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Management of MASLD patients in primary care

With the increasing prevalence of obesity and diabetes worldwide—a true epidemic in the 21st century—hepatic steatosis has become a public health issue. It is the fastest-growing complication in the last 20 years and is currently the second leading cause of liver transplantation (1). .

Previously known as NAFLD (non-alcoholic fatty liver disease), the term **metabolic dysfunction-associated steatotic liver disease (MASLD)** has recently been proposed because it better describes the dysfunction associated with fatty liver, avoiding the stigma of alcohol and the term "fatty," which in English can also mean "fat" (3).

PREVALENCE

MASLD is defined as fat **infiltration in the liver of, at least, 5% of hepatocytes, measured by imaging or histology** (4).

MASLD overall prevalence is 37.8% and is higher in men vs women (39.7% vs 25.6%, respectively) (5). Additionally, it interacts synergistically with type 2 diabetes mellitus (T2DM), which it often coexists with. The prevalence of MASLD in patients with diabetes is estimated to reach 55.5% (6).

ASSOCIATED COMORBIDITIES

- Obesity: Excess body weight, particularly central obesity—fat around the abdomen—is strongly associated with MASLD, though there are thin patients with MASLD, especially among Asian races, who generally have a better prognosis. Obesity is associated with:
  - Metabolic syndrome: A set of conditions including abdominal obesity, hyperten- »

sion, hyperglycemia, and abnormal cholesterol or triglyceride levels. People with metabolic syndrome are at higher risk of MASLD.

- Diet: High consumption of refined carbohydrates, sugary foods and beverages, and saturated fats can contribute to MASLD.
- Sedentary lifestyle: Lack of physical activity is a risk factor for MASLD. Regular exercise can help prevent and manage the disease.

- Insulin resistance and T2DM
- Age: Although MASLD is more common with increasing age, it can appear at any age. There is an increase starting from age 45.
- Genetics: There seems to be a genetic predisposition.
- Other conditions: Polycystic ovary syndrome, sleep apnea, and hypothyroidism are associated with MASLD.
- Drugs such as corticosteroids, tamoxifen, and certain antiretrovirals *(Table 1)*.
- Microbiota: Changes in the composition of the gut microbiota also seem to be involved in the development of MASLD.
- Ethnicity: Particularly Hispanic and Asian populations.
- Environmental factors (7)

DIAGNOSIS

The diagnosis of MASLD is often raised when hepatic aminotransferases are elevated or more commonly, when abdominal imaging detects hepatic fat incidentally. Less frequently, MASLD is suspected when there are metabolic comorbidities, and it should be investigated in all patients with risk factors for its development.

The diagnosis of MASLD is characterized by hepatic steatosis detected by imaging or biopsy, plus, at least, 1 of 5 criteria:

1. BMI ≥ 25 kg/m2 (≥ 23 kg/m2 in Asians) or waist circumference > 94 cm in men, > 80 cm in women, or adjusted for ethnicity.
2. Fasting serum glucose ≥ 100 mg/dL (≥ 5.6 mmol/L) or glucose level at 2 hours after an oral glucose tolerance test ≥ 140 mg/dL (≥ 7.8 mmol/L) or HbA1c ≥ 5.7% or specific pharmacological treatment.
3. Blood pressure ≥ 130/85 mmHg or specific pharmacological treatment.
4. Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/L) or specific pharmacological treatment.
5. Plasma HDL cholesterol < 40 mg/dL (< 1.0 mmol/L) for men and < 50 mg/dL (< 1.3 mmol/L) for women or specific pharmacological treatment (8).

TABLE 1. Drugs with potential to cause MASLD or MASH

DRUG	MECHANISM	HISTOLOGICAL PATTERN
Amiodarone	Promotion of de novo lipogenesis (DNL), alteration of β-oxidation	Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis
5-FU	Accumulation of 5-FU catabolites reduces the liver ability to metabolize lipids	Hepatic steatosis
Irinotecan	Induces mitochondrial dysfunction, alters autophagy	Steatohepatitis
Tamoxifen	Estrogen receptor modulation, promotion of DNL, alteration of β-oxidation. May or may not be independent of concomitant metabolic risk factors	Steatosis and steatohepatitis
Methotrexate	Mitochondrial injury (inhibits mitochondrial electron transport chain), damage to Hering channels	Steatosis, steatohepatitis, cirrhosis
Corticosteroids	Exacerbation of metabolic comorbidities, alteration of β-oxidation, alteration of hepatic triglyceride secretion, lipid peroxidation	Steatosis

Tomada de (13).

