HCFI Dr KK Aggarwal Research Fund

Minutes of an International Weekly Meeting on "MASLD/MASH"

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- MASLD or metabolic dysfunction-associated steatotic liver disease is a new name for an old entity, but there are certain changes.
- It is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor in the absence of harmful alcohol intake or other identifiable causes of steatotic liver disease.
- This definition marks a shift towards an inclusion-based diagnosis, which focuses on metabolic dysfunction as the primary driver of the disease.
- The global prevalence is rising over the years. The prevalence in South East Asia is 33.07%. A very high prevalence is seen in Latin America (44%).
- MASLD is closely linked to diabetes. It is estimated that ~40% of individuals with diabetes have MASLD.
- It is the second leading cause of liver transplant in non-HCC (hepatocellular carcinoma) patients and most common in HCC patients.
- Individuals with obesity, diabetes, dyslipidemia, hypertension, and of Hispanic heritage are at higher risk.
- Fatty liver was first described almost 200 years ago in 1836. In 2020, the name was changed to MAFLD (metabolic dysfunction-associated fatty liver disease). In 2023, the name MASLD was proposed. Non-alcoholic steatohepatitis (NASH) was changed to MASH (metabolic dysfunction-associated steatohepatitis).
- Steatotic liver disease can be MASLD (which can progress to MASH), alcohol-associated liver disease, other causes such as drug-induced, celiac disease, and cryptogenic steatotic liver disease.
- If fatty liver is associated with low amount of alcohol intake (20 g/day for females and 30 g/day for males), it is metabolic and alcohol-associated liver disease (MetALD), but if high intake (50 g/day for females and 60 g/day for males) it is alcohol related MAFLD.
- The cardiometabolic criteria in adults, in addition to fatty liver, include fasting blood sugar (FBS) ≥100 mg/dL, glycated hemoglobin (HbA1c) ≥5.7%, blood pressure (BP) ≥130/85, plasma triglycerides ≥150 mg/dL and plasma high-density lipoprotein (HDL) cholesterol ≤40 mg/dL.
- The MASLD continuum describes the progression of the disease, which begins from simple fatty liver with trivial or no inflammation and no hepatocyte ballooning (steatosis or "MAFL"), which progresses to significant inflammation and hepatocyte ballooning (steatohepatitis or "MASH") and finally, the increasing fibrosis leads to cirrhosis and HCC (cirrhosis).
- Physical inactivity and obesogenic diet increase adiposity and insulin resistance → increase in free fatty acids, glucose → type 2 diabetes → MASLD. Activation of Kupffer cells and stellate cells increases progression of fibrosis resulting in cirrhosis.
- The major risk factor for progression of fibrosis in MASLD is type 2 diabetes. Other factors include genetics, unhealthy diet and alcohol, gut dysbiosis and visceral obesity.
- The major comorbidities are type 2 diabetes, dyslipidemia, obesity, and metabolic syndrome. Other associations include hypothyroidism, sleep apnea, hypopituitarism, hypogonadism, polycystic ovary syndrome (PCOS) and pancreatic resection.
- MASLD is a complex disease trait with genetic, environmental, and epigenetic modifiers. The environmental modifiers include sedentary lifestyle, snacking, fast food, saturated fats, trans fats, and processed red meat.
- Obesity and insulin resistance play a very important part. An interplay of various factors such as hypertension, hyperuricemia, dyslipidemia, hyperglycemia, macrovascular disease, type 2 diabetes leads to MASLD.
- According to the multiple-hit hypothesis of MASLD, a single factor is not responsible; several interacting risk factors such as genetic predisposition, inflammatory cytokines, gut microbiota, dietary and environmental factors, oxidative stress, and insulin resistance are involved in the pathogenesis.
- Diagnostic evaluation includes assessment of fibrosis and hepatic inflammation, risk stratification, evaluation for comorbidities, screening for HCC and extrahepatic malignancies (thyroid, lung, colon, and pancreas).

