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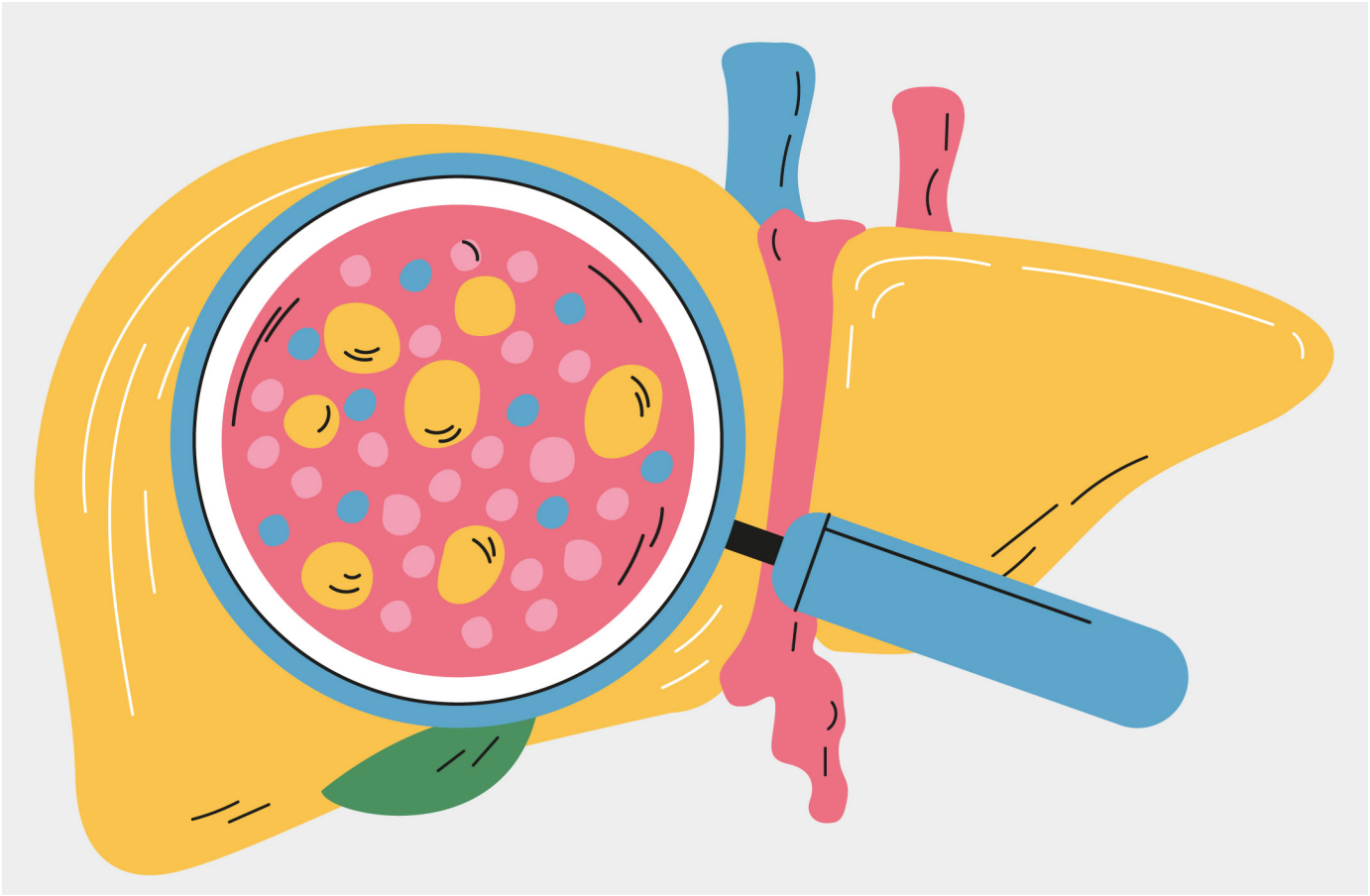

# Updates to Clinical Guidelines for Managing MASLD

**Metabolic dysfunction-associated steatotic liver disease (MASLD) is a term including changes caused by fat deposition in the liver in patients with one or more cardiovascular risk factors (diabetes, obesity, increased waist circumference, etc.), after excluding alcohol abuse.**

MASLD has become the most common chronic liver disease worldwide, and its prevalence is increasing. Furthermore, this disorder is currently the leading cause of cirrhosis and hepatocellular carcinoma.

As Dr. Tinahones explained to us in issue 85 of Diabetes (**https://www.revistadiabetes.org/complicaciones/esteatohepatitis-como-enfermedad-metabolica/**), MASLD is a progressive disease. The first phase of this disease is simple hepatic steatosis (fat deposition in the liver without inflammation), followed by steatohepatitis (nonalcoholic steatohepatitis-NASH), where signs of inflammation are observed along with varying degrees of fibrosis in hepatocytes. This fibrosis can range from stage 0 (F0, no fibrosis) to F4 (cirrhosis), and it is at this stage where complications significantly increase. Therefore, the objective of MASLD treatment should be aimed at reducing hepatic fat deposition (triglycerides) and reversing fibrosis when present.

