum glucose of at least 100 mg/dL, or 2-hour post-load glucose of at least 140 mg/dL, or HbA1c of at least 5.7%
- **3. Blood pressure**
- Blood pressure of at least 130/85 mmHg, or treatment with specific antihypertensive drugs
- **4. Triglycerides**
- Plasma triglycerides of at least 150 mg/dL, or treatment with lipid-lowering drugs
- **5. High-Density Lipoprotein (HDL)**
- Plasma HDL-cholesterol of less than 40 mg/dL for men and less than 50 mg/dL for women, or treatment with lipid-lowering drugs

Fig. 1. Cardiometabolic criteria for MASLD in adults.

criteria for diagnosing sarcopenia. Low muscle strength is defined as handgrip strength <28 kg for men and <18 kg for women, criteria for low physical performance are 6-m walk <1.0 m/s, Short Physical Performance Battery score ≤9, or 5-time chair stand test ≥12 s. AWGS 2019 retains the original cutoffs for height-adjusted muscle mass by DXA <7.0 kg/m2 in men and <5.4 kg/m2 in women and BIA <7.0 kg/m2 in men and <5.7 kg/m2 in women. In addition, the AWGS 2019 update proposes separate algorithms for community vs hospital settings, which both begin by screening calf circumference or SARC-F.

SARC-F examines five domains: 1) strength, 2) assistance in walking, 3) rising from a chair, 4) climbing stairs, and 5) falls, and is scored from 0 to 2. AWGS 2019 considers calf circumference <34 cm in men, <33 cm in women or SARC-F ≥4, or SARC-CalF ≥11 as criteria for earlier identification of people at risk for sarcopenia [45]. Many Asian patients with MASLD are lean with increased visceral fat. The natural course of lean MASLD is affected by the additional pathophysiological factors related to increased inflammation of the visceral fat [46].

2.2. Management of MASLD - Recommendations for physical activity

The Asian Pacific Association for the Study of the Liver (APASL) guidelines recommend gradual weight loss for the management of MASLD. This can be achieved by eating a healthy diet, restricting calories, and increasing physical activity. Many studies showed that a 7–10% of weight loss led to resolution of the histological changes in MASH and significant improvement of MASLD [47–49].

Regular physical activity is recommended to achieve healthy weight loss. Talk test is used to distinguish between the intensity of physical activity. If patients are able to talk but not sing while exercising, it is considered to be of moderate intensity. If patients are unable to have a conversation while exercising, it is considered to be vigorous physical activity. Moderate physical activity of at least 30 min/day for at least 5 days per week or a total of 150 min per week is recommended. Those who are able to do vigorous intensity exercise can do 25 min/day for at least 3 days per week or a total of at least 75 min per week. Weight loss can also help in managing comorbid conditions like Diabetes mellitus, Hypertension and Hyperlipidemia to reduce cardiovascular risks [50].

Table 1
Markers for fibrosis.

TYPE OF TEST	TESTS	SENSITIVITY	SPECIFICITY
Direct serum Biomarkers	Enhanced Liver Fibrosis (ELF) panel	69 [28]	98 [28]
Indirect serum Biomarkers	Fibrosis-4 index (FIB-4)	72.6[a] [29]	66.7[a] [29]
	NAFLD fibrosis score (NFS)	32.1[a] [29]	83.5[a] [29]
	Steatosis-associated fibrosis estimator (SAFE) score	53.3[b] [30]	88.3[b] [30]
	Body mass index, AST/ALT ratio, Diabetes (BARD)	73.3 [31]	66.4 [31]
Imaging Markers	Magnetic imaging elastography (MRE)	73.2[a] [32]	90.7[a] [32]
	Vibration controlled transient elastography (VCTE) – M probe	91.7[a] [32]	57.4[a] [32]

[a] = Significant fibrosis F2–F4.
[b] = SAFE score ≥100.