- Assessment of fibrosis is important as it is the most accurate predictor of overall mortality, liver-related mortality and liver-related events in MASLD patients. Early diagnosis and management prevents progression to cirrhosis and its complications.
- In an individual with suspected MASLD, the first step is risk identification (presence of metabolic syndrome or other high prevalence group such as type 2 diabetes, metabolic risk factors (body mass index [BMI] >25 or >23 in Asians, lipids, PCOS, obstructive sleep apnea) or first-degree relatives with MASLD, cirrhosis or HCC.
- Ask about history of alcohol intake and any known pre-existing liver.
- Investigations include liver biochemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], etc.). Basing diagnosis only on abnormal liver enzymes is not enough.
- Tests to exclude other liver diseases – negative hepatitis B virus and hepatitis C virus serology, negative autoantibodies (ANA, AMA, SMA, ANCA), negative celiac serology, normal immunoglobulins, ferritin, copper, etc.
- Liver ultrasound shows increased echogenicity (steatosis).
- Abnormal ALT may warrant workup for MASLD, but is not sensitive to confirm, rule out or characterize MASLD.
- Ultrasound can identify fatty liver (steatosis), but cannot distinguish between steatosis vs. MASH vs. fibrosis/early cirrhosis. The last stage, cirrhosis, can be picked up on USG, but not the intermediate stages of inflammation and fibrosis.
- Noninvasive blood-based scores include FIB-4 index, aspartate transaminase-to-platelet ratio index (APRI), and NAFLD Fibrosis score (NFS).
- Commonest among these is the FIB-4 index; the cut-off is 1.30-2.67 with sensitivity ~84%. A score of <1.30 indicates low risk of fibrosis, while a score >2.67 indicates high risk of fibrosis. However, this may not be so clear in diabetes as in other individuals or in the elderly where a lower cut-off of 2.0 applies; its ability to detect fibrosis is limited in the intermediate range (1.30-2.67).
- NFS >0.676 indicates high risk of fibrosis. It incorporates age, BMI, impaired fasting glucose, AST/ALT ratio, platelet count, and albumin.
- APRI calculated by the formula: AST/ULN AST) x (100/platelet count). Cut-off is 0.5-1.5 with sensitivity of 83%.
- Other noninvasive blood-based scores are Enhanced Liver Fibrosis (ELF) score and ADAPT score.
- Imaging techniques include elastography, vibration-controlled transient elastography (VCTE) or Fibro-Scan and two-dimensional shear wave elastography (2D-SWE) and point shear wave elastography (p-SWE). In FibroScan, if kPA is ≥8, it indicates advanced fibrosis risk.
- Magnetic resonance elastography (MRE) measures whole liver stiffness. It is more convenient and provides at least equal quality in fibrosis staging as USG-based elastography techniques. Cost, however, is a concern. Other magnetic resonance imaging (MRI)-based methods are MR-proton density fat fraction (PDFF) and corrected T1 (cT1).
- Combined scores using a combination of blood tests and imaging results can also be used for diagnosing fibrosis; these include MAST (MRE + MRI-PDFF + AST), FAST (VCTE + AST) and MEFIB (MRE + FIB-4).
- Liver biopsy is still the gold standard for definite diagnosis of steatohepatitis (MASH), but with limitations such as invasive, painful, expensive, associated morbidity/mortality, sampling variability, observer variable, expertise to perform and impractical for population screening.
- In patients at risk or established fatty liver disease, do a primary risk assessment e.g., FIB-4. If score is <1.3, do not worry and re-assess the patient after 1 to 2 years. If >1.3, then do a FibroScan; if >8, refer for gastrointestinal/hepatology care, if <8, then reassess periodically.
- Treatment of MASLD involves lifestyle interventions and pharmacotherapy. Lifestyle interventions are the cornerstone of treatment; the key components include weight loss, dietary changes, physical exercise, and quitting alcohol intake.
- In persons with MASLD and overweight/obesity, reduction of ≥5% of body weight reduces liver fat; reduction of 7%-10% improves liver inflammation and reduction of ≥10% improves fibrosis. In persons with MASLD and normal weight, reduction of 3%-5% of body weight reduces liver fat.
- Sustained weight loss through lifestyle modification helps in NASH resolution, improvement of steatosis and inflammation, and fibrosis regression.
- Exercise has multisystemic effects on the muscles, adipose tissue, liver, and cardiovascular system. In the muscle, exercise increases muscle mass and glucose uptake; in the liver, it increases insulin sensitivity, glucose uptake and reduces oxidative

stress; in the adipose tissue it increases insulin sensitivity, lipolysis and reduces visceral adiposity and in the cardiovascular system, it improves endothelial function, VO_2 max and reduces heart rate.

