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Management of patients with type 2 diabetes and MASLD: An overview and joint statement

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ABSTRACT

Type 2 diabetes (T2D) and metabolic dysfunction-associated steatotic liver disease (MASLD) are two highly prevalent diseases with rapidly growing incidences worldwide. They are frequently associated due to their shared pathophysiology and their bidirectional influence. MASLD-related liver fibrosis is a major driver of hepatic complications and is associated with increased risk of extrahepatic complications, such as cardiovascular and renal diseases in patients with T2D. In this setting, systematic screening for advanced fibrosis related to MASLD is now unanimously recommended for patients with T2D, due to its high prevalence and specific therapeutic management. The French Association for the Study of the Liver (AFEF) and the Francophone Diabetes Society (SFD) convened a group of experts to summarize the current knowledge on MASLD screening and therapeutic management in patients with T2D and thus provide a roadmap to healthcare professionals, especially diabetologists or primary care physicians. Our focus will be on the particularities of dietary and behavioral management, pharmacological treatment of T2D, and bariatric procedures in cases of MASLD. Our goal is to provide clinical guidance for adapting drug therapy in the presence of significant fibrosis in order to slow the progression of liver disease and reduce the risk of associated clinical events.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the first cause of chronic liver disease in the world and is emerging as a leading cause of cirrhosis and hepatocellular carcinoma (HCC) [1]. MASLD and type 2 diabetes (T2D) share pathogenic mechanisms, such as insulin resistance recognized as key driver of MASLD pathophysiology [2]. Hence, MASLD directly parallels the pandemic of obesity and T2D in the general population [2].

Given the strong link between T2D and MASLD, the French Association for the Study of the Liver (AFEF) and the Francophone Diabetes Society (SFD) convened a group of experts to promote research, education, and patient care in the field of MASLD and T2D. The aims of this expert panel were to address: *i*) MASLD screening in patients with T2D, and *ii*) T2D management in the specific context of MASLD. The panel identified key relevant topics requiring specific attention in patients with T2D in relation to the presence of MASLD. Following, two−four experts were assigned to each topic to provide a comprehensive overview of the current guidelines and best practices, serving as a practical resource for healthcare professionals, especially general practitioners and diabetologists. All experts met on three occasions to discuss and approve the different statements of this position paper. This manuscript presents an in-depth analysis of these topics, highlighting key points from the existing literature and offering a road map for healthcare professionals. The final manuscript was approved by all experts.

2. Definitions, natural history, and epidemiology of MASLD

- MASLD diagnosis requires the presence of liver steatosis with one or more cardiometabolic risk factor(s), and alcohol consumption below 20 g/day in women and 30 g/day in men.
- MASLD affects approximately one-third of adults worldwide and is twice more prevalent in patients with T2D reaching two-thirds of these patients.
- MASLD and T2D have a bidirectional influence, with T2D worsening MASLD progression, and MASLD increasing the risk of developing T2D and cardiovascular complications.
- Liver fibrosis, with the risk of developing cirrhosis and its complications, drives liver-related-mortality and is associated with increased risk of extra-hepatic mortality, underscoring the need for multidisciplinary management.

Abbreviations: AF, advanced fibrosis; BMI, body mass index; BS, bariatric surgery; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; DSE, diabetes support and education; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; GLP1-RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event; LSM, liver stiffness measurement; MACE, major adverse cardiovascular events; MARE, major adverse renal events; MALO, major adverse liver outcomes; MASH, metabolic dysfunction-associated liver steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol associated liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-derived proton-density fat fraction; MRS, magnetic resonance spectroscopy; MS, metabolic surgery; NIT, non-invasive test; PA, physical activity; PRO-C3, type III collagen propeptide; RCT, randomized controlled trial; RR, relative risk; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SLD, steatotic liver disease; SWE, shear wave elastography; TIPS, transjugular intrahepatic portosystemic shunt; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

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MASLD is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factor(s) and without excessive alcohol consumption or other concomitant cause of chronic liver disease [3]. In case of moderately increased alcohol consumption between 20–50 g/day in women and 30–60 g/day in men, MASLD is reclassified as MetALD (metabolic and alcohol-associated liver disease) [4].

