The Next Frontier in Metabolic Dysfunction-Associated Steatotic Liver Disease

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THE FUTURE of metabolic-dysfunction associated liver disease (MASLD) was discussed in an insightful session chaired by Hannes Hagström, Karolinska Institutet, Stockholm, Sweden; and Dina Tiniakos, National and Kapodistrian University of Athens, Greece, during the European Association for the Study of the Liver (EASL) Congress 2024, held in Milan, Italy from the 5th–8th June. Hot topics included the evolving role of hepatologists, novel treatments and biomarkers for MASLD, and the promise of AI in the field.

CLINICAL PATHWAYS IN 2030: WHAT, WHO, AND WHERE?

"What will the role of the hepatologist be in 2030?" Opening the session, Ian Rowe, Leeds Institute for Medical Research, UK, emphasised the importance of simplifying testing and risk prediction for MASLD. Standard routine liver ultrasound has low specificity, with the probability of steatosis remaining at almost 30% after a negative test. Recently, the LiverRisk score, developed by the LiverScreen consortium to predict liver stiffness using blood parameters, showed good performance in prediction of liver-related events; however, there is still potential for further improvement.

> **The role of the hepatologist will return towards management of those with most severe disease**

Rowe noted that, when developing new diagnostic pathways, a low risk of false negatives cannot be balanced with a sufficient risk to justify cost and burden of treatment. For 2030, he outlined a more simplified pathway for MASLD, with no need for confirmation of steatosis in at-risk patients; a straightforward, individualised risk prediction for management decisions; and risk thresholds for treatment defined by effectiveness, notably cost-effectiveness, of treatment. With many people with MASLD already receiving likely effective treatment (e.g., glucagon-like peptide-1 [GLP-1] receptor agonists) from primary care, the role of the hepatologist will return towards management of those with most severe disease. However, clinicians should not stop advocating for population-level interventions.

BREAKING THE BARRIER WITH MASLD TREATMENT

Elizabetta Bugianesi, University of Torino, Italy, reminded the audience that, in order to gain provisional drug approval, resolution of metabolic dysfunction-associated steatohepatitis (MASH) with no worsening of liver fibrosis, and/or fibrosis improvement ≥1 stage, need to be demonstrated. However, full approval would be based on long-term outcomes of randomised clinical trials, involving 4–5 years of follow-up.

Bugianesi outlined the key mechanisms involved in the pathophysiology of MASLD and MASH: lipolysis and *de novo*

lipogenesis, leading to overflow of fatty acids, which causes formation of lipotoxic species and hepatocyte injury through mitochondrial dysfunction, endoplasmic reticulum stress, and apoptosis. These pathways serve as potential targets for the development of new treatments.

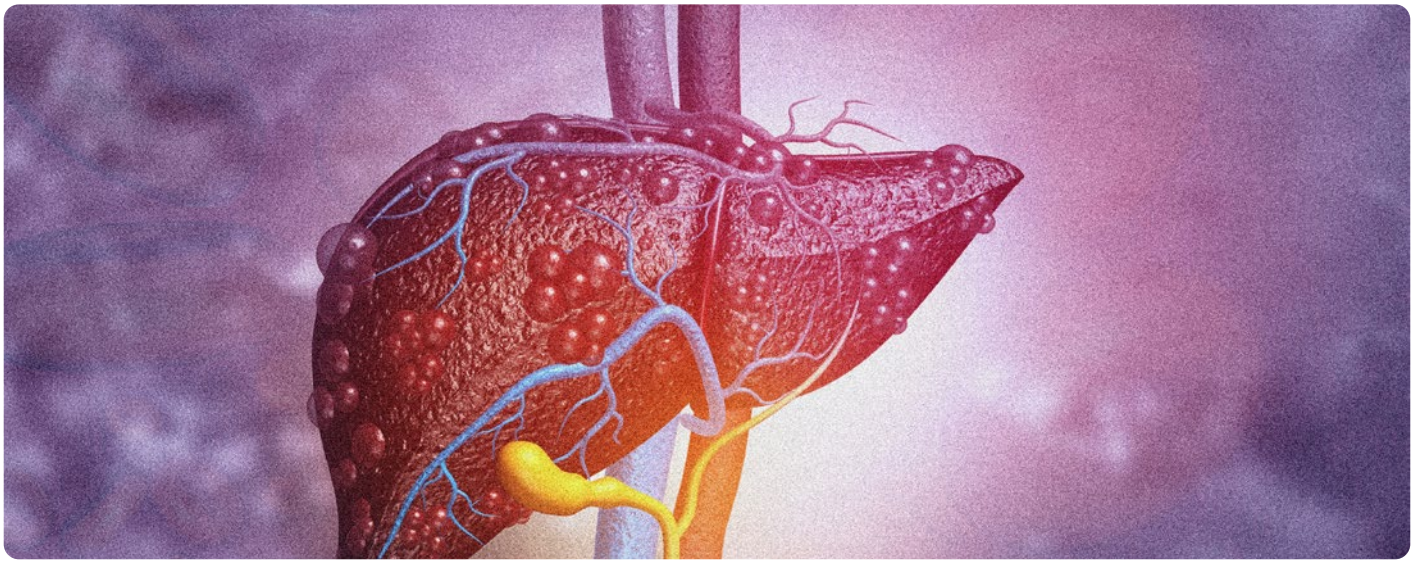
GLP-1 receptor agonists, a very successful class of drugs for MASLD, decrease hepatic glucose production, increase hepatic insulin sensitivity, and reduce *de novo* lipogenesis, subsequently reducing steatosis. They also offer nephroprotection and cardiovascular protection.

