Brazilian evidence-based guideline for screening, diagnosis, treatment, and follow-up of metabolic dysfunction-associated steatotic liver disease (MASLD) in adult individuals with overweight or obesity: A joint position statement from the Brazilian Society of Endocrinology and Metabolism (SBEM), Brazilian Society of Hepatology (SBH), and Brazilian Association for the Study of Obesity and Metabolic Syndrome (Abeso)

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ABSTRACT

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as Nonalcoholic fatty liver disease (NAFLD), is one of the most common hepatic diseases in individuals with overweight or obesity. In this context, a panel of experts from three medical societies was organized to develop an evidence-based guideline on the screening, diagnosis, treatment, and follow-up of MASLD. **Material and methods:** A MEDLINE search was performed to identify randomized clinical trials, meta-analyses, cohort studies, observational studies, and other relevant studies on NAFLD. In the absence of studies on a certain topic or when the quality of the study was not adequate, the opinion of experts was adopted. Classes of Recommendation and Levels of Evidence were determined using prespecified criteria. **Results:** Based on the literature review, 48 specific recommendations were elaborated, including 11 on screening and diagnosis, 9 on follow-up, 14 on nonpharmacologic treatment, and 14 on pharmacologic and surgical treatment. **Conclusions:** A literature search allowed the development of evidence-based guidelines on the screening, diagnosis, treatment, and follow-up of MASLD in individuals with overweight or obesity.

Keywords

Clinical guidelines; overweight; obesity; non-alcoholic fatty liver disease; metabolic dysfunction-associated steatotic liver disease

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of steatosis in more than 5% of the hepatocytes in the absence of excessive alcohol consumption (≥30 g daily for men and ≥ 20 g daily for women) or other chronic liver diseases (1,2). It is currently the most common cause of chronic liver disease worldwide, with prevalence ranging from 13.5% in Africa to 31.8% in the Middle East and showing a substantial increase over the last decade in South America (30%) (3,4). NAFLD covers a wide disease spectrum and may present as simple steatosis, nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (1,5).

The most important risk factors for the development of steatosis are those related to metabolic syndrome, *i.e.*, central obesity, insulin resistance, T2DM, and dyslipidemia. The prevalence of NAFLD ranges from 47.3 to 63.7% in individuals with T2DM and is up to 80% in those with obesity (6,7). Although less than 10% of the patients with NAFLD develop cirrhosis-related complications (*e.g.*, hepatic decompensation and hepatocellular carcinoma), the absolute numbers of patients with these complications are still substantial (8,9). Most patients have a good prognosis, but recent data from a prospective cohort show that more than 40% of the patients with simple steatosis at baseline may progress to NASH, contrasting with previous data that predicted a more benign behavior for this condition (10).

More recently, in 2020, an expert panel proposed a new nomenclature for NAFLD. Considering that the main pathogenic process leading to NAFLD is a systemic metabolic dysfunction, the name Metabolic dysfunction-associated fatty liver disease (MAFLD) was introduced (11). At European Association for the Study Liver (EASL) Congress 2023, the multinational liver societies leaders from *La Asociación Latinoamericana para el Estudio del Hígado* (ALEH), American Association for the Study of Liver Diseases (AASLD), and European Association for the Study of the Liver (EASL) announced metabolic disfunction-associated steatotic liver disease (MASLD) as the new nomenclature for NAFLD. As the course of the condition remains identical in nature, and nearly all patients with NAFLD meet the criteria outlined for MASLD, we have opted to employ the latter terminology within this guideline (12).

MATERIAL AND METHODS

The first step in the preparation of this document was to divide the authors into subcommittees to define the topics to be addressed. The members of each subcommittee were responsible for carrying out a detailed bibliographic survey including mainly randomized clinical trials and meta-analyses of randomized clinical trials and observational studies of good quality and low heterogeneity. The following terms (MeSH) were used: [Nonalcoholic Fatty Liver Disease (NAFLD)], [Nonalcoholic Steatohepatitis (NASH)], [Obesity/complications], and [Excess weight]. As with the Brazilian evidence-based guideline on the prevention of cardiovascular disease in Diabetes Mellitus (DM) (13), low-quality observational studies, meta-analyses with high heterogeneity, and cross-sectional studies were not included, although they may have had an impact on the indicated Level of Evidence. The opinion of the experts was considered in the absence of adequate evidence on the subject or when the existing evidence had low methodological quality.

The second step was the preparation of a preliminary manuscript by the Editorial Committee highlighting the recommendations prepared by the different subcommittees. The manuscript was then extensively discussed and reviewed by all authors. Once all recommendations were approved along with their respective Levels of Evidence, the manuscript was again reviewed by the Editorial Committee and then submitted for publication.

The adopted Classes of Recommendation and Levels of Evidence were based on the American Heart Association Guidelines (14) and are described in Table 1.

Theoretically, an ideal intervention for MASLD would have an effect on both histological findings and prevention of "hard" outcomes, defined as clinical complications related to hepatic causes and/or increased overall mortality. However, taking into account the heterogeneity in the clinical presentation of MASLD and the long and insidious evolution of this disease, to prove that a single treatment has effect on multiple liver outcomes and their complications is not a very tangible goal and has not been achieved until today since randomized controlled trials would require a large number of participants with significant and/or advanced fibrosis and long follow-up (15).

Table 1. Classes of recommendation and levels of evidence (adapted from 13)

Class (Strength) of Recommendation
Class I (Strong) Benefit >>> Risk • Is recommended • Is indicated/effective/beneficial • Should be performed
Class IIa (Moderate) Benefit >> Risk • Is reasonable • Can be useful • Should be considered
Class IIb (Weak) Benefit ≥ Risk • May be reasonable • May be considered
Class III (No Benefit) Benefit = Risk • Not recommended • Should not be performed
Level (Quality) of Evidence
Level A • High-quality evidence from more than one randomized clinical trial • Meta-analysis from high-quality randomized clinical trials • One or more randomized clinical trials corroborated by high-quality registry study
Level B • Moderate-quality evidence from one or more randomized clinical trial • Meta-analysis of moderate-quality randomized clinical trials • Moderate-quality evidence from one or more nonrandomized studies, observational studies, or registry studies • Meta-analysis of the above studies
Level C • Expert Opinion

In this context, the evaluation of intermediate outcomes (*i.e.*, based on histological criteria) has been used for the development and approval of medications for the treatment of NASH without cirrhosis. Such criteria include (a) resolution of steatohepatitis without worsening of fibrosis, (b) improvement of at least one fibrosis stage (NASH CRN Fibrosis Score) without worsening of steatohepatitis, (c) resolution of steatohepatitis with improvement of fibrosis, and (d) reduction in hepatic outcomes (progression to clinical or histologic cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related mortality) (16,17). The use of such outcomes takes into account the correlation (especially in the presence of stage F2-3 fibrosis) with a greater chance of progression to decompensating events (hemorrhagic varices, ascites, or encephalopathy), progression to cirrhosis, liver failure or transplantation, and increase in the risk of cancer and all-cause mortality (18).

Considering the available evidence for treatment of individuals with overweight/obesity and NAFLD/MASLD and the criteria used by regulatory agencies (17), the list of outcomes that will be used in the recommendations of this manuscript is described in Table 2.

Table 2. Outcomes related to the treatment of nonalcoholic fatty liver disease in individuals with overweight or obesity

A. Improvement in steatosis: reduction in hepatic fat content assessed by magnetic resonance imaging, improvement in the controlled evaluation parameter (CAP) assessed by VCTE, improvement in fat infiltration assessed by ultrasonography and/or computed tomography.
B. Improvement in steatohepatitis without worsening of fibrosis: evaluated by liver biopsy.
C. Improvement in steatohepatitis and fibrosis: evaluated by liver biopsy.
D. Reduction in hepatic outcomes (progression to clinical or histologic cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related mortality)

RESULTS

Screening and diagnosis

Recommendation 1 – Screening for MASLD should be considered in adult individuals with body mass index > 25 kg/m² (IIa, C)

Screening for MASLD should be considered in adult individuals (age ≥ 18 years old) with overweight or obesity, even in those without T2DM or any component of metabolic syndrome. Individuals with obesity who are "metabolically healthy" are also at risk of development and progression of NAFLD, with a risk of clinical events related to chronic liver disease (19,20).

A systematic review and meta-analysis of 22 cohort studies involving 24 million individuals evaluated the risk factors associated with the incidence of clinical outcomes related to chronic liver disease (development of cirrhosis, complications of cirrhosis, and death from chronic liver disease). The evaluation of obesity included 14 observational studies involving 19.3 million participants with a median follow-up of 13.8 years and a total of 49,541 events related to liver disease. Obesity (body mass index [BMI] equal to or higher than 30 kg/m²) was associated with a 20% increased risk of events related to liver disease (21).