In 20–25 % of patients with MASLD, steatosis is associated with lobular inflammation and hepatocyte damage (ballooning), defining metabolic dysfunction-associated steato-hepatitis (MASH) [4,5]. The transition of steatosis to steatohepatitis (MASH) is driven by hepatic alteration (lipid overload, lipotoxicity, endoplasmic reticulum and/or oxidative stress) and extra-hepatic signals derived from gut, adipose tissue, skeletal muscle and bone marrow [6]. Liver inflammation promotes hepatic stellate cells activation, leading to fibrogenesis. Ultimately, the disease evolves to cirrhosis and its complications, including HCC. Hepatocarcinogenesis in MASLD may differ from other liver diseases [7], with notably the occurrence of a large proportion (up to 40 %) of HCCs in non-cirrhotic patients [7].

Liver fibrosis is the main prognostic factor in MASLD, both associated with liver-specific and overall mortality [3]. The risk of liver-related events (LREs) increases significantly from fibrosis stage F2, with a relative risk (RR) of 2.7 [8]. This risk exponentially rises in patients with stage of fibrosis ≥ F3 (RR: 5.2) and F4 (cirrhosis, RR: 12.8). In a large U. S. cohort of 1773 patients with biopsy-proven MASLD, 92 % of LREs occurred in those with liver advanced fibrosis (AF) (F3-F4) at baseline [9]. The different categories of SLD are shown in Fig. 1 [4].

From 20 % in 2000–2005, the worldwide prevalence of MASLD is now estimated at 38 % in 2016–2019, affecting all continents [10]. Projections estimate that LREs, HCC and liver-related deaths due to MASLD will more than double between 2016 and 2030 [1]. MASLD was the fastest growing etiology of incident liver cancer (+39 %) and liver cancer deaths (+38 %) worldwide between 2010 and 2019 [11]. As a result of the disease burden, MASLD is the fastest growing indication and now the second leading cause of liver transplantation in the United States of America and in Europe [12–14].

The prevalence of MASLD among children and adolescents is also increasing, reaching 7.4 % globally, but with important geographic variations ranging from 1.7 % in Europe to 7.0 % in Asia and up to 8.5 % in North America [15].

MASLD and T2D are strongly linked and have a bidirectional influence: on the one hand, T2D acts as a strong modifier of the course of MASLD and, on the other, MASLD patients are at higher risk of developing T2D and have increased risk of T2D complications, especially cardiovascular disease and chronic kidney disease (CKD) [16].

In fact, T2D was identified as a risk factor independently associated with both MASLD onset and progression. MASLD affects 65 % of patients with T2D [17], and the prevalence of AF has been reported up to 14–38 % in patients with T2D from tertiary care centers, higher than in non-diabetic patients [18–21]. In a large study including 447 patients with MASLD and paired liver biopsies, patients with T2D showed faster progression of liver fibrosis compared to those without T2D [22]. A meta-analysis including 1737 patients with MASLD from six cohorts in the USA, Japan, and Turkey reported that patients with T2D are at higher risk of developing HCC and cirrhosis decompensation [23]. In a French nationwide study, the cumulative incidence of LREs was significantly increased in patients having both T2D and MASLD, compared to patients with T2D but without MASLD, and those without T2D [24]. T2D was also the strongest independent risk factor for MASLD-related HCC in a large European population-based cohort [25], and severe insulin resistance is equally associated with disease progression [26].