» Although transaminase values—especially AST—may be mildly elevated, they can also be normal even in patients with cirrhosis.

Progression to fibrosis and the development of metabolic-associated steatohepatitis (MASH) marks the prognosis of the disease, as it can progress to cirrhosis and hepatocellular carcinoma, while MASLD patients are more associated with cardiovascular mortality.

MASH is the most severe form of MASLD and is histologically defined by the presence of lobular inflammation and hepatocyte ballooning, and it is associated with a higher risk of fibrosis progression (9). MASH has been detected in 63% of MASLD patients undergoing liver biopsy in a multicentric Asian cohort (10). Among MASLD patients without a liver biopsy indication, the prevalence of MASH is 7% (6). Although cardiovascular disease (CVD) is the leading cause of mortality in MASLD patients, those with more severe hepatic fibrosis have a higher risk of liver-related mortality, and the risk increases exponentially with the stage of fibrosis (11).

The diagnosis of MASLD allows for the presence of other associated conditions, such as viral hepatitis and MASLD or autoimmune hepatitis (12), in addition to being associated with extrahepatic cancers such as stomach, kidney, breast, gallbladder and bile duct, colon, and rectum cancers.

In differential diagnosis, it is important to consider **MetALD**, which is steatosis associated with alcohol consumption > 20 g/day in women or > 30 g/day in men.

Other causes of MASLD include metabolic liver diseases, such as lysosomal acid lipase deficiency, Wilson's disease, hypo- »

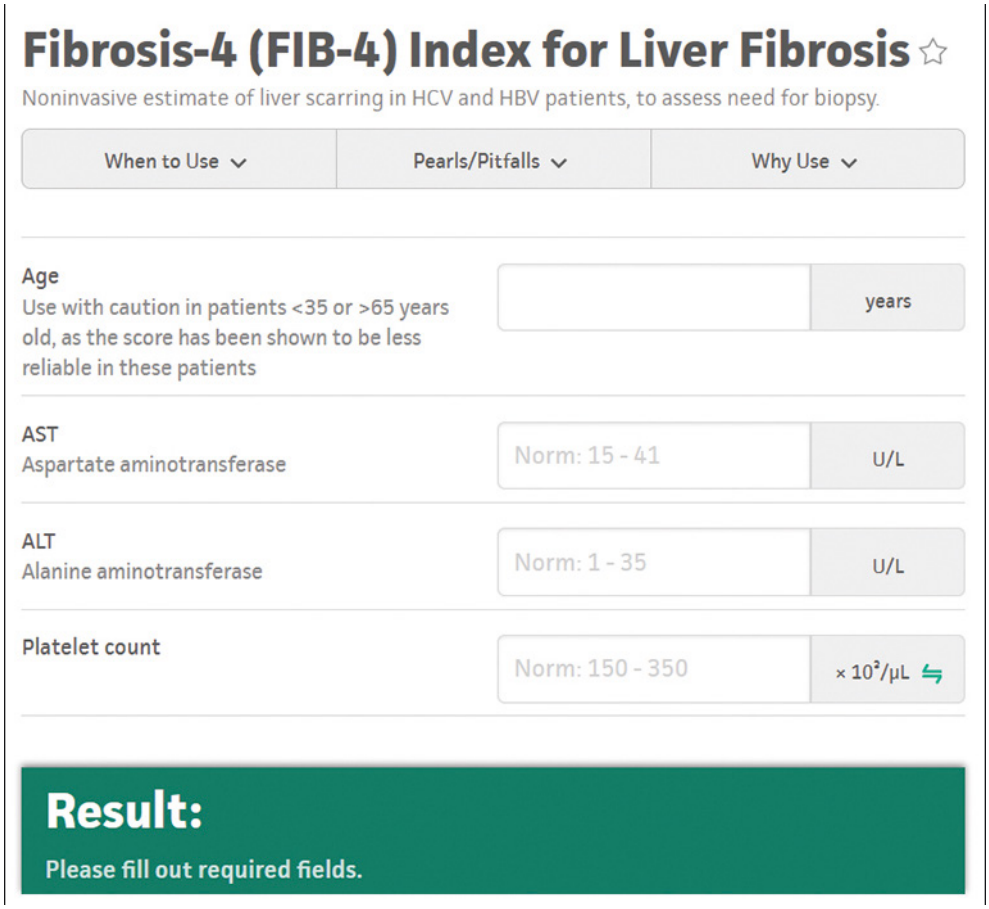

FIGURE 1. FIB-4 test to assess the likelihood of fibrosis in patients with steatosis (taken from MDCalc, available at: https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis

THE DIAGNOSIS OF MASLD IS OFTEN CONSIDERED WHEN AMINOTRANSFERASES ARE ELEVATED OR, MORE FREQUENTLY, WHEN ABDOMINAL IMAGING DETECTS HEPATIC FAT INCIDENTALLY

» betalipoproteinemia, inborn errors of metabolism, genotype 3 hepatitis C, malnutrition, celiac disease, HIV, and some environmental factors (12).