In patients with risk factors for NAFLD, including individuals with overweight or obesity, screening for NAFLD may be an effective strategy to identify those at increased risk of advanced fibrosis and rationalize the referral to a tertiary care center of hepatology, resulting in reduced costs (22,23). Finally, considering

that individuals of Asian origin represent a significant proportion of the Brazilian population, a lower cut-off value for screening should be considered. In this population, and in accordance with recommendations from a World Health Organization expert panel (24), this panel suggests that screening for MASLD should be considered in adult individuals with BMI > 23 kg/m².

Recommendation 2 – In patients with overweigh/obesity, abdominal ultrasonography is recommended as a method for screening of hepatic steatosis (I, C)

In the general population, ultrasonography has been considered the initial method for MASLD screening because it is noninvasive, relatively inexpensive, and easily accessible. In a meta-analysis of 34 studies involving 2,815 patients with suspected or known liver disease (25), the sensitivity and specificity of pooled ultrasonography data in distinguishing moderate to severe steatosis from the absence of steatosis, considering liver biopsy as reference were 85% (80%-89%) and 93% (87%-97%), respectively. In clinical practice, ultrasonography detects the presence or absence of steatosis but does not quantify the degree of steatosis; it is limited to detecting steatosis when the fat content is greater than 12.5%, thus missing a relevant number of patients who have fat content between 5%-12.5% (26).

In individuals with obesity, especially those with a BMI equal to or higher than 35 kg/m², the diagnosis of liver fat infiltration by ultrasonography may be challenging due to the thickness of the subcutaneous fat, potentially resulting in an unreliable assessment. In patients with Class 2 obesity (BMI equal to or higher than 35 kg/m²), ultrasonography is able to detect steatosis but with sensitivity and specificity of 49.1% and 75%, respectively (27).

Recommendation 3a – In patients with overweight/obesity, magnetic resonance imaging with proton-density fat fraction (MRI-PDFF) may be considered in the screening of hepatic steatosis (IIb, B)

Recommendation 3b – In patients with overweight/obesity, magnetic resonance imaging with proton-density fat fraction (MRI-PDFF) is recommended for quantification of hepatic steatosis (I, B)

Magnetic resonance imaging (MRI) with proton-density fat fraction (PDFF) analysis has as an advantage greater accuracy in patients with obesity and greater sensitivity for detecting hepatic steatosis ≥ 5%. In a recent meta-analysis of six studies in patients with histologically proven NAFLD, the sensitivity and specificity for detection of steatosis ≥ 5% were 93% and 94%, respectively (28). However, the use of this imaging technique in practice is still limited by high cost and lower availability. Still, due to its greater accuracy for the detection and quantification of hepatic steatosis, this is the most used imaging method in clinical trials (29).

Recommendation 4 – In patients with overweight/obesity, measurement of the controlled attenuation parameter by liver elastography using FibroScan® can be considered as a screening and diagnostic method for hepatic steatosis (IIb, B)

Hepatic steatosis can be evaluated in patients with obesity using controlled attenuation parameter (CAP), which is coupled to the FibroScan® equipment. With the use of the XL probe, the failure rates are below 5% (30). In a recent meta-analysis including 930 patients with histological confirmation of NAFLD, the accuracy for the detection of hepatic steatosis measured by CAP (XL probe) was 0.82, with the best cutoff value identified as 294 and a > 0.90 sensitivity value of 263 dB/m. The accuracy for the quantification of hepatic steatosis was 0.75 (31).

Another recent meta-analysis evaluated the performance of CAP in patients diagnosed with NAFLD. In all, 61 studies were included, with a total of 10,537 individuals with NAFLD. The area under the receiver-operating characteristic curve (AUROC) of CAP was better for the diagnosis of steatosis ≥ S1 (0.92); among patients with a BMI equal to or higher than 30 kg/m², the performance was lower (AUROC = 0.88) but still satisfactory. The results of this meta-analysis showed that CAP is a useful, albeit less accurate, noninvasive tool for the diagnosis of hepatic steatosis in individuals with obesity (32).

The performance of CAP in patients with obesity was recently evaluated by Tavaglione and cols. (33). The study included 120 candidates for bariatric surgery with a mean BMI of 41 ± 4 kg/m² who underwent transient elastography with CAP (XL probe) and liver biopsy in the perioperative period. The accuracy for the identification of steatosis ≥ S1 assessed by AUROC was 0.91 (95% confidence interval [CI] 0.86-0.97).

The cutoff value for identification of steatosis ≥ S1 was 300 dB/m, demonstrating an excellent performance of CAP in diagnosing steatosis in patients with obesity who are candidates for bariatric surgery. In conclusion, CAP evaluated using the XL probe can be used to identify steatosis in individuals with obesity.

Recommendation 5 – In patients with overweight/obesity, measurement of liver enzymes alone is not recommended for screening of hepatic steatosis (III, B)

There is a great deal of discussion in most studies about the value of elevated transaminases as a biomarker of more advanced forms of NAFLD. Verma and cols. observed that the accuracy of alanine aminotransferase (ALT) assessed by AUROC in detecting NASH and advanced fibrosis was 0.62 and 0.46, respectively. In their study, ALT levels were not considered an ideal indicator for the diagnosis of NASH and advanced fibrosis (34). Moreover, recent evidence suggested that reference values, particularly upper limit, of ALT may need to be reviewed in specific populations (35). In the context of morbidly obese patients, lowering the transaminase cut-off has been proposed to improve the detection of cases with NASH while maintaining acceptable sensitivity (36). However, this proposal still needs to be validated.

Mofrad and cols. (37) observed that the prevalence of advanced fibrosis was similar in groups with and without ALT elevation (5 out of 15 versus 13 out of 36, respectively), concluding that the entire histological spectrum of NAFLD can be seen in individuals with normal ALT values. Furthermore, the histologic spectrum is not significantly different in these individuals compared with those with elevated ALT levels, and a normal ALT does not guarantee the absence of underlying steatohepatitis with advanced fibrosis. These results were confirmed in 2019 by Ulasoglu and cols. (38), who also suggested that ALT levels may be an indication of a more severe metabolic profile of individuals with NAFLD.

A meta-analysis evaluating the proportion of patients with NAFLD and steatohepatitis with normal levels of transaminases found that 25% of the patients with NAFLD and 19% of those with NASH had normal ALT values (39). The study, which evaluated ALT levels in patients with NAFLD, included 4,094 patients, including 1,023 with a diagnosis of steatohepatitis. The study concluded that the relevance of the ALT level in the clinical diagnosis of NAFLD and NASH remains to be confirmed.

Recommendation 6 – In patients with overweight/obesity and hepatic steatosis and/or increased liver enzymes, the exclusion of other causes of liver disease is recommended (I, C)

Other causes of liver disease should always be investigated in individuals with steatosis or increased levels of transaminases. The diseases to be investigated, along with their respective tests, are shown in Table 3.

Table 3. Liver diseases to be investigated in individuals with obesity and hepatic steatosis and/or increased levels of transaminases

Disease	Tests to be requested
Hepatitis A	Anti-HAV IgM
Hepatitis B	HbsAg
Hepatitis C	Anti-HCV
Hemochromatosis	Ferritin and transferrin saturation
Autoimmune hepatitis	Anti-smooth-muscle antibody, anti-KLM, ANF
Primary biliary cholangitis	Antimitochondrial antibody
Wilson's disease	Urinary copper, serum copper, and ceruloplasmin
Alpha 1-antitrypsin deficiency	Alpha 1-antitrypsin
Celiac disease	Antiendomysial and antitransglutaminase IgA antibodies
Use of alcohol and medication	

Abbreviations: anti-HAV IgM, hepatitis A IgM antibody; anti-HBs, hepatitis B surface antibody; anti-HCV, hepatitis C antibody; HbsAg, hepatitis B surface antigen; anti-KLM, anti-kidney-liver microsome antibody; ANF, antinuclear factor.

Recommendation 7. In patients with overweight/obesity and MASLD, screening for liver fibrosis using the Fibrosis-4 (FIB-4) Index for Liver Fibrosis or Vibration Controlled Transient Elastography (VCTE) with FibroScan® is recommended to rule out the presence of advanced fibrosis (I, A)

The prognosis of individuals with MASLD is related to the presence of fibrosis, especially advanced fibrosis. A recent systematic review has shown that advanced fibrosis is an independent risk factor for hepatic and extrahepatic events, as well as death from hepatic or overall causes; hence, the importance of detecting advanced fibrosis (40). Once the diagnosis of hepatic steatosis is established, hepatic fibrosis must be stratified to identify individuals at low risk for follow-up in primary care, with exclusive emphasis on lifestyle changes (41). A recent study by Avcu and cols. with

126 obese individuals without history of NAFLD also demonstrated that the evaluation of steatosis and fibrosis using FibroScan® are reliable tools for the early diagnosis of hepatic steatosis and fibrosis in obese individuals (42). A more detailed of FIB-4 and VCTE with FibroScan® can be found in Recommendations 8 and 9 below.