Conversely, the presence of MASLD is associated with higher risk of T2D occurrence during follow-up. A meta-analysis of 33 studies including 501,022 participants found that the incidence of T2D during follow-up was increased by 2.2 [95 %CI 1.9;2.5]-fold in patients with

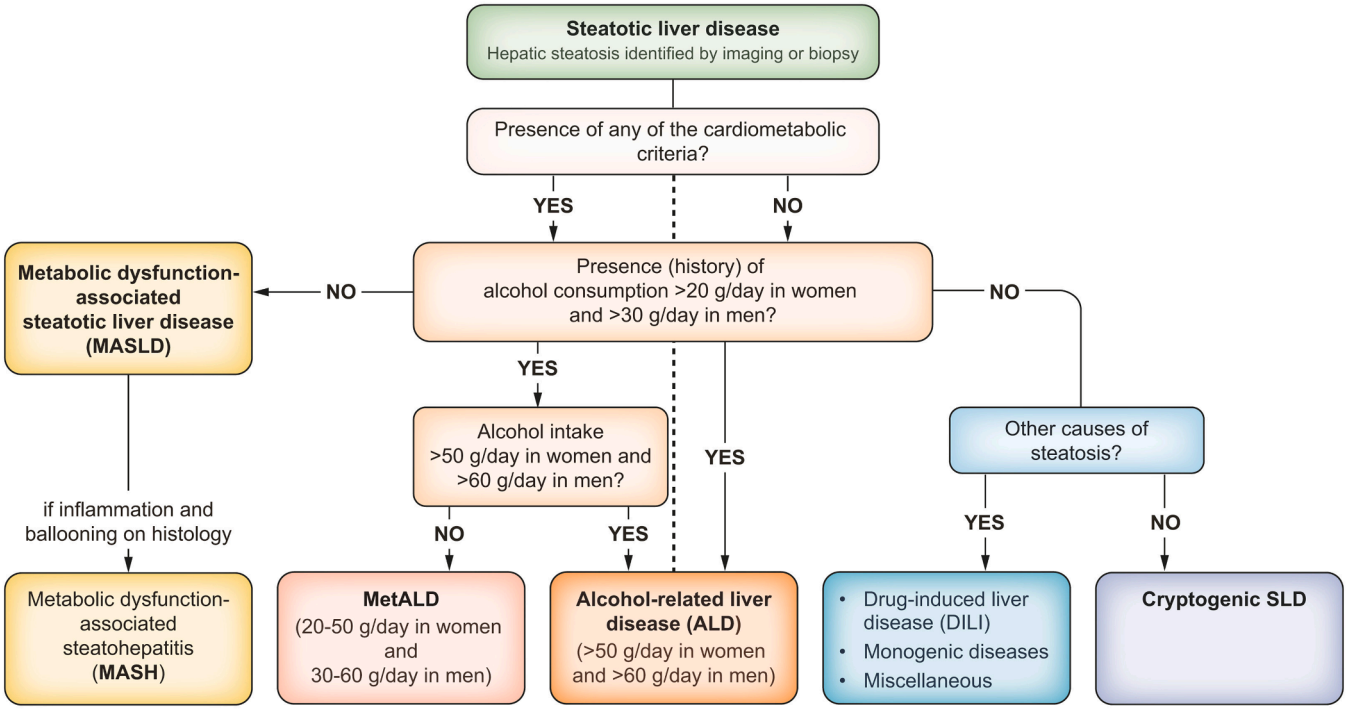

Fig. 1. Classification of steatotic liver diseases (SLD). Reprinted from EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81:492–542, European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO) [3], Copyright (2025), with permission from Elsevier. Cardiometabolic criteria encompass overweight or obesity (defined by BMI or waist circumference), prediabetes or T2D, increase in plasma triglycerides ≥ 1.7 mmol/l or lipid-lowering treatment, decrease in HDL-cholesterol ≤ 1.0 mmol/lL in men and ≤ 1.3 mmol/l in women, and arterial hypertension.
Abbreviations: ALD: alcohol-related liver disease, DILI: drug-induced liver disease, MASH: metabolic dysfunction associated steatohepatitis, MASLD: metabolic dysfunction-associated steatotic liver disease, MetALD: metabolic and alcohol associated liver disease, SLD: steatotic liver disease.