2.3. Management of MASLD -Recommendations for healthy nutrition

Healthy nutrition is recommended for patients with MASLD. For those who have obesity, healthy weight loss can be achieved with a calorie deficit of 500–1000 kcal per day. Patients with sarcopenia are encouraged to increase protein intake, but protein supplementation alone without resistance exercise is ineffective in improving muscle mass and strength [51]. Some studies show beneficial results with oral supplementation of branched-chain amino acids in patients with end stage liver cirrhosis and hepatic encephalopathy [52]. The European Society for Clinical Nutrition and Metabolism recommends a Mediterranean diet for patients with MASH. The Mediterranean diet also shows improvement in muscle mass in patients with sarcopenia. This diet has increased polyphenols, fiber carotenoids, and omega-3 polyunsaturated fatty acids which are protective in nature [53–56]. Protein intake of at least 1.2–1.5 g/kg/d is recommended according to the degree of malnourishment and sarcopenia in patients with compensated cirrhosis [56]. Different diets with varied rates of carbohydrate intake including a moderate carbohydrate diet (26–45 % of total calories per day), low carbohydrate diet (<26 % of total calories per day or > 30 g per day) and very low carbohydrate diet/Ketogenic diet (<10 % of total calories per day or < 30 g per day) showed benefits with MASLD as long as patients

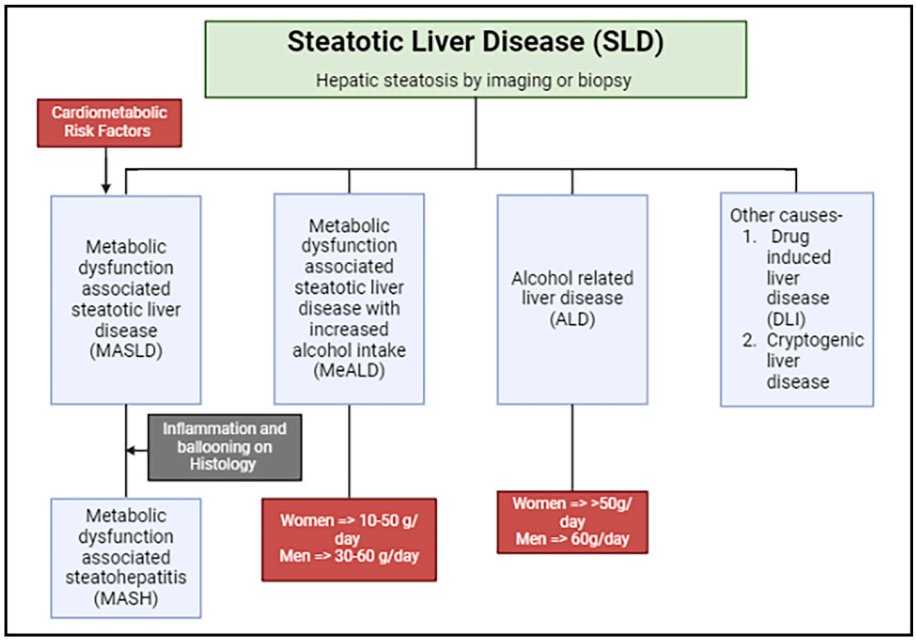

Fig. 2. Classification of steatotic liver disease (SLD).

achieved weight loss. A plant-based diet rich in healthy plant foods may be associated with lower odds of developing MASLD [34,57–59]. Intermittent fasting and time restricted eating is found to be beneficial in patients with MASLD [60]. With the cultural and ethnic preferences that South Asians have, a custom-tailored diet incorporating healthy amount of macro and micronutrients that can be adhered should be suggested to them.

US National cohort study suggests MASLD to be a state of increased oxidative stress and pro-inflammatory state possibly related with certain specific diets that are deficient in certain micronutrients. This study showed vitamin E and vitamin K, may play a protective role against MASLD. Vitamin E is generally recommended in patients who are at a risk for MASLD [61]. Vitamin D supplementation has been reported to improve insulin resistance in patients with MASLD [62]. Studies suggest that Vitamin D supplementation improves muscle strength in patients with sarcopenia [63,64]. Carotenoids are potent antioxidant and anti-inflammatory micronutrients and have been investigated in the prevention and treatment of MASLD [65].

Coffee consumption has been associated with a reduced risk of developing features of metabolic syndrome and liver fibrosis in MASLD [52,66]. It is important to remember that MASLD also occurs in Non-Obese and Non-Diabetic patients. Non-Obese MASLD in South Asians may be related to alcohol use and the presence of Hepatitis C and Hepatitis B infections. Abstinence from alcohol and counseling against substance use is essential for reversal of MASLD in this group [27].