- Ultra-processed foods are significantly associated with increased liver fat accumulation. The triglyceride glucose-waist to height ratio is a predictor of liver fibrosis.
- Pharmacotherapy in MASH targets steatosis, inflammation, insulin resistance, liver fibrosis.
- Drugs that reduce liver fat accumulation include glucagon-like peptide-1 receptor agonists (GLP-1RAs) (semaglutide, tirzepatide), peroxisome proliferator-activated receptor (PPAR) agonists (pioglitazone, saroglitazar, lanifibranor), sodium-glucose cotransporter-2 inhibitors (SGLT2i) (dapagliflozin, empagliflozin), thyroid hormone receptor (THR)-β agonists (resmetirom), farnesoid X receptor (FXR) agonists (obeticholic acid, cilofexor) and omega-3 fatty acids.
- Drugs that improve insulin sensitivity include GLP-1RAs (semaglutide, tirzepatide), PPAR agonists (pioglitazone, saroglitazar, lanifibranor), SGLT2i (dapagliflozin, empagliflozin), THR-β agonists (resmetirom), and fibroblast growth factor 21 (FGF21) analogs (efruxifermin, pegozafermin).
- Drugs that reduce hepatic inflammation include vitamin E (antioxidant effect), GLP-1RAs (semaglutide, tirzepatide), PPAR agonists (pioglitazone, saroglitazar, lanifibranor), FGF21 analogs (efruxifermin, pegozafermin), and omega-3 fatty acids (anti-inflammatory properties).
- Drugs that have anti-fibrotic effects include PPAR agonists (pioglitazone, saroglitazar, lanifibranor), FGF21 analogs (efruxifermin, pegozafermin), THR-β agonists (resmetirom), FXR agonists (obeticholic acid), fatty acid synthase inhibitor (denifanstat) and GLP-1RAs (semaglutide).
- Resmetirom is a selective THR-β-agonist. It reduces fat in liver, fibrosis in the liver, intrahepatic inflammation and interferes with fibrogenesis in the liver. It was FDA approved for NASH treatment in March 2024.
- Resmetirom dose for patient <100 kg is 80 mg and in persons >100 kg, the dose is 100 mg.
- PPAR agonists improve insulin sensitivity, glucose and lipid metabolism and reduces hepatic steatosis, inflammation, and fibrosis.
- Saroglitazar is a novel dual regulator of lipid and glucose homeostasis with >1,000-fold selectivity for PPAR-α over PPAR-γ. It significantly improved serum ALT, hepatic steatosis, insulin resistance and dyslipidemia in MASLD/MASH (EVIDENCE IV study).
- Saroglitazar treatment is effective and there is a significant difference in SGOT and SGPT, triglycerides and liver stiffness measurement levels after treatment.
- Lanifibranor, a pan-PPAR agonist, which targets multiple pathways is undergoing phase III studies.
- GLP-1RAs (semaglutide, liraglutide, dulaglutide), dual (survodutide) and triple (retatrutide) agonists have mainly indirect benefit in MASLD (incretin effect). They lead to significant weight loss of 5%-15%; ESSENCE phase 3 trial (semaglutide).
- SGLT-2i reduce hepatic steatosis and improve serum transaminases and noninvasive scores for fibrosis; dapagliflozin (DEAN trial).
- FGF21 analogs protect hepatocytes, reduce inflammation and prevent progression of hepatic fibrosis; efruxifermin (HARMONY trial phase 2b) and pegozafermin (phase 2b). These are undergoing phase III trials.
- Fatty acid synthase inhibitors like denifanstat are currently in phase III trials.
- Some natural products like flavonoids, terpenoids, saponins, polyphenols, alkaloids, polysaccharides have also been used in MASLD because of their antioxidant, anti-inflammatory, and hepatoprotective properties.
- Applications of AI in MASLD: deep learning (EMRs, prediction models, NASHMap), digital pathology (WSI, SHG microscopy, qfibrosis, TPEF microscopy), ultrasound imaging (HRIA, TE, implemented fat quantification), CT and MRI imaging (implement fat quantification), chatbots (patient education, histological diagnosis, clinician support), and drug development.

Participants – Member National Medical Associations: Dr Yeh Woei Chong, Singapore, Chair of Council CMAAO; Dr Akhtar Hussain, South Africa; Dr Prakash Budhathoki, Nepal

Invitees: Dr Monica Vasudev, USA; Dr Arpit Punetha; Dr Harbans Gulati; Dr Naorem Sharat Kumar; Dr Nishi Arora; Dr Poonam Chablani; Dr Ravindra Kuntal; Dr Shashi Khanna; Dr Ranjit Singh; Dr PC Pahwa; Dr Geeta Dutta; Dr Shagufta Yasmin; Dr Ashok Shukla; Dr S Sharma, Editor-IJCP Group

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