MASLD [27], and by 3.4 [95 %CI 2.3;5.1]-fold in case of AF.

In addition, MASLD is an independent risk factor for major adverse cardiovascular events (MACE), which are the first cause of deaths in MASLD patients [28]. This risk could be underpinned by low-grade systemic inflammation induced by MASLD, promoting accelerated atherosclerosis and cardiovascular complications [28]. In a Swedish population-based cohort, MASLD increased the risk for MACE with an adjusted hazard ratio (HR) of 1.63, independently of age and sex [29]. This risk increased proportionally with the stage of fibrosis, with an adjusted HR of 2.15 in individuals with cirrhosis.

Epidemiological evidence also shows an independent link between MASLD and CKD [30]. This association is observed both in patients with and without T2D, and is independent from common renal risk factors (age, sex, obesity, hypertension, T2D) [30]. A meta-analysis of 13 longitudinal studies reported an independent increased risk of incident CKD stage $\geq$ 3 in case of MASLD with a random-effect HR of 1.43, further increased in case of AF [31].

All these results from epidemiological studies highlight the bidirectional association and effects between MASLD/MASH and T2D and its cardiorenal complications, and underscore the need for a global and multidisciplinary management of these patients.

3. Screening methods for liver fibrosis in patients with T2D

- Systematic screening for MASLD-related AF is recommended in all individuals with T2D.
- Detecting liver fibrosis at an early stage can promote regression and prevent its progression to cirrhosis through effective therapeutic interventions.
- Identifying patients with cirrhosis enables initiation of HCC surveillance as recommended.
- International recommendations strongly support a two-step screening approach: after identifying patients with a FIB-4 > 1.30, second-line NITs with superior diagnostic accuracy should be used to further stratify the risk of MASLD-related AF.
- Patients with a LSM $\geq$ 8 kPa should be referred to a hepatologist.
- In patients with low FIB-4 at initial management, the frequency of repeat testing is not well defined, but could be proposed every 1 to 3 years.

3.1. Initial screening

Early diagnosis of liver fibrosis may prevent progression to cirrhosis by optimal therapeutic management, and AF diagnosis enables the identification of patients requiring hepatologist referral for appropriate therapeutic management and HCC screening. Fibrosis regression is also possible even in advanced stages through targeted intervention, emphasizing even more the importance of screening for liver fibrosis. Risk stratification focusing on high-risk populations enhances active case finding of AF and could be easily implemented in annual medical check-ups for other complications [32]. Hence, patients with T2D are considered as a priority target, and the recent EASL-EASD-EASO Clinical Practice Guidelines [3] and American Diabetes Association (ADA) guidelines [33] recommend systematic screening for MASLD-related AF in these individuals. In contrast, given the high prevalence of liver steatosis and its lack of prognostic value, systematic ultrasound screening for liver steatosis in patients with T2D is currently not recommended and has limited cost-effectiveness [3].

Several non-invasive biomarkers for the detection and staging of liver fibrosis in patients with MASLD have been developed, including blood-based scores and imaging-based techniques. The different available non-invasive tests (NITs) of liver fibrosis and their utility in clinical practice have been previously reviewed elsewhere [34]. Among them, the Fibrosis-4 index (FIB-4) score is a widely available non-patented test that can be easily calculated from liver enzyme (AST and ALT) levels, platelet counts, and age [3]. The interpretation of this score is based on a low threshold below 1.30 with a very high negative predictive value to rule out the presence of AF and a high threshold above 2.67 associated with a high probability of AF. The specificity of the 1.30 threshold for AF is lower in patients aged > 65 years, resulting in a high false positive rate [35]; thus a higher low threshold (> 2.0) has been proposed for these patients [3]. However, a recent prospective multi-center French study on AF screening in patients with diabetes found that applying the age-adjusted low threshold for FIB-4 led to a reduced negative predictive value (75 %) and positive predictive value (70 %) [36]. Therefore, we recommend using a fixed low threshold of 1.3 for patients with T2D, regardless of age, as proposed by the ADA and global consensus recommendations [33,37,38]. Importantly, the FIB-4 score lacks specificity for confirming the diagnosis of AF and additional specialized hepatology assessment is warranted in patients with a FIB-4 above 2.67 or in the intermediate zone (FIB-4 = 1.3–2.67). The utility of FIB-4 is now well established, and it is currently unanimously recommended as a first-line test to rule out patients with a very low probability of having AF below the threshold of 1.30 [3.39–41] (Fig. 2). Finally, physicians should avoid using the FIB-4 score in patients aged under 40 years with extrahepatic causes of thrombopenia or acute liver injury because of the high false positive or false negative rates.