Link for FIB-4: https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

Recommendation 8 – In patients with overweight/obesity and MASLD in whom the presence of advanced fibrosis by the clinical score (FIB-4 ≥ 1.3) cannot be ruled out, another method to evaluate fibrosis should be considered (IIa, B)

A study conducted by Alqahtani and cols. evaluated serum markers in individuals with Class 3 obesity undergoing bariatric surgery, comparing the performance of the NAFLD, FIB-4, and AST to Platelet Ratio Index (APRI) scores. The authors showed that most patients with Class 3 obesity and advanced fibrosis had high NAFLD, FIB-4, and APRI scores, but a considerable number of patients in this group had low values in these scores (43). The accuracy of FIB-4 and APRI was significantly higher for the diagnosis of advanced fibrosis compared with the NAFLD score, although they all had AUROCs below 0.80. Drozl and cols. evaluated retrospectively a group of 368 individuals with Class 3 obesity and biopsy proven NAFLD and pointed out that the NAFLD score may overestimate fibrosis because it includes BMI among its variables (44).

Even with limitations in estimating fibrosis in individuals with obesity, a cutoff value of 1.3 should be adopted for FIB-4 to rule out advanced fibrosis. A study published by Kaya and cols. in 2020 demonstrated that the main utility of the FIB-4 in patients with NAFLD lied in the ability to exclude, not identify, advanced fibrosis (45). Same results were demonstrated also in individuals with morbid obesity (46), with results more accurate than the NAFLD Fibrosis Score for this population (47). In a meta-analysis of 37 studies (n = 5,735; BMI ≥ 30 kg/m^2) evaluating the diagnostic performance of Vibration Controlled Transient Elastography (VCTE), FIB-4, and liver biopsy (NAFLD Fibrosis Score) to estimate advanced fibrosis, the AUROC for each were 0.85, 0.76, and 0.73, respectively (48). If the FIB-4 value is below 1.3, the risk of advanced fibrosis is ruled out, with a negative predictive value of approximately 91% (49). If the FIB-4 is greater than 1.3, the patient should be evaluated with another method for assessment of fibrosis (48,49). Finally, FIB-4 is straightforward to calculate, making it an appropriate scoring system for primary care settings (50).

Recommendation 9 – In patients with overweight/obesity and MASLD, Vibration Controlled Transient Elastography (VCTE) should be considered when FIB-4 is unable to exclude the presence of advanced fibrosis (FIB ≥ 1.3) (IIa, B)

Among available physical methods, **VCTE** with FibroScan® is the most validated, with a meta-analysis showing that its accuracy for diagnosing advanced fibrosis in patients with NAFLD is 85% (51). Another meta-analysis of 17 studies using the M probe in 2,642 patients and 3 studies with the XL probe in 318 patients demonstrated good diagnostic accuracy for fibrosis (AUROC 0.87 with the M probe and 0.86 with the XL probe) and cirrhosis (AUC 0.92 with the M probe and 0.94 with the XL probe) (52). The XL probe was developed for individuals with BMI equal to or higher than 30 kg/m^2 and/or skin-capsule distance greater than 25 mm, reducing the failure rate to below 5% of the cases (30). A recent study suggests the use of the same cutoff values for M and XL probes in individuals without and with obesity, respectively (53). VCTE has a high negative predictive value (greater than 90% to rule out advanced fibrosis) but a modest positive predictive value in NAFLD when compared with viral hepatitis, resulting in a greater number of false positive results in NAFLD (30).

Contrasting results have been described on the impact of ALT levels, BMI, skin-capsule distance, and steatosis assessed by CAP on the accuracy of the validation of hepatic stiffness and risk of false positive results (30,54,55). There is no consensus in clinical practice regarding the cutoff values of **VCTE** in ruling out advanced fibrosis, although 8 kPa is the most validated cutoff value (48). Values of hepatic stiffness > 12-15 kPa measured by **VCTE** can be adopted to determine the presence of advanced fibrosis (48). It has also been demonstrated that the sequential use of **VCTE** followed by FIB-4 is an adequate strategy that allows ruling out the presence of advanced fibrosis with good accuracy (48), especially when both methods are concordant.

A study of two cohorts demonstrated that the presence and degree of obesity were determining factors for discordance in fibrosis staging on **VCTE** and magnetic resonance elastography (MRE). Higher rates of discordance were observed with BMI equal to or higher than 35 kg/m^2 (56). In a recent systematic review of three prospective studies involving 318 patients with histologically proven NAFLD, Hsu and cols. compared the accuracy of these two methods for fibrosis staging. Overall, MRE showed better accuracy than **VCTE**, with superior results for all stages of fibrosis, despite adjustment for factors including age, sex, BMI, time from histology to elastography, and type of probe used in **VCTE** (57).

Recommendation 10 – In patients with overweight/obesity and MASLD, Enhanced Liver Fibrosis test may be considered for screening of hepatic fibrosis (IIb, B)

A second-choice serological test that can be used with good accuracy, even in patients with obesity, is the patented Enhanced Liver Fibrosis (ELF) test. In a study of patients with obesity, ELF demonstrated good accuracy in detecting steatohepatitis and advanced fibrosis at a cutoff of 8.7 (58). However, as highlighted in another meta-analysis of 16 studies, levels above 9.86 have a better positive predictive value for suggesting significant fibrosis (59).

Recommendation 11 – In patients with overweight/obesity and MASLD, liver biopsy should be considered in those in whom noninvasive methods have failed to indicate a low probability of significant fibrosis (IIa, A)

As previously mentioned, MASLD is a clinical condition that ranges from isolated steatosis to steatohepatitis with or without fibrosis and cirrhosis. Identifying those patients at higher risk of disease progression is essential. Usually, individuals with isolated steatosis have a more favorable disease evolution, while the presence of fibrosis imposes a greater risk of progression to unfavorable clinical outcomes in the future (40,60).

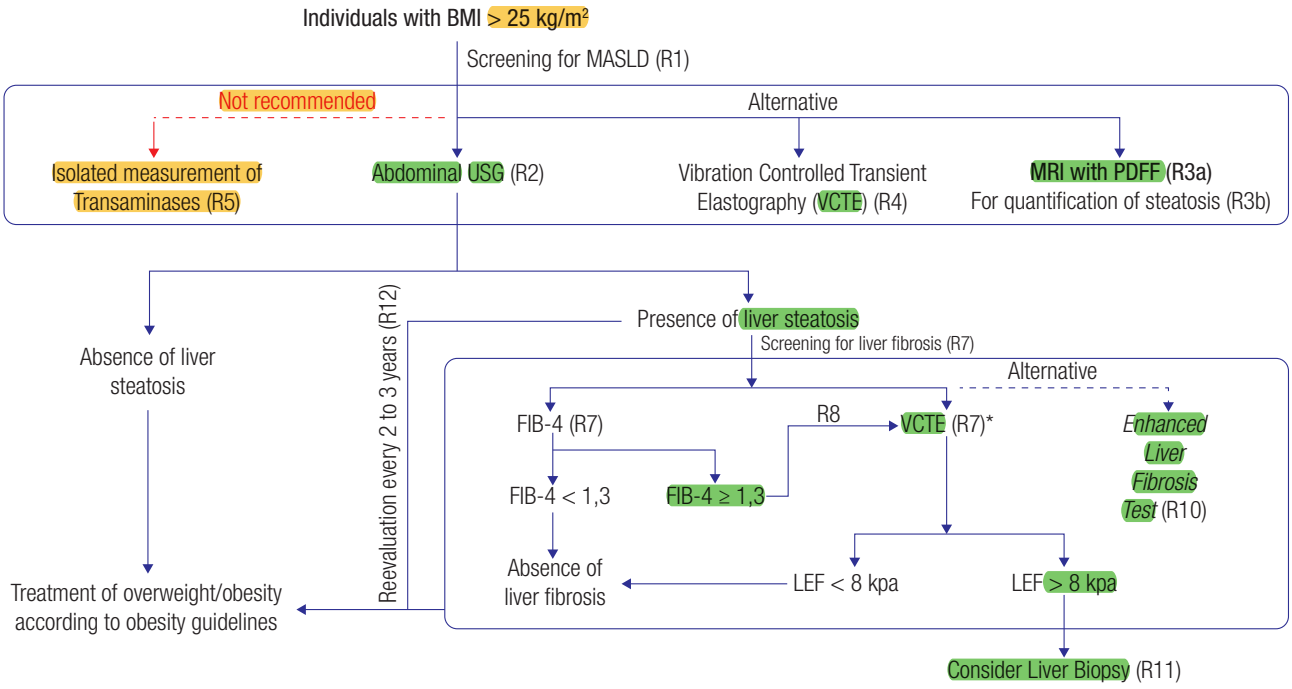
Noninvasive methods are commonly used to evaluate the presence of fibrosis. A recent meta-analysis has suggested that sequential combinations of noninvasive markers with a lower cutoff value to rule out advanced fibrosis and a higher cutoff value to rule out cirrhosis may reduce the need for liver biopsies (48). Another meta-analysis of 82 studies involving 14,609 patients evaluated the accuracy of different methods of elastography (VCTE, point shear wave elastography [pSWE], two-dimensional shear wave elastography [2DSWE], MRE, and MRI) for the diagnosis of fibrosis and steatohepatitis compared with liver biopsy, concluding that they all have acceptable diagnostic accuracy for the diagnosis of advanced fibrosis and cirrhosis, specifically, 0.85 for VCTE, 0.92 for MRE, 0.89 for pSWE, and 0.72 for 2DSWE. The AUROC for the diagnosis of cirrhosis was 0.89 for VCTE, 0.90 for MRE, 0.90 for pSWE, and 0.88 for 2DSWE (51). A low aspartate aminotransferase (AST)/ALT ratio at the time of baseline biopsy was associated with the development of progressive fibrosis in a meta-analysis. Liver biopsy may also be considered in cases where noninvasive methods fail to indicate a low probability of significant fibrosis (61), in cases with discordant non-invasive test results or discrepancies between clinical presentation and non-invasive test outcomes (62).