Certain diets increase the rate of MASLD and should be discouraged in high risk patients. This includes a diet rich in processed meats, sweetened beverages, saturated fats, and high glycemic index carbohydrates [35]. In particular, the use of high fructose in beverages is found to be a major culprit in increasing the risk of MASLD and fibrosis. This is found to be independent of calorie intake in patients. Sweetened beverages cause lipogenesis in the liver, increasing lipid accumulation and lipid-driven oxidative stress [54,67]. Excessive intake of selenium may be associated with an increased risk of MASLD. Increased intake of macronutrients, such as carbohydrates, cholesterol, total saturated fatty acids, and total caloric intake, may promote the development of MASLD and so should be discouraged [61].

2.4. Management of MASLD - Pharmacotherapy

In a randomized clinical trial of patients with MASLD, 6 months of daily low-dose aspirin significantly reduced hepatic fat quantity compared with placebo. Aspirin use, shown to reduce hepatic fat, coupled with the cardiovascular benefits should be considered in treatment of patients with MASLD [68]. Treatment of MASLD with Glitazones demonstrated a more histological and biological benefit than Metformin in patients with Diabetes [38,69]. There are several medications that show promise in treatment of MASLD. These include agents targeting first- and second-generation Farnesoid X receptors (FXR), Peroxisome proliferator activated receptors (PPAR), C-c chemokine receptors, GLP-1 (glucagon-like peptide-1) receptors, and Thyroid hormone receptor (TRs). FXR agonists have been shown to decrease portal hypertension by targeting vascular remodeling and sinusoidal dysfunction in human cells and likely to have some potential for treatment of MASLD specifically when used in combination therapy with either Retrovirals or Propranolol. PPAR agonists showed promise initially, however large-scale studies are still needed to evaluate both efficacy and safety of these agents [70]. GLP-1 agonist, Liraglutide has been shown to decrease hepatic fat content in patients with Type 2 DM with MASLD. In a pilot study, it was shown to stop progression to cirrhosis in a 48-week treatment period [71,72]. Semaglutide was shown to improve steatosis but had no effect in the fibrosis stage [73]. Studies have demonstrated the improvement in liver fat content when Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are used. In patients with T2DM with MASLD, improvement ranging from 3.9 % to 6.9 % has been noted with these agents. Some of these newer medications are not yet available in South Asia. Cost of these medications are high and is a major limiting factor. Bariatric surgeries for weight loss have also shown promising results with long term resolution and regression of fibrosis in patients with MASLD [74].

3. Limitations

Despite significant prevalence of MASLD in the South Asian population, we found in the literature review that a specific algorithm is not yet formulated for diagnosing and managing MASLD in this population. So, we have listed the diagnostic criteria and the available tests that are applicable to general population. Further prospective studies must be conducted in order to develop an algorithm that is specific for the South Asian population. The diagnostic criteria use Fibroscans, however the high cost of Fibroscans make their availability limited in low resource settings. More nutritional studies targeting on the efficacy of the customized diet recommendations in prevention and management of MASLD in South Asians to be conducted in future.

4. Conclusion

With an increasing risk of MASLD in South Asians, it is important to educate providers and patients on the diagnostic tools and treatment options available. Due to the limited resources, risk-stratifying patients will help us use available resources effectively. Community awareness programs, educating patients on leading a better lifestyle with the help of dietitians, social workers and community care workers will be very beneficial. Finally, further research targeting this special population is needed to offer much more effective pharmacotherapy for better outcomes.

Key takeaways-

- The interrelationships and overlap of metabolic diseases should be understood and a multidisciplinary program focusing on identification and management of metabolic disorders such as MASLD should be considered by healthcare systems to provide an opportunity to prevent and treat MASLD.
- A practice toolkit using the available calculators such as FIB4, NFS, BARD, ELF and SAFE score should be embedded in the electronic health record system in the obesity clinics, so that clinicians can risk stratify patients effectively.
- Integrated approaches should be individualized and customized for the patients from different communities according to their cultural and ethnic preferences for better outcomes.

Author contribution via CrediT format

The concept of the submission was added by Dr. Niranjan and Dr. Ramesh. Dr. Niranjan, Dr. Ramesh and Dr. Krishnan wrote the first draft. Dr. Prabu and Dr. Srinivasan together reviewed, edited, and approved the final submission and publication.

Ethical adherence and ethical review

This submission did not involve experimentation of human test subjects or volunteers.

Declaration of artificial intelligence (AI) and AI-assisted technologies

During the preparation of this work the authors did not use AI or AI-assisted technologies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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