The recent recommendations [3] also strongly agree on a two-step screening strategy, using a second-line NIT with higher diagnostic performance to further stratify risk in patients with a FIB-4 > 1.30 prior to or after referral to a hepatologist depending on local availability and pathways. The second-line test can be either a liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE), two-dimensional shear wave elastography (SWE) or an enhanced liver fibrosis (ELF) score with an adapted threshold, depending on availability [3,40] (Fig. 2). LSM using VCTE has been the most validated ultrasound-based modality in patients with MASLD [34]. After a FIB-4 > 1.3, a second-line LSM < 8 kPa allows to reclassify patients as having a low risk of AF and no need for hepatology referral. Conversely, patients with LSM greater or equal to 8 kPa are considered at intermediate or high risk for AF and need additional hepatology assessment. Physicians should be aware that the risk of LSM false positives increases with body mass index (BMI) (especially if $\geq$ 35 kg/m^2), with no clear high threshold established, and in specific situations, such as heart failure or a high transaminases elevation (> 5x LSN) [41,42]. T2D also impacts the performance of the sequential FIB-4-VCTE algorithm, with an accuracy of 79.0 % compared to 90.3 % in patients without T2D [43]. Alternatively, the ELF test is also proposed as a second-line patented blood-based biomarker [3]. An ELF test below 9.8 rules out AF whereas patients with an ELF $\geq$ 9.8 have a significant risk of AF and will need additional specialized hepatology assessment [33]. A lower cut-off of 7.7 has been suggested by others [3,44] but rules out too few cases in the diabetic population [36]. Other ultrasound-based methods (two-dimensional SWE, point SWE) perform equally well as VCTE [45,46] but are less widely used and cutoffs are not consensual. MRE might be the best NIT to rule in AF in MASLD [3] but its use in clinical practice is limited by availability and cost. Liver biopsy is usually performed to rule out other causes of liver diseases, in case of discordant NITs or for clinical trials.

The screening strategy for AF in patients with T2D is shown in Fig. 2, and the practical classification of liver fibrosis depending on the different NITs available is presented in Figure S1 (see supplementary materials associated with this article on line). In case of NITs suggesting the presence of AF, patients should be referred to hepatologists. Patients