Follow-up

Recommendation 12 – In patients with overweight/obesity and MASLD, liver biopsy is recommended for the differential diagnosis of other liver diseases (I, C)

Recommendation 13 – Patients with hepatic steatosis without advanced fibrosis should be reevaluated by an hepatologist every 2-3 years with clinical/laboratory scores (I, C)

Individuals with MASLD must be monitored with noninvasive tests for liver fibrosis to identify those who progress to an advanced disease stage. Patients without advanced liver fibrosis or presenting only with mild fibrosis have a good prognosis and low progression to advanced disease and can be reassessed every 2-3 years. A meta-analysis of 11 cohort studies involving 411 patients with biopsy-proven NAFLD (150 with steatosis and 261 with NASH) with paired biopsies has shown that patients without steatohepatitis and without or with fibrosis progress more slowly, with an estimate of one stage of progression every 14 years (61). Thus, it is suggested that patients without any risk factor be followed every 3 years, and those with risk factors such as metabolic syndrome or T2DM be evaluated at a shorter interval of 2 years.



* R9 - When FIB-4 ≥ 1.3, magnetic resonance elastography can be used as an alternative to VCTE, particularly in individuals with BMI equal to or higher than 35 kg/m².

Abbreviations: BMI, body mass index; FIB-4, Fibrosis-4 Score; VCTE, Vibration Controlled Transient Elastography; MASLD, metabolic dysfunction-associated steatotic liver disease, MRI, magnetic resonance imaging; PDFF, proton-density fat fraction; R, recommendation.

Figure 1. Algorithm for clinical assessment of patients with overweight or obesity and clinical suspicion of metabolic dysfunction-associated steatotic liver disease.

Recommendation 14 – Patients with overweight/obesity and MASLD with fibrosis stages 2 and 3 should be reevaluated every 12 months for assessment of disease progression and response to treatment (I, C)

Recommendation 15 – Patients with overweight/obesity, MASLD, and liver cirrhosis should be reevaluated every 6 months for assessment of disease progression, response to treatment, and screening of hepatocellular carcinoma (I, C)

The presence of NASH on histology, when associated with risk factors (such as age > 45 years, obesity, T2DM, and metabolic syndrome), is associated with a greater risk of NAFLD progression (61). The presence of hepatic fibrosis, in turn, is the factor most directly related to disease progression, hepatic decompensation, and mortality or liver transplantation in patients with the disease (9,63). The risk of death in NAFLD is greater with increasing stage of fibrosis, and the liver-related risk is statistically greater after progression to stage 2 fibrosis or higher (significant fibrosis). Hepatic fibrosis also increases the risk of associated diseases and all-cause mortality in these patients (60). This panel suggests that patients with significant fibrosis (≥F2) should be evaluated yearly, and those with cirrhosis (F4) should be evaluated every 6 months for assessment of disease progression and screening for hepatocellular carcinoma.

Recommendation 16 – In patients with overweight/obesity and MASLD, serum biomarkers and VCTE may be considered for monitoring fibrosis progression (IIb, B)

Monitoring should include biometric tests as a parameter for evaluating obesity (at least BMI and waist circumference) and assessment of routine biochemical evaluation, liver enzyme, and comorbidities. Longitudinal evaluation with noninvasive biomarkers such as APRI, FIB-4, and NAFLD Fibrosis Score may predict fibrosis progression (64) or regression (65). In one study, these three biomarkers at baseline were associated with decompensation of cirrhosis and progression of bridging fibrosis to cirrhosis. Both APRI and ELF scores were able to detect progression over time, while longitudinal assessment of FIB-4 predicted liver-related clinical events in patients with cirrhosis

(66). Likewise, a multicenter retrospective analysis of consecutive patients with NAFLD (n = 1,039) with histological diagnosis of F3-F4 fibrosis and/or **VCTE** showing liver stiffness measurement > 10 kPa, followed up for at least 6 months, showed that changes in hepatic stiffness were associated with increased risk of liver-related events and mortality (67). Although subject to limitations, changes in liver disease staging can be detected by **VCTE** (68,69).

Despite such positive evidence, the lack of further validation and progress standardization prevents a clearer indication of these noninvasive methods in the follow-up of patients with NAFLD.

Recommendation 17 – In patients with overweight/obesity and MASLD, liver biopsy for the follow-up of MASLD may be considered every 5 years or sooner if disease progression is suspected (IIb, C)

Recommendation 18 – Patients with overweight/obesity and hepatic cirrhosis should be screened for hepatocellular carcinoma every 6 months using ultrasonography with or without measurement of serum alpha-fetoprotein (I, C)

Patients with cirrhosis due to NAFLD should be included in a program for screening of hepatocellular carcinoma using imaging tests (usually abdominal ultrasonography, due to its simplicity, effectiveness, and lower cost) every 6 months (70). Although 10%-30% of all hepatocellular carcinomas may develop in patients with noncirrhotic livers (71,72), routine surveillance for hepatocellular carcinoma in noncirrhotic patients has not been recommended, since the large number of NAFLD cases at risk of hepatocellular carcinoma would make systematic surveillance difficult to carry out and not cost-effective.

Among patients without liver cirrhosis, some studies indicate that patients with obesity and T2DM, PNPLA3 rs738409 C>G polymorphism, and persistently high FIB-4 are at greater risk of developing hepatocellular carcinoma (73,74). Ultrasonography is the method of choice for this screening, while CT and MRI should only be used in cases where ultrasonography cannot be adequately employed.

Recommendation 19 – In patients with overweight/obesity and MASLD, stratification of cardiovascular risk should be considered at the time of diagnosis (IIa, C)

Patients with MASLD have a higher prevalence and incidence of cardiovascular diseases (CVDs) compared with controls adequately matched for the same cardiovascular risk factors. A cohort study of 229 patients with NAFLD characterized by biopsy demonstrated that, at a mean follow-up of 26.4 years, the overall mortality was 29% higher than in sex- and age-matched controls, with a higher risk of death from CVD or hepatic causes observed in the subgroup with advanced fibrosis (F3-F4) (11).

Robust evidence correlates NAFLD with objectively assessed subclinical atherosclerosis in adults and adolescents and increased prevalence of clinically overt CVD (75). Although the increased CVD risk is driven by the association between NAFLD and components of the metabolic syndrome and T2DM, the remaining question is whether the hepatic disease in NAFLD confers any additional risk of fatal CVD. Several systematic reviews reaffirm the higher cardiometabolic risk in this population and emphasize that the presence of NAFLD confers a greater risk of cardiovascular events than the sum of the other risk factors individually (75-77). A large part of this divergence can be attributed to the methodology used for the diagnosis of NAFLD, which ranges from increased levels of transaminases and steatosis on ultrasonography to liver biopsy findings. In morphologic studies, the presence of significant fibrosis is generally associated with a higher rate of nonfatal events, even in studies that have found no association between NAFLD and cardiovascular mortality (76). Although previous studies (18) have shown an association of NAFLD with advanced fibrosis (F3-F4) and increased mortality from global and hepatic causes, a more recent meta-analysis (78) of 36 longitudinal studies found association between NAFLD and a moderately increased risk of fatal and nonfatal cardiovascular events (hazard ratio 1.45), reinforcing the observation that cardiovascular risk is considerably increased with fibrosis worsening (hazard ratio 2.50). The increased risk was independent of other variables, including age, sex, T2DM, adiposity, and other cardiovascular risk factors, reinforcing the strong association between NAFLD and CVD, especially in the presence of NASH or significant fibrosis (78,79).

Cardiovascular risk stratification in patients with overweight/obesity and NAFLD should be carried out in the first visit, with the application of global cardiovascular risk stratification scores (14,15). The

presence of NAFLD will be considered an aggravating factor for estimating the global cardiovascular risk and may change treatment goals; however, screening for subclinical atherosclerosis or further investigation for CVD will depend on the individualized assessment of each patient (77).

Recommendation 20 – In patients with overweight/obesity and MASLD, there is no indication for screening of extrahepatic malignancies, except in those already defined for the general population (III, C)

Patients with NAFLD and overweight or obesity have an increased incidence of extrahepatic malignant neoplasms (63,75), especially those of the gastrointestinal tract (colorectal, esophagus, stomach, and pancreas) and, outside the gastrointestinal tract, primarily the kidney (in men) and breast (in women). The frequent association of NAFLD and metabolic risk factors, especially obesity and T2DM, may be the reason for this increased incidence of malignancy, but evidence suggests that NAFLD may be an additional risk factor, particularly for colorectal cancer (80,81). Still, available data are insufficient to recommend screening with colonoscopy, which should be performed following recommendations for the general population.