Further treatment options have been explored in recent trials. In a Phase IIb trial, semaglutide 0.4 mg led to resolution of MASH with no worsening of liver fibrosis in 60% of patients, and no serious adverse events reported.[1] Bugianesi also spoke about twincretins, a potential therapeutic for the management of MASLD, which couple the effects of GLP-1 with those of glucagon and gastric inhibitory polypeptide (GIP). The addition of the glucagon effect enhances liver function, with increase in lipid oxidation and decrease in lipid synthesis; increases thermogenesis in brown adipose tissue; and improves cardiomyocyte survival in the heart. The addition of GIP increases the potency of GLP-1 effects. In a recent Phase IIb trial assessing the dual GIP receptor/GLP-1 receptor agonist tirzepatide in MASH, the percentage of patients showing resolution of MASH with no worsening of liver fibrosis 48 weeks after treatment (primary endpoint) increased with tirzepatide dose (5, 10, or 15 mg), to reach almost 74% resolution with tirzepatide 15 mg.[2] The same was observed for dual GCG receptor/GLP-1 receptor agonist survodutide in MASH, with 83% of patients on survodutide 4.8 mg achieving the primary endpoint compared to 19.2% of the placebo group.

Resmetirom, a thyroid hormone receptor-β agonist approved for treatment of MASH F2–F3, has also been found to lower liver fat, resolve non-alcoholic steatohepatitis, and lower low-density lipoprotein cholesterol and triglycerides. In a Phase III trial, continued Bugianesi, resmetirom 100 mg led to MASH resolution in 29.9% of patients, compared to 9.7% of the placebo group; as well as a 25.9% fibrosis improvement ≥1, compared to 14.2% placebo.[4]

Another drug currently in clinical development, lanifibranor, a pan-peroxisome proliferator-activated receptor agonist, carries anti-inflammatory and anti-fibrotic properties, beyond lowering steatosis. A Phase IIb trial showed that 1,200 mg of lanifibranor reduced MASH in 49% of patients, and improved fibrosis in 42% of patients, with only mild side effects.[5]

Finally, fibroblast growth factor 21 (FGF21), an endogenous metabolic hormone with pleiotropic effects, reduces fatty acid



oxidation and lipogenesis, while also reducing inflammation and oxidative stress in the heart. However, native FGF21 has a short half-life (<2 hours). Long-acting fusion protein, pegozafermin, and long-acting FGF21 analogue, efruxifermin, were recently tested in Phase IIb trials, with promising results of NASH resolution and fibrosis improvement.