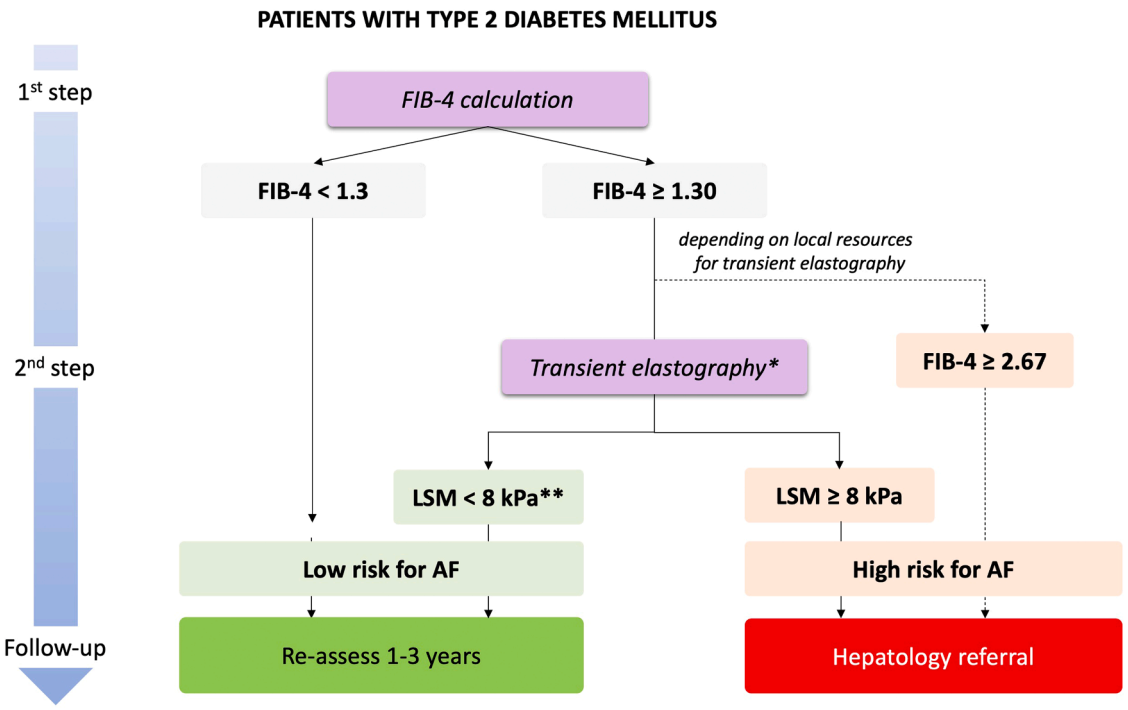

Fig. 2. Currently recommended two-step screening of advanced fibrosis in patients with T2D according to international societies' guidelines. After a first step based on FIB-4 calculation, a second line (before or after referral to hepatology depending on local availability and pathways) based on VCTE should be used to reclassify patients with elevated FIB-4 ≥ 1.3.
*Other techniques such as dimensional SWE or point SWE can also be used to measure LSM according to reference, or other NITs as ELF or MRE [3,33,39]. Abbreviations: cT1: corrected T1, ELF: enhanced liver fibrosis, LSM: liver stiffness measurement, MRE: magnetic resonance elastography, NIT: non-invasive test, SWE: shear wave elastography, VCTE: vibration-controlled transient elastography. **The LSM threshold is indicated using VCTE.

with significant fibrosis (≥ F2) may be considered for a clinical trial dedicated to MASH or, once approved, for MASH-specific therapy [3]. HCC monitoring should be applied to individuals with MASLD-related cirrhosis (F4) and may be considered in patients with AF (from F3 stage) based on an individual risk assessment [3].

Overall, these novel recommendations to screen for MASLD place the diabetologists and primary care physicians involved in T2D management at the center of the screening for MASLD-related AF prior to referral to hepatology. Thus, they need to be trained to use and interpret these biomarkers according to the recommended thresholds. Ultimately, this will help physicians decipher whether their patients require specialized care and follow-up in hepatology or if they are at low risk of AF and can be managed as part of usual clinical care for T2D.

3.2. *Monitoring frequency for MASLD-related fibrosis*

The screening frequency of MASLD and MASLD-related fibrosis in T2D patients is not yet well validated, and should be adapted to individual risk factors for progression. Males aged > 50 years, postmenopausal women, individuals with several cardiometabolic risk factors, and/or with other co-factors of liver disease (notably alcohol intake) are at increased risk of fibrosis progression [3] and LREs. Although genetic testing is not currently recommended in clinical practice, different gene polymorphisms, such as *PNPLA3* and *TM6SF2*, also contribute to MASLD progression [47], and could help future risk stratification of MASLD disease progression and sub-phenotyping [3].

However, it is acknowledged that sequential screening for MASLD-related fibrosis with NITs may assist in ruling out fibrosis progression and to predict the risk of liver-specific and overall mortalities. To date, the modalities of such monitoring (frequency and type of NIT) are based solely on expert recommendations. In patients with low FIB-4 on initial assessment, the recent EASL-EASD-EASO Clinical Practice Guidelines [3] recommend to perform FIB-4 every 1–3 years according to the risk factors for fibrosis progression.