Treatment – nonpharmacologic measures

Lifestyle changes aiming at weight loss and, subsequently, weight maintenance, are considered a primary strategy for MASLD management and are recommended for all patients with overweight or obesity. They are associated with improvements in hepatic inflammation, liver function tests, markers of insulin resistance, histological parameters, and quality of life (82). Even though considered as one of the pillars in the treatment of MASLD, studies have revealed that only a small percentage of patients maintain long-term lifestyle modifications and strategies are necessary to improve these numbers (83,84). In this sense, this therapeutic modality covers different goals according to the definition of what one wants to achieve with the therapy, as described below.

Recommendation 21 – In patients with overweight/obesity and MASLD, interventions to reduce and subsequently maintain body weight are recommended to improve hepatic steatosis, with a dose-response relationship between the magnitude of the weight loss and improvement in steatosis (I, A)

A recent meta-analysis of 43 clinical trials of weight loss intervention (n = 2,809) with lifestyle changes, pharmacotherapy, or bariatric surgery showed a 5% clinical improvement in steatosis with a minimum initial loss of 5 kg of body weight. For each 1 kg of weight lost, there was a 0.77% reduction in steatosis assessed by radiologic or histologic parameters, *i.e.*, for each loss of 6 kg, the degree of steatosis was reduced by an additional 5%. Notably, a dose-response relationship between weight loss and reduction in steatosis was observed with all treatment modalities (85).

Recommendation 22 – In patients with overweight/obesity and MASLD, a greater than 7% reduction in body weight should be considered to improve steatohepatitis without worsening fibrosis (IIa, A)

In a longitudinal study, 293 individuals with biopsy-proven NASH were followed up for 52 weeks. Lifestyle changes targeting weight loss resulted in NASH resolution in 25% of the cases. The NAFLD activity score (NAS), obtained through liver biopsy and histological analysis, improved in 47% of the cases, and liver fibrosis regressed in 19% of them. Weight losses between 7%-10% were associated with a higher proportion of participants with improved NAS (88%) and NAFLD components (steatosis, 76%; lobular inflammation, 88%; ballooning, 84%) (86). A 48-week randomized clinical trial involving 31 individuals with overweight/obesity and a diagnosis of NASH established by biopsy, evaluated intensive lifestyle changes similar to those adopted in the Diabetes Prevention Program study, consisting of a hypocaloric diet, physical activity, and behavioral interventions, aimed at a loss of 7%-10% of the weight. Weight loss was greater in the group submitted to intensive lifestyle changes compared with the group with structured educational recommendations (9.3 *versus* 0.2%, respectively) (87). A greater proportion of participants undergoing intensive lifestyle changes achieved NAS improvement when compared with the education group (72% *versus* 30%, respectively). The percentage of weight reduction correlated with improvement in histological pattern on liver biopsy.

Participants who lost ≥ 7% of weight had significant improvements in steatosis, lobular inflammation, ballooning, and NAS. At the end of the study, a greater proportion of participants in the intensive lifestyle changes group compared with the control group no longer met the histological criteria for NASH (67% *versus* 20%, respectively) (87).

The benefits of weight loss in improving NAFLD have also been demonstrated in individuals with T2DM. In a sub analysis including 96 participants of the Look AHEAD (Action for Health in Diabetes) trial, which aimed for weight loss ≥ 7% and included participants with obesity and T2DM across 16 centers in the United States, there was greater weight loss in the intensive lifestyle intervention group compared with the DM support and education control group after 1 year (-8.5 versus -0.05%, respectively) (88). The study demonstrated that intensive lifestyle changes were associated with greater improvement in steatosis estimated by proton magnetic resonance spectroscopy compared with supportive therapy and DM education (-50.8 *versus* -22.8%, respectively) (88).

In a meta-analysis by Koutoukidis and cols. (85), which included 43 clinical studies of intervention for weight loss (n = 2,809) with lifestyle changes, pharmacotherapy, or bariatric surgery, the magnitude of weight loss was associated with improvement in histological markers of inflammation, ballooning, and NAFLD resolution. Changes in histological parameters of fibrosis were inconsistent and imprecise, and there was no evidence that weight loss was associated with NAS improvement.

Recommendation 23 – In patients with overweight/obesity and MASLD, weight loss intervention can be considered as a strategy to delay the development and progression of NAFLD (IIb, B)

In a longitudinal study described above (74), most participants (43 of 46; 93%) who experienced worsening fibrosis lost < 5% of body weight. In a sub-analysis of the Look AHEAD study of participants without NAFLD in the initial evaluation, after 12 months of intervention, fewer participants in the intensive lifestyle changes group compared with the control group of support and education in DM developed NAFLD (3% versus 26%, respectively; $p < 0.05$), suggesting that significant weight loss in this population prevents the development of NAFLD (88). Although a significant number of patients often experience weight regain, evidence suggests that the positive effects of weight loss on liver health persist even after regaining weight (89).

Recommendation 24 – In patients with overweight/obesity and MASLD, the adoption of lifestyle modification measures, including aerobic and resistance physical exercise of moderate to high intensity at least three times a week, is recommended for the reduction of hepatic steatosis (I, A)

A 2017 meta-analysis of 20 randomized clinical trials involving 1,073 patients with NAFLD found that exercise, compared with no exercise, improved serum levels of ALT and AST and reduced intrahepatic fat – effects that were independent of weight changes (90). Regarding the type of exercise (aerobic or resistance), there was no difference in hepatic parameters. On the other hand, continuous training of moderate intensity and moderate to high volume was more beneficial compared with continuous training of moderate intensity and low to moderate volume or high-intensity interval training. Interventions combining exercise and diet showed a reduction in levels of transaminases and improvement in NAS.

Another more recent meta-analysis evaluated the effect of isolated physical exercise (without dietary intervention) on NAFLD to examine correlations between changes in hepatic fat and metabolic markers during exercise (91). The meta-analysis included 16 studies with 706 participants and found that exercise had a beneficial effect on liver fat. There was a significant relationship between changes in liver fat and changes in weight, AST and ALT, and cardiorespiratory fitness peak volume oxygen consumption (VO_2peak). Changes in weight and VO_2peak contributed independently to changes in liver fat. These results suggest that exercise without dietary intervention improves hepatic fat and that clinical markers can be useful proxies for quantifying changes in liver fat.

Recommendation 25 – Lifestyle changes have not been shown to improve long-term clinical outcomes (death and cirrhosis complications) in patients with MASLD (III, A)

A Cochrane meta-analysis and systematic review (92) published in 2021 showed no long-term benefit

of lifestyle changes on NAFLD hard outcomes (including improvement in life expectancy, health-related quality of life, and chronic liver disease and its complications). The final analysis included 28 studies involving 1,942 participants and a follow-up ranging from 2-24 months. The review concluded that future well-designed randomized clinical trials are needed to identify the best lifestyle modifications for individuals with NAFLD. Related to the liver, complications develop over the course of 8-28 years. Therefore, differences in clinical outcomes are unlikely to become apparent in trials with follow-up shorter than 5-10 years. Sample sizes also need to be much larger, especially if testing an intervention in subjects in the early degrees of NAFLD.

Recommendation 26 – In patients with overweight/obesity and MASLD, the Mediterranean diet should be considered for improvement of hepatic steatosis, regardless of weight loss (IIa, B)

The Mediterranean diet was prospectively tested with or without antioxidant supplementation in individuals with overweight and NAFLD. Fifty participants were randomly allocated into three groups for 6 months. A moderately hypocaloric Mediterranean diet (1,400-1,600 kcal) was prescribed to all participants in two groups, one of which also received antioxidant supplementation. The third group did not receive any guidance. Liver fat content was assessed using ultrasound and a liver fat index. At the end of the study, the Mediterranean diet determined a reduction in fat infiltration and liver stiffness in both groups, and the antioxidant supplementation did not add improvement (93).

Another study with a duration of 18 months randomized 278 individuals with abdominal obesity to a low-fat diet or the Mediterranean diet (lower percentage of carbohydrates, poultry and fish in place of red meat, and addition of walnuts and chestnuts). Despite inducing a modest weight reduction (-3 kg), the Mediterranean diet was more efficient in reducing liver fat (assessed by MRI) compared with the low-fat diet, even after adjustments for differences in total weight loss and weight loss and visceral fat. The impact of reducing liver fat was accompanied by improvement in gamma-glutamyltransferase (GGT), ALT, and glycated hemoglobin (HbA1c). Of note, even though the authors identified the diet in one of the groups as "low fat," the percentage of fat in the diet can be considered normal for dietary fat recommendations (94).