The most common form of diagnosis is incidental detection on an abdominal ultrasound requested for other reasons.

MASLD should be suspected in all patients with risk factors, obesity, diabetes, metabolic syndrome, hyperlipidemia, hypertension, etc.

Once suspected, a laboratory test with transaminases (AST and ALT), complete blood count, and lipid profile should be requested to perform simple calculations such as the **fatty liver index (FLI)**, which uses routine variables to calculate the probability of having MASLD.

The most common approach is to perform an **abdominal ultrasound** and compare hepatic echogenicity with that of the renal cortex, which should be the same, and in the case of steatosis, it is increased. Ultrasound cannot detect the early stages of steatosis, as it only detects if the proportion of affected hepatocytes is > 12%.

Once the diagnosis of MASLD has been established, it is crucial to rule out the presence of fibrosis. Guidelines recommend using the **FIB-4 index** (Figure 1), which is easy to calculate with routine consultation data. The result can fall into 3 different categories:

1. Patients with a result of **< 1.3:** The probability of steatosis is very low, and it can be re-evaluated annually if risk factors are present or every 3 years in thin patients without risk factors.

2. Patients with a result between **1.3 and 2.67:** the probability of fibrosis is moderate, and a test such as the FibroScan should be requested to confirm it.

3. Patients with a result **> 2.67** should be referred to a gastroenterology consultation.

In patients older 65 years, the cutoff point can be raised from > 1.3 up to > 2.

FibroScan results correlate well with the degrees of fibrosis found in pathological anatomy, and the result is expressed in KPa. »

MASLD IS DEFINED AS FAT INFILTRATION IN THE LIVER OF, AT LEAST, 5% OF HEPATOCYTES, MEASURED BY IMAGING MODALITY OR HISTOLOGY