For T2D patients with intermediate FIB-4 and second-line NIT showing low risk for AF, the relevance of repeating FIB-4 is not determined. Recommended monitoring frequency for MASLD and MASLD-related fibrosis is summarized in Fig. 2.

4. Non-pharmacological management in patient with T2D and MASLD: impact of dietary and behavioral therapies and physical activity

- Non-pharmacological treatment of patients with T2D and MASLD includes improvement in nutritional quality, reduction of caloric intake, and increase in physical activity, with the objective of weight loss in patients with overweight or obesity.
- The Mediterranean diet should be preferred, while the consumption of ultra-processed food and sugar-sweetened beverages should be limited.
- Alcohol consumption should be discouraged in all MASLD patients, and total abstinence should be advised in case of advanced fibrosis.
- A weight loss greater than 10 % of initial body weight has the strongest impact on improving histological features of MASH and liver fibrosis.

Lifestyle factors and particularly dietary pattern including excess of caloric intakes and sedentary behavior are key components in the pathogenesis of both T2D and MASLD [44,48]. The relationship between

MASLD and dietary intake or habits is now well established and was demonstrated by several prospective longitudinal or cross-sectional cohort studies highlighting the association between high consumption of processed meats, sugar-sweetened beverages, saturated fat, low consumption of fibers or fish and high risk of developing MASLD [49,50]. Furthermore, lifestyle intervention including diet modification, reduction of caloric intake and increase in physical activity (PA) remains the foundation of the management of both T2D and MASLD [3,44,51]. In this section, we will address the main evidence supporting lifestyle intervention including the type of dietary and PA interventions currently recommended for the management of patients with MASLD and T2D.

4.1. Dietary management of patient with T2D and MASLD

4.1.1. Weight loss target through hypocaloric diet

Very few nutritional interventions have had their impact on MASLD assessed using liver biopsy as a gold standard. However, it is commonly acknowledged that gradual weight reduction achieved through the implementation of a caloric restriction is a central element in the management of patients with obesity or overweight and MASH [3,44]. Vilar-Gomez *et al.* demonstrated the positive impact of weight loss on the histological features of MASLD, with improvement in steatosis at 5 % weight loss, MASH at 7 %, and fibrosis at 10 % [52]. Of note, histological resolution of MASH was lower in patients with T2D or prediabetes, with equal weight loss. In MASLD patients with overweight or obesity, the objective of weight loss should therefore to be at least of 5 % to reduce liver steatosis, $\geq$ 7–10 % to promote MASH resolution and $\geq$ 10 % to improve liver fibrosis [3]. Of note, the impact of weight loss is not well established in MASLD patients with normal BMI. Lifestyle interventions should be recommended as they are effective in reducing liver fat content [53], but no data on fibrosis or clinical events are currently available.

Weight loss $\geq$ 5 % improves glycemic control, lipid levels, and blood pressure in overweight and adult individuals living with obesity and T2D [54]. Although this weight reduction is relatively well tolerated, it should be supervised by a trained healthcare team to avoid excessive restrictive diets that could lead to vitamin deficiencies or deficits and increase the risk of weight rebound and weight cycling [55]. In patients with compensated cirrhosis, weight loss must be advised with caution due to the risk of sarcopenia. In terms of weight reduction effectiveness, any hypocaloric diet regardless of the composition of the macronutrients (protein/carbohydrate/fat) is associated with clinically meaningful weight loss [56]. Finally, in randomized controlled trials (RCTs), intensive weight loss intervention in recent onset T2D is associated with 40 to 60 % T2D remission along with improvement of hepatic steatosis and cardiometabolic risk factors [57]. However, the Look AHEAD study, including 5145 patients with T2D and overweight, failed to demonstrate a significant reduction of MACE in the intensive lifestyle intervention group versus controls [58].