Recommendation 27 – In patients with overweight/obesity and MASLD, replacement of carbohydrates with proteins should be considered for reduction of hepatic steatosis (IIa, B)

Recommendation 28 – In patients with overweight/obesity and MASLD, replacement of saturated fat sources with unsaturated fats should be considered for improvement of hepatic steatosis (IIa, B)

Recommendation 29 – In patients with overweight/obesity and MASLD, replacement of fats with carbohydrates is not recommended for reduction of hepatic steatosis (III, B)

A meta-analysis of randomized controlled trials (n = 26) published in 2021 evaluated the effect of different macronutrients in isocaloric diets on liver fat content assessed by MRI, CT, or biopsy. The analysis of five studies demonstrated that replacing carbohydrates with proteins can be effective in reducing hepatic fat content (five comparisons; standardized mean difference [SMD] -0.33). Likewise, replacing saturated fats with unsaturated ones also seems to have the same effect (five comparisons; SMD -0.80). Finally, replacing fats with carbohydrates showed no effect in reducing hepatic steatosis (12 comparisons, SMD 0.01) (95).

Recommendation 30 – In patients with overweight/obesity, dietary fiber intake appears to be associated with a lower MASLD risk (IIb, B)

A study using data from the National Health and Nutrition Examination Survey analyzed fiber intake via a 24-hour dietary recall and used the United States Fatty Liver Index (USFLI) method to diagnose NAFLD in 6,613 participants. The study compared the highest and lowest quartiles of consumption of fiber-rich foods like cereals, fruits, and vegetables and found an inverse association between dietary fiber intake and NAFLD risk (96). No randomized studies have evaluated different proportions of dietary fiber and their impact on intrahepatic fat.

Recommendation 31 – In patients with overweight/obesity and MASLD, excessive consumption of fructose in the form of free sugar and sugar-sweetened beverages is not recommended (III, B)

The effect of fructose in 341 participants undergoing liver biopsy was assessed using a food frequency questionnaire. After controlling for age, sex, BMI, and caloric intake, daily consumption of sweetened beverages and fruit juices was associated with higher fibrosis stage. Among individuals ≥ 48 years, daily fructose consumption was associated with hepatic inflammation and hepatocyte ballooning (97).

A randomized study found increased intrahepatic fat and ectopic fat accumulation after a 6-month consumption of sucrose-sweetened soft drinks compared with isocaloric semiskim milk, aspartame-sweetened diet cola, and water (98).

One of the arms of the Framingham Offspring and Third Generation Cohorts study estimated the consumption of sweetened beverages using a food frequency questionnaire and evaluated liver fat content by CT in 2,634 participants and plasma ALT concentration in 5,908 participants. The participants were categorized as either nonconsumers or consumers of sugar-sweetened beverages or diet soda (three categories: 1 serving/month to < 1 serving/week, 1 serving per week to < 1 serving/day, and ³ 1 serving/day). After adjustment for age, sex, BMI, and other variables, the odds ratios for NAFLD were 1.16, 1.32, and 1.61 across the three categories ($p < 0.05$). Consumption of sugar-sweetened beverages was also associated with higher ALT levels, but no significant association was observed between ALT level and consumption of diet soda intake and measures of fatty liver disease (99).

A 2014 meta-analysis of controlled studies comparing isocaloric intake of fructose versus other carbohydrates found no independent effect of fructose on the development of NAFLD or liver markers. However, fructose at extreme doses leading to excess energy intake increased hepatic fat and other markers related to hepatic fat accumulation (100).

More recently, another randomized, double-blind study named FRUITLESS found a slight difference between fructose and glucose supplementation (101). In the study, individuals with overweight and hepatic steatosis were instructed to follow a low-fructose diet and were given sachets of glucose or fructose to add to their diet. The study found a significant but clinically very small difference of 0.7% in liver fat between groups.

Recommendation 32 – In individuals with overweight/obesity and MASLD, the consumption of ultra-processed foods is not recommended (III, B)

A study from an ongoing prospective cohort included 16,168 participants who underwent abdominal ultrasound and blood collection and completed a food frequency questionnaire at the time of recruitment and throughout the study. Screening was carried out from 2013 onwards, and those with a minimum follow-up of 1 year were included in the analysis. The study revealed that the consumption of ultra-processed foods was related to an increase of 13%-18% in the risk of NAFLD development in all multivariate analyses (102).

Recommendation 33 – In patients with overweight/obesity and MASLD, regular consumption of 1 to 3 cups of coffee/day can be considered for reduction of the risk of progression of hepatic fibrosis (IIb, B)

Regular consumption of coffee has been associated with a reduced risk of hepatic fibrosis and cirrhosis both in animal and human models (103). Interestingly, some published meta-analyses based on observational studies have shown results with a reduction in the incidence of steatosis, fibrosis, and cirrhosis and a decreased mortality from hepatic disease (104-107).

A recent meta-analysis compiling data from 11 good-quality studies (including four prospective cohort studies) demonstrated that individuals who consumed coffee regularly, compared with those who did not, had a 23% lower risk of NAFLD (108). Similarly, three of the included studies showed that the risk of fibrosis – estimated by liver biopsy or **VCTE** – was 32% lower among individuals who already had a diagnosis of NAFLD and consumed at least one cup of coffee daily. In addition to the low degree of heterogeneity, a dose-response effect was observed between coffee intake and fibrosis, with a reduction in risk among those who drank more than three cups daily.

Recommendation 34 – In patients with overweight/obesity and MASLD, especially in the presence of NASH with or without fibrosis, safe amounts of alcohol consumption have not been established (IIb, B)

The safe amounts of alcohol allowed for individuals who have overweight/obesity and MASLD are still controversial. Dunn and cols. (109) studied 331

adults who consumed alcohol in moderate amounts, excluding those who consumed > 20 g/ethanol/day, binge drinkers, and individuals with previous alcohol consumption. This group was compared with lifetime nondrinkers, and the odds of having a diagnosis of NASH were evaluated in both groups. Surprisingly, modest drinkers had a lower risk of NASH and a lower risk of hepatic fibrosis. However, this was a cross-sectional study and, therefore, did not assess long-term outcomes. Kwon and cols. (110) evaluated the impact of alcohol consumption in 77 adults who drank more than 40 g/day of ethanol. The average lifetime cumulative alcohol consumption was 24 grams per year. While increasing age was associated with severe hepatic disease, alcohol intake above 24 grams per year was associated with less severe disease. Individuals who continued to consume alcohol or were abstinent for ≤ 1 year had less severe disease. Despite the limitations of an observational study, the results suggest that some degree of regular alcohol intake during a lifetime compared with negligible intake appears to have a protective effect on the severity of hepatic histology among patients with NAFLD. In contrast, Ekstedt and cols. investigated in 2009 whether low alcohol intake in 71 patients with NAFLD with histological reevaluation and a mean follow-up of 13 years was associated with fibrosis progression (111). At follow-up, 17 patients (24% of the participants) met the criteria for significant fibrosis progression. The proportion of patients who reported heavy episodic drinking at least once a month was higher among those with substantial fibrosis progression. In addition, a trend toward higher weekly alcohol consumption was observed. Thus, moderate alcohol consumption in patients with biopsy proven NAFLD may be associated with fibrosis progression. Episodic excessive alcohol consumption should be avoided in these patients to prevent fibrosis progression.

Many recent studies have shown that alcohol intake within the safe limits of the current definition poses a significant risk for the progression of hepatic disease. In a study of 58,927 Korean individuals with NAFLD and low baseline fibrosis scores, as assessed by NAFLD Fibrosis Score and FIB-4, mild (1.0-9.9 g/d) or moderate (10.0-29.9 g/d or, in women, 10.0-19.9 g/d) alcohol intake relative to no alcohol consumption (0 g/d) was independently associated with worsening hepatic fibrosis over an average follow-up of 4.9 years (112). The study concluded that even moderate alcohol intake could be harmful in patients with NAFLD. Hart and cols. (113) evaluated two prospective cohorts in Scotland to investigate the additive effect of alcohol consumption and BMI on increased risk of liver disease. Patients were categorized according to alcohol consumption into no drinks, 1-14 drinks/week, and ≥ 15 drinks/week, and according to BMI into normal, overweight, and obese. The authors found that increased BMI and alcohol consumption were related to hepatic disease, with evidence of a supra-additive interaction between both since the relative risk of excess due to the interaction between BMI and alcohol consumption was observed.

Pharmacologic treatment

Metformin

Recommendation 35 – In patients with overweight/obesity and MASLD, treatment with metformin is not recommended for reducing steatosis, steatohepatitis, or fibrosis (III, B)

A systematic review and meta-analysis of nine studies involving 417 patients with NAFLD has shown that metformin improves liver enzymes (ALT, AST) but not liver steatosis or fibrosis. Even a sub-analysis including only individuals with NASH found no improvement in these outcomes (114). More recent evidence also demonstrates metformin effects on reducing liver enzymes but no effect on liver steatosis of fibrosis (115,116).