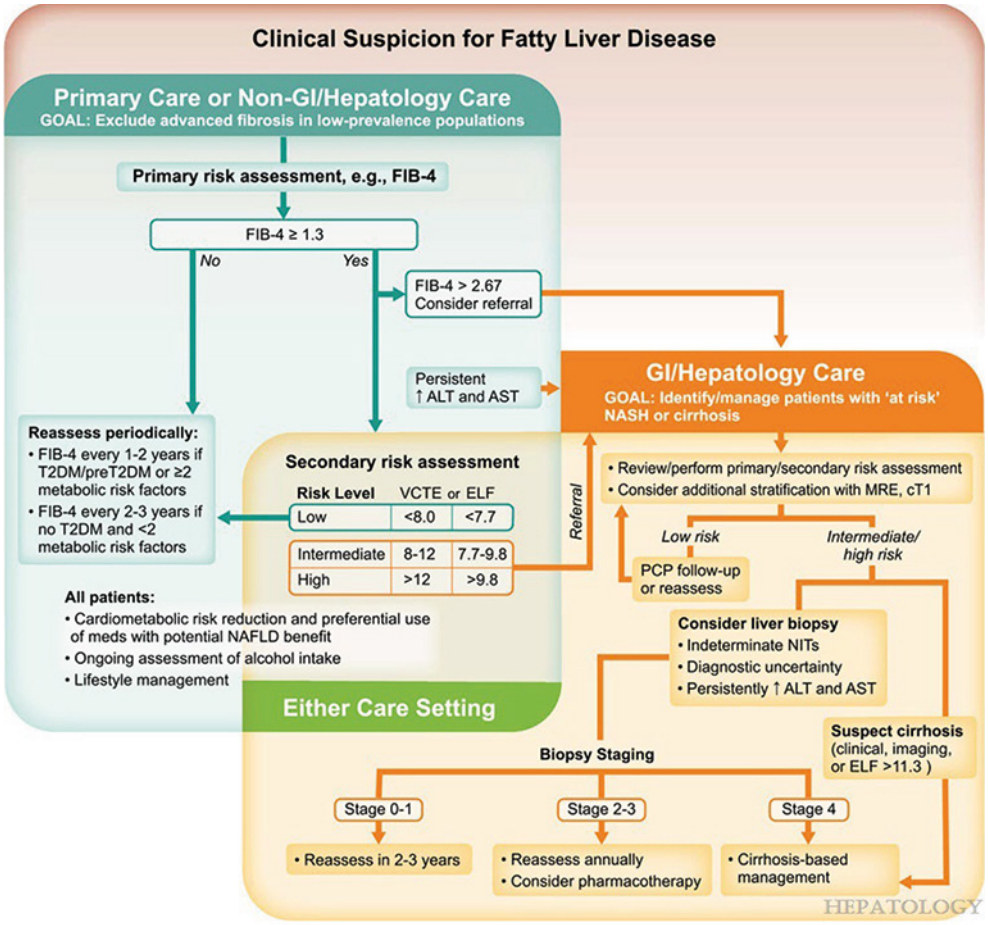

FIGURA 2. Manejo clinico y criterios de derivación a digestivo de los pacientes con sospecha de MASH según AASLD. Tomada de (13).

» **Criteria for referral to gastroenterology *(Figure 2)*:**

1. Patients with FIB-4 > 2.67, to assess whether to perform FibroScan or directly a biopsy.
2. Patients with FibroScan results > 8 KPa, corresponding to a fibrosis grade of F2.
3. Patients with FIB-4 > 1.3 and < 2.67 should undergo a FibroScan, and if it is < 8 KPa, it will be repeated in 1 year. If > 8 KPa, they should be referred to gastroenterology to assess biopsy (13).
4. Patients with persistent elevation of transaminases for more than 6 months.

TREATMENT

As with any metabolic disease, nutritional guidelines and exercise are fundamental parts of the treatment for MASLD patients.

- Even in patients who do not lose weight, exercise improves cardiovascular risk, as well as associated comorbidities and hepatic fat deposition.
- Modest weight loss of just 3% up to 5% improves MASLD, yet to improve MASH and fibrosis, > 10% weight loss is necessary. Maintaining weight loss is a challenge for both family members and professionals, requiring a multidisciplinary team.
- A hypercaloric diet—particularly rich in saturated fats—as well as excessive fructose consumption, increases the risk of MASLD regardless of calorie intake. The Mediterranean diet is recommended for treating this condition. On the other hand, consuming 3 cups of coffee a day may be beneficial.
- Bariatric surgery is an option for patients with BMI > 40, or > 35 with comorbidities, resolving MASH and improving hepatic fibrosis.
- Drug:
  - Vitamin E: Although 800 IU/day improve steatosis, there is no data on benefits for fibrosis. »

- Pioglitazone: The only drug that has been shown to decrease hepatic fibrosis and improve steatosis despite causing weight gain.
- Liraglutide: Although an ARGLP-1 used for diabetes treatment improves cardiovascular risk, promotes weight loss, and improves steatosis, it does do so on fibrosis.
- Semaglutide: An ARGLP-1 approved for diabetes and obesity treatment at doses from 0.25 up to 2.4 mg weekly. Although it improves steatosis and slows MASH no results on fibrosis have been described, although it seems to slow its progression.
- Tirzepatide: Not yet marketed in Spain, it is a dual agonist of ARGLP-1 and GIP approved for diabetes and obesity treatment. It results in significant weight loss, reducing steatosis in imaging modalities.
- SGLT2i: Approved for treating chronic kidney disease, heart failure, and type 2 diabetes mellitus, improves steatosis measured by imaging modalities. It causes modest weight loss.
- Other drugs such as metformin, ursodeoxycholic acid, statins, obeticolic acid, elafibranor, saroglitazar, etc., have not shown benefits.

ADVICE FOR CONSULTATION

- Suspect MASLD in patients with T2DM, hypertension, hyperlipidemia, obesity, cardiovascular risk factors, or mildly elevated transaminases.
- Transaminases can be normal even in the presence of cirrhosis.
- MASLD increases cardiovascular mortality, while MASH increases the risk of cirrhosis, hepatocellular carcinoma, and extrahepatic tumors.
- Diagnose by ultrasound or FLI.
- Rule out fibrosis with FIB-4.
- If FIB-4 > 1.3 and < 2.67, request a FibroScan. If < 1.3, repeat in 2 or 3 years or annually if risk factors are present.
- Refer to gastroenterology if FibroScan is > 8 KPa or FIB-4 > 2.67 or persistent hypertransaminasemia for more than 6 months.
- Although no drug has been authorized for MASH treatment, pioglitazone has shown to decrease hepatic fibrosis in MASH, making it the treatment of choice. D

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