Moving onto comorbidities for liver disease, Bugianesi stressed that, while weight loss is important in disease management, key lessons should be learned from bariatric surgery outcomes. For instance, a study showed that a range of 20–25% body weight loss led to the highest response rate of NASH regression without worsening of fibrosis. Moreover, after 1 year of bariatric surgery, the percentage of patients with fibrosis decreased to 66%, but after 5 years, this number fell drastically to 36.5%. Bugianesi added that the liver should be considered as a component of the cardio-renal-metabolic system. MASLD/MASH can worsen the detrimental effects of metabolic syndrome, leading to interrelated diseases such as Type 2 diabetes, cardiovascular disease, and chronic kidney disease. She concluded that interdisciplinary management is key: "All these organs belong to the same body."

BIOMARKERS FOR MEASURING MASLD PROGRESSION

"Is liver biopsy suitable to monitor disease progression/therapeutic response in clinical practice?" was the question addressed by Raluca Pais, Pitié Salpetriere Hospital, Paris, France. Pais explained that, while liver biopsy has long been the 'gold standard' and a 'reasonably likely' surrogate endpoint for accelerated approval in MASH clinical trials, it is now recognised as an imperfect tool, and unsuited for use in real-life clinical practice. Several challenges are currently associated with liver biopsy, especially regarding inter-observer variability in liver fibrosis assessments, and the complexity of ballooned hepatocyte feature recognition, which is a significant issue as ballooned hepatocytes are essential for the diagnosis of MASH.

Pais stated that non-invasive tests (NIT) are having a growing role in clinical practice to replace liver biopsies. A recent study showed that simple NITs like liver stiffness and the fibrosis-4 index (FIB-4) performed as well as histology in predicting clinical outcomes in patients with MASLD. Furthermore, changes in FIB-4 have been associated with risk of severe liver disease; however, more studies will be required to assess if FIB-4 can predict response to treatment. According to Pais, direct fibrosis biomarkers, which reflect the balance between fibrogenesis and fibrolysis, are probably more suitable than a simple fibrosis marker to assess disease progression. Enhanced Liver Fibrosis (ELF) score and hepatic collagen have been associated with a risk of progression to cirrhosis. Liver stiffness thresholds may also be useful for risk stratification of patients with NASH in clinical practice. Patients who progressed to a liver stiffness threshold ≥10 kPa had an almost four-fold increase in the risk of liver-related events.[6]

Pais emphasised that NITs should become 'reasonably accepted' tools to monitor disease progression and treatment response, with several levels of evidence required to select an NIT for clinical practice. These should include context of use, disease severity, drug mechanism of action, and availability of NITs in real-life setting. She also noted that a panel of NITs should be preferred to a single biomarker.

AI IN MASLD: PROMISE OR HYPE?

"Are we as physicians ready to apply AI to our patient data?" asked Jörn Schattenberg, Saarland University Medical Center, Homburg, Germany.

While AI can be harnessed to support research models for detection and risk stratification based on big data, it is only limited to the data that are available, and could be missing crucial data points, which is a significant challenge for using AI in a clinical research setting. In a recent study, Schattenberg and colleagues aimed to separate NASH versus non-NASH cases using the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) dataset. The AI Light Gradient Boosting Model identified a 14-parameter algorithm to identify NASH versus non-NASH, which could prove useful in the clinic to predict at-risk patients.[7] However, he emphasised that clinicians may not always have ready access to the 14 parameters required by the AI system. "What we really need," continued Schattenberg, "is prospective data, to collect the data points that are really important." He highlighted the significance of prospective studies, where data points that are actually of interest to clinicians can be integrated, therefore gaining more reliability.

Schattenberg explained that, while AI can be used to refine imaging technology, like ultrasound, and detect the degree of steatosis with high precision and recall, this is very dependent on the operator. If the operator does not give AI the right angle or liver section, precision will be lost. He also added that liver histology is an attractive area where AI can be used to identify different histological features, reduce challenges with the reference standard, and even generate new fibrosis categories and markers of regression and progression.

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Schattenberg also noted that AI-language models could be used to empower patients and support education; for instance, ChatGPT can help translate and customise answers for patients who have questions about management of their MASLD. He concluded the session by highlighting the importance of harmonising data, and adopting a data security standard. For physicians, AI can help overcome issues like low awareness and expertise, but he stressed that "AI must be explainable". Before basing any decisions for patients on the results of an algorithm, physicians must first understand it.

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