Orlistat

Recommendation 36. In patients with overweight/obesity and MASLD, treatment with orlistat for reduction of steatosis, steatohepatitis, or fibrosis is not recommended (III, B)

A meta-analysis of seven studies, of which only three were randomized clinical trials, evaluated the effect of orlistat in patients with overweight or obesity and NAFLD. In all, 330 patients with hepatic steatosis or NASH were evaluated. Despite improvement in laboratory parameters (transaminases), no improvement in steatosis, steatohepatitis, or fibrosis was found (117).

Glucagon-like peptide 1 (GLP-1) analogues

Recommendation 37 – In patients with overweight/obesity and MASLD, the use of GLP-1 analogues (liraglutide, semaglutide, or dulaglutide) or GLP-1

receptor agonists (exenatide) is recommended to reduce steatosis (I, A)

A systematic review of six randomized clinical trials of GLP-1 analogues (aGLP-1) or GLP-1 receptor agonists (GLP-1 RAs) included four studies with liraglutide and two with exenatide for the treatment of individuals with NAFLD and obesity with or without T2DM. The two medications, particularly liraglutide, promoted a dose-dependent reduction in liver enzymes and liver fat assessed by imaging methods (ultrasonography or MRI) (118).

Another meta-analysis evaluated the safety and impact of aGLP-1 and GLP-1 RAs in patients with NAFLD. Eight randomized clinical trials involving 396 patients using liraglutide or exenatide were analyzed. The results showed an important reduction in liver fat content, ALT level, GGT level, and metabolic parameters like reduction in weight and abdominal circumference (119).

A third meta-analysis evaluated the impact of aGLP-1 or GLP-1 RA (liraglutide, dulaglutide, exenatide, and semaglutide) in 11 randomized clinical trials involving 936 patients with NAFLD. As in the other two meta-analyses described above, the diagnosis of NAFLD was established through biopsy or imaging techniques. As a result, aGLP-1 and GLP-1 RA were associated with a reduction in the percentage of liver fat content measured using MRI techniques (-3.92%) (120).

Recent evidence points out that new GLP-1/GIP receptor agonists (*e.g.*, tirzepatide) might also be effective treatments for NAFLD. However, further studies are necessary to confirm initial findings (121).

Recommendation 38 – In patients with overweight/obesity and MASLD with proven steatohepatitis with or without fibrosis, the use of liraglutide and semaglutide is recommended for improvement of steatohepatitis without worsening of fibrosis (I, A)

A meta-analysis by Manitoban and cols., including studies with other medications (liraglutide, dulaglutide, exenatide, and semaglutide), showed a reduction in hepatic fat, improvement in liver enzymes, and greater histological resolution of inflammation without worsening of fibrosis in patients treated with liraglutide or semaglutide. Of note, most participants were overweight or obese, and only 30% had no diagnosis of T2DM (120).

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Recommendation 39 – In patients with overweight/obesity, T2DM, and MASLD, treatment with SGLT2 inhibitors should be considered for reduction of steatosis (IIa, B)

A systematic review evaluating the impact of SGLT2 inhibitors (iSGLT2) on liver outcomes found a significant reduction in liver fat content associated with the use of this class of medications (122). More recently, a meta-analysis evaluated data from 12 randomized clinical trials involving 850 patients using iSGLT2 (dapagliflozin, empagliflozin, ipragliflozin, and canagliflozin) in the treatment of NAFLD in patients with overweight or obesity over a median period of 24 weeks. The use of iSGLT2 was associated with a reduction in ALT and GGT levels, along with a reduction in hepatic fat content assessed by MRI (118). Similar results were found in another meta-analysis that included only individuals with T2DM (123).

Pioglitazone

Recommendation 40 – In patients with overweight/obesity and MASLD with proven steatohepatitis with or without fibrosis, treatment with pioglitazone is recommended for the improvement of steatosis, steatohepatitis, and fibrosis (I, A)

A meta-analysis of eight studies using thiazolidinediones in individuals with and without T2DM confirmed that these agents reduce advanced fibrosis and may lead to NAFLD resolution. The significance of this effect was restricted to pioglitazone, and the results were similar even after excluding randomized controlled trials involving patients with T2DM (124).

A hierarchical networked meta-analysis evaluated different treatments for steatohepatitis, including 48 randomized clinical trials involving 2,356 adults. The primary outcome was NAS reduction with the use of various medications in addition to bariatric surgery. The treatments with the best reduction in NAS per semester were first pioglitazone and second Roux-en-Y gastric bypass (RYGB) surgery. Pioglitazone was also the best treatment for steatosis and reduction of lobular inflammation (125). In most studies with pioglitazone, BMI at baseline ranged from 31-34 kg/m^2, *i.e.*, the evaluation was performed in individuals with obesity. In the PIVENS study, the initial BMI was approximately 35 kg/m^2, the abdominal circumference ranged from

107-109 cm between the groups, and the average fat percentage was 40% (126).

Vitamin E

Recommendation 41 – In individuals with overweight/obesity and MASLD with proven steatohepatitis with or without fibrosis and without a diagnosis of Diabetes Mellitus, treatment with vitamin E may be considered for improvement of steatohepatitis without worsening of fibrosis (IIb, B)

Some randomized placebo-controlled therapeutic trials have shown NASH improvement in patients without cirrhosis. Among these, the PIVENS study evaluated the efficacy of vitamin E (800 IU/day) in patients with Class 2 obesity (BMI 35-39.9 kg/m^2) without DM and with biopsy-proven NASH. After 2 years of follow-up, there was a reduction in NAS, *i.e.*, improvement in steatosis, inflammation, and ballooning without fibrosis worsening (126).

In another study, Vilar-Gomez and cols. demonstrated that vitamin E improves liver histology in adults with NASH and advanced fibrosis. Their retrospective analysis evaluated 236 patients with Class 2 obesity and NASH with advanced fibrosis, among which 180 were exposed to 800 IU/day of vitamin E or placebo for a minimum period of 2 years (the median follow-up was 5.62 years). In both groups, the analyses were adjusted for the degree of fibrosis, age, sex, BMI, comorbidities and their treatments, LDL cholesterol, and liver biochemistry. The results showed that the use of vitamin E was associated with a significant reduction in overall mortality, hepatic decompensation, and survival without liver transplantation in patients with or without DM with bridging fibrosis and cirrhosis due to NASH (127). Still, the recommendation of vitamin E in this population requires more analyses from randomized clinical trials enrolling individuals with overweight/obesity, NASH, and advanced fibrosis.

Surgical treatment

Recommendation 42 – Bariatric surgery should be considered for reduction of steatosis, steatohepatitis, and fibrosis in individuals with Class 2 or 3 obesity (IIa, B)

A systematic review and meta-analysis evaluated the effects of bariatric surgery on NAFLD in patients with obesity. Data from 32 cohort studies including 3,093 biopsy samples were analyzed. Bariatric surgery was associated with resolution of biopsy-confirmed steatosis in 66% of the patients, inflammation in 50%, ballooning in 76%, and fibrosis in 40%. There was a significant reduction in the mean NAS after surgery (128).

A prospective study followed up 180 patients with obesity and biopsy-proven NASH who were candidates for surgical treatment of obesity. These individuals underwent bariatric surgery at a single center in France and were followed up for 5 years. Liver biopsy was repeated at 1 year in 125 of 169 patients (76%) and 5 years in 64 of 94 patients (68%). The primary endpoint was NASH resolution without worsening fibrosis at 5 years. Secondary endpoints were improvement in fibrosis (≥1 stage reduction) at 5 years and regression of fibrosis and NASH at 1 and 5 years. At 5 years after bariatric surgery, NASH resolved without worsening fibrosis in samples from 84% of the patients, and fibrosis decreased compared with baseline in 70.2% of them. Fibrosis disappeared in samples from 56% of all patients and from samples from 45.5% of the patients with fibrosis in the baseline biopsy. Persistence of NASH and no decrease in fibrosis were associated with less weight loss (BMI reductions of 6.3 ± 4.1 kg/m^2 in patients with persistent NASH and 13.4 ± 7.4 kg/m^2 in those with NASH resolution). At 1 year after bariatric surgery, NASH resolution was observed in biopsies from 84% of the patients, with no significant recurrence between 1 and 5 years. Fibrosis began to decrease at 1 year after surgery and continued to decrease up to 5 years. However, 20% of the patients did not respond to surgery and had persistent NASH at 5 years. Furthermore, reversal was observed in patients with advanced F3 fibrosis but not in those with cirrhosis (129).

Recommendation 43 – Bariatric surgery appears to be effective in reducing hepatic outcomes in the long term (IIb, B)

A retrospective cohort study – SPLENDOR (Surgical Procedures and Long-term Effectiveness in NASH Disease and Obesity Risk) – investigated the relationship between bariatric surgery and major adverse hepatic events in patients with obesity and NASH with fibrosis and without cirrhosis. The study included 1,158 patients, of whom 650 had undergone bariatric surgery (537 underwent RYGB and 113 vertical sleeve gastrectomy) and 508 were nonsurgical controls (identified among 25,828 patients with data

on liver biopsy). The mean follow-up of the entire cohort, including that of patients in the nonsurgical control group, was 7 years. The group of patients who were operated on had a significantly lower risk of major adverse hepatic outcomes (progression to clinical or histologic cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related mortality). The cumulative incidence of major adverse hepatic outcomes over 10 years was 2.3% (95% confidence interval [CI] 0-4.6%) in the bariatric surgery group and 9.6% (95% CI 6.1-12.9%) in the control group (130).