It is known that MASLD is associated with an increased risk of cardiovascular events, and the presence of other metabolic factors, such as obesity, hypertension, hyperglycemia, among others can accelerate its progression to cirrhosis. Today, diabetes is considered the greatest risk factor for cirrhosis in a patient with MASLD. Hence, another treatment objective is to improve metabolic control (blood pressure, glucose, cholesterol, etc.). For this reason, lifestyle changes based on a healthy diet, regular physical activity, low or no alcohol consumption, and weight loss in patients who are overweight or obese are fundamental pillars for correctly addressing MASLD.

Recently, an update on the management of MASLD has been published through a new clinical practice guideline developed jointly by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO). This guideline reviews the main updates on the management of MASLD. The foundation of treatment is lifestyle changes, with a particular emphasis on weight loss in all patients, even those with normal weight. Weight loss of 5% can help reduce hepatic steatosis, and if it exceeds 10%, a decrease in fibrosis parameters has been observed. To achieve these goals, a proper diet plan based on the Mediterranean diet, encouraging physical activity, quitting smoking, and reducing or abstaining from alcohol consumption (in cases of advanced fibrosis or cirrhosis) is crucial. Additionally, incretin-based treatments with a positive effect on weight reduction or even bariatric surgery should be considered. Furthermore, treating associated risk factors (diabetes, hypercholesterolemia, hypertension, etc.) is a key part of managing patients with MASLD (1).

The list of drugs under investigation for MASLD in recent years has increased exponentially. We already knew the results of some antidiabetic drugs that had shown improvements in transaminase levels and hepatic fibrosis parameters. GLP-1 analogs (liraglutide and semaglutide) or pioglitazone have demonstrated a reduction in liver fat content, but with a limited effect on fibrosis. However, data has been published on other drugs initially designed for diabetes, such as dual analogs, which have potential effects on MASLD. One of them is tirzepatide, an innovative molecule combining a GLP-1 analog and a GIP receptor analog, which has demonstrated a powerful effect in reducing glycated hemoglobin and weight. A recent phase 2, multicenter, randomized study evaluated the use of tirzepatide for 52 weeks in hepatic biopsies (2). The percentage of patients meeting the criteria for MASLD resolution (significant reduction in hepatic fat content) in the tirzepatide group was 44%, 56%, and 62% with 5 mg, 10 mg, and 15 mg doses, respectively, compared to 10% in the control group. Additionally, 50% of tirzepatide patients showed a reduction in hepatic fibrosis markers vs 30% in the control group. Similarly, survotide, a dual analog of GLP-1 and glucagon, has demonstrated a significant reduction in liver fat content (at least 30%) in 63% of patients treated with 2.4 mg, 67% of those treated with 4.8 mg, and 57% of those treated with 6.0 mg, vs 14% in the placebo group (3). Similarly, a reduction of fibrosis parameters was observed in 34%, 36%, 34%, and 22% of patients treated with 2.4 mg, 4.8 mg, 6.0 mg, or placebo, respectively. Other drugs, such as empagliflozin, a sodium-glucose co-transporter inhibitor used widely in diabetes treatment, have also demonstrated a positive effect on reducing liver fat content in studies using magnetic resonance imaging (4). Despite these promising one »

**IT IS WELL KNOWN THAT MASLD IS ASSOCIATED WITH AN INCREASED RISK OF CARDIOVASCULAR EVENTS AND THAT THE PRESENCE OF OTHER METABOLIC FACTORS (OBESITY, HYPERTENSION, HYPERGLYCEMIA, AMONG OTHERS) CAN ACCELERATE ITS PROGRESSION TO CIRRHOSIS**

» of these drugs have been approved for MASLD indication.

In early 2024, the U.S. Food and Drug Administration (FDA) approved the first drug specifically indicated for MASLD. Resmetirom is an oral selective agonist of the hepatic TSHβ receptor that has shown reductions in weight, cholesterol, and hepatic steatosis. The MAESTRO-NASH study (5), a phase 3 clinical trial, was designed to assess the safety and efficacy profile of resmetirom in MASLD patients diagnosed via liver biopsy. Over 52 weeks, nearly 1000 patients were randomized to receive either 80 mg or 100 mg of resmetirom or placebo. The group treated with this drug showed resolution of hepatic steatosis in 25.9% of patients treated with 80 mg and 29.9% of those treated with 100 mg vs 9.7% in the placebo group. Regarding fibrosis, 24.2% of the patients in the 80 mg resmetirom group and 25.9% in the 100 mg group showed a reduction in fibrosis scores on liver biopsies vs 14.2% in the placebo group. The rate of adverse events was similar across all 3 groups.

The future of new drug development for this prevalent disease is very promising. There are currently ongoing efforts to develop antifibrotic drugs such as cenicriviroc or FGF-21, antioxidant modulators, cannabinoid receptor agonists/antagonists, and others, which may help cure or reverse the hepatic alterations associated with MASLD. However, we must not forget that the best way to tackle this disease is through prevention. Healthy lifestyle choices, regular physical exercise, and reducing or abandoning alcohol consumption are fundamental pillars for prevention in this highly prevalent condition. D

## CONCLUSIONS

The newly published clinical practice guidelines reinforce the importance of lifestyle measures, particularly weight loss, even for normal-weight individuals. Obesity drugs, such as GLP-1 analogs, dual agents, and bariatric surgery are essential considerations for managing MASLD and associated comorbidities. For the first time, a treatment specifically targeting MASLD demonstrates reduced liver fat and fibrosis regression.

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