Recommendation 44 – It is recommended for every candidate of bariatric surgery to undergo screening for MASLD, especially cirrhosis with portal hypertension, before undergoing the surgical procedure (I, C)

Patients with cirrhosis are at increased risk of complications when undergoing bariatric surgery. A systematic review and meta-analysis of 18 studies evaluated the outcomes of bariatric surgery in 471 patients with obesity and cirrhosis (131). The endpoints were general complications, intraoperative complications, liver-related complications, 90-day all-cause mortality, and liver-related mortality. General complications among patients with cirrhosis occurred in 22.14% of the patients. Among three comparative studies, there was a significant increase in the occurrence of general complications and complications related to the liver in patients with cirrhosis compared with those without cirrhosis, but no significant difference in intraoperative complications or 90-day all-cause mortality. Liver-related mortality was low but significantly higher than in patients without cirrhosis. Postoperative complications were significantly lower in patients undergoing sleeve gastrectomy compared with RYGB.

In a recent US population-based cohort, among 1,679,828 patients undergoing bariatric surgery, 9,802 patients had cirrhosis. Mortality was 1.81% in patients with cirrhosis and 0.17% in those without cirrhosis. However, the authors reported a change in the type of surgery during the study period, switching from mixed procedures (RYGB and biliopancreatic diversion) to restrictive procedures (sleeve gastrectomy and adjustable gastric banding) resulting in fewer in-hospital complications and decreased mortality (132).

Recommendation 45 – Bariatric surgery using the RYGB technique may be considered for improvement in steatohepatitis and liver fibrosis in patients with Class 2 and 3 obesity without cirrhosis (IIb, B)

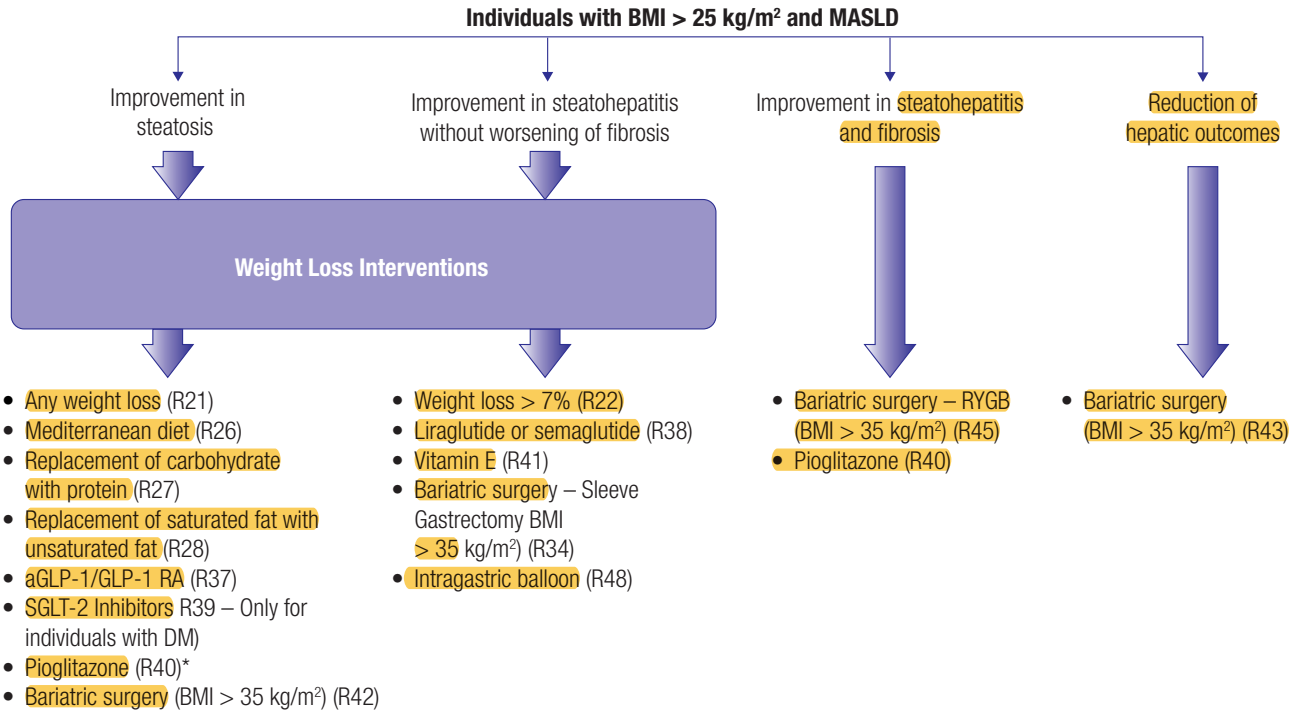
Recommendation 46 – Bariatric surgery using the sleeve gastrectomy technique may be considered for the improvement of steatohepatitis without fibrosis progression in patients with Class 2 and 3 obesity without cirrhosis (IIb, B)

A systematic review and meta-analysis compared the impact of RYGB and sleeve gastrectomy on NAFLD. Patients undergoing RYGB had a significant reduction in steatohepatitis and fibrosis, while those undergoing sleeve gastrectomy had a significant reduction in steatohepatitis but not fibrosis. There was a significant improvement in NAS after both procedures. Only seven cohort studies compared biopsy data between different surgical techniques (133).

Recommendation 47 – Hepatic monitoring with laboratory and imaging tests is recommended in the postoperative period of bariatric surgery due to the possibility of worsening of MASLD in some cases (I, C)

A systematic review and meta-analysis evaluated the effects of bariatric surgery on NAFLD in patients with obesity. Histologic worsening of NAFLD-related outcomes after bariatric surgery was reported in a limited number of studies. Nineteen studies reported histologic worsening after bariatric surgery and new or worsening NAFLD features such as fibrosis (12 studies), steatosis (two studies), and inflammation (four studies). The development or worsening of NAFLD occurred in 12% of the patients (128).

The type of surgery must be considered when the risks and benefits of bariatric surgery are considered in patients with cirrhosis. A systematic review of 122 patients with compensated cirrhosis (96.5% with Child-Pugh A and 3.4% with Child-Pugh B) undergoing bariatric surgery showed that mortality related to simple steatosis was only observed in those undergoing biliopancreatic surgery and RYGB (20% and 3.9%, respectively). No mortality was observed with sleeve gastrectomy and adjustable gastric banding. In total, nine patients (7.3%) decompensated after surgery, but all episodes of decompensation in patients with bariatric surgery were self-limited, and none resulted in mortality. Long-term data on the



* Pioglitazone should not be used for the treatment of isolated hepatic steatosis and should be used only for the treatment of steatohepatitis with or without fibrosis.

Abbreviations: aGLP-1, glucagon-like peptide 1 (GLP-1) analogues; BMI, body mass index; DM, diabetes mellitus; GLP-1 RA, GLP-1 receptor agonist; MASLD, metabolic dysfunction-associated steatotic liver disease; R, recommendation; RYGB, Roux-en-Y gastric bypass surgery; SGLT-2, sodium-glucose cotransporter-2.

Figure 2. Clinical management of patients with overweight or obesity and metabolic dysfunction-associated steatotic liver disease.

outcome for these patients are not available, and the extent to which cirrhosis may regress in this situation is unknown (134).

A long-term (8-10 years) follow-up of a small cohort of 10 patients with compensated hepatic cirrhosis who underwent sleeve gastrectomy showed sustained weight loss and stable liver function after surgery, although one patient developed hepatic encephalopathy 3 years after the procedure. None of the other patients presented disease progression or hepatic dysfunction during a 10-year follow-up (135).

Recommendation 48 – In patients with overweight/obesity, treatment with intragastric balloon for 06 months may be considered for the improvement of steatohepatitis without worsening of fibrosis (IIb, B)

Two studies have evaluated the impact of intragastric balloon (IGB) on NAFLD. A small, randomized study evaluated the impact of 6 months treatment with intragastric balloon (IGB) in a sample of 18 individuals with histologic evidence of NASH. Patients randomized to IGB presented a significantly higher BMI reduction in comparison to the sham-treated group. Moreover, the median nonalcoholic fatty liver disease activity scores at the end of treatment were significantly lower in the IGB-treated compared with the sham-treated groups (136). The second study was an open label, prospective study. Twenty-one patients with early hepatic fibrosis and average body mass index of 44 kg/m² underwent MRE and endoscopic ultrasound with core liver biopsy collection at time IGB placement and removal. Nonalcoholic fatty liver disease activity score (NAS) improved in 18 of 20 patients (90%) and histologic fibrosis improved in 3 of 20 subjects, remained unchanged in 12 of 20 subjects and worsened in 5 of 20 subjects (137).

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