4.1.2. Low-saturated fatty acid diet

The impact of the different types of diet and macronutrient compositions on hepatic steatosis have mainly been assessed using non-invasive methods such as magnetic resonance spectroscopy (MRS) or magnetic resonance imaging-derived proton-density fat fraction (MRI-PDFF). In isocaloric diet conditions, a low-fat high-carbohydrate diet is associated with a reduction of hepatic fat content and is more beneficial than a high-fat low-carbohydrate diet, which increases hepatic fat content [59]. However, an ad libitum isocaloric diet with a Mediterranean diet and a low-fat diet demonstrated similar effects on hepatic fat content reduction after 12 weeks [60]. Finally, reducing the consumption of saturated fatty acid intake and increasing polyunsaturated fatty acids appears to improve MASLD [59].

4.1.3. Mediterranean diet

Several studies suggest the superiority of the Mediterranean diet rich in polyunsaturated fatty acids and fiber, compared to Western diets rich in saturated fatty acids with low fiber, in MASLD [61]. The Mediterranean diet also plays a well-established protective role against cardiovascular disease and T2D [62]. The Mediterranean diet is characterized by reduced carbohydrate intake, especially sugars and refined carbohydrates (40 % of the calories vs. 50–60 % in a typical low-fat diet), and increased monounsaturated and omega-3 fatty acid intake [63]. In addition, this diet reduces postprandial insulin secretion, synthesis and storage of intrahepatic lipids [62,63]. Hence, the Mediterranean diet is currently recommended for the prevention and treatment of MASLD [3,44], obesity [51], T2D [48] and cardiovascular diseases [64].

4.1.4. Added sugar restriction

Regarding the consumption of fructose, it is well established that high consumption of sugar-sweetened beverages, enriched in fructose or glucose, worsens metabolic syndrome, insulin resistance, and MASLD [65]. Previous studies have demonstrated that a reduction of fructose consumption in adolescents even for a short period had a beneficial effect on MASLD [66]. In addition, an isocaloric fructose restriction in participants with MASLD demonstrated a higher decrease in hepatic fat content compared to controls [67].

4.1.5. Alcohol consumption

Since alcohol consumption significantly promotes fibrosis progression in MASLD (or MetALD) [68], the amount, pattern, and history of alcohol intake should be investigated in all individuals with MASLD and should be discouraged. In case of AF, alcohol consumption should be stopped completely and permanently [3,44].

4.1.6. Coffee consumption

Coffee consumption, regardless of caffeine content, may be beneficial to prevent MASLD [69]. Observational studies also report that coffee consumption in patients with MASLD may be associated with a reduced risk of developing fibrosis [70]. Likewise, the effects of coffee appear to be beneficial in T2D [71]. Hence, drinking three cups or more per day could be recommended in the absence of contraindications, due to the potential reduced risk of MASLD and liver fibrosis demonstrated in epidemiological studies and meta-analyses [3,44].

4.2. Physical activity management

PA is widely recommended for the management of T2D and MASLD as a means of achieving and maintaining stable weight following weight loss through lifestyle modification, and promoting metabolic improvements and enhanced insulin sensitivity [3,33,44,51,72]. Importantly, PA has shown benefits on hepatic steatosis even without significant weight loss [73]. Several meta-analyses suggest that high or medium aerobic and resistance training can improve liver enzymes, intrahepatic fat, and lipid profiles [55]. However, in patients with both T2D and MASLD, evidence is limited as fewer than 10 high-quality RCTs are available with small sample size, short-term duration, and using various supervised PA protocols. Several small studies reported improvements in hepatic fat, HbA1c, insulin sensitivity, and cardiovascular health following interventions combining diet and exercise or exercise alone, including aerobic, resistance, and high-intensity interval training [55,74,75]. No trials have specifically evaluated PA in patients with MASLD-related cirrhosis and T2D. However, several reports suggest that supervised PA may improve portal pressure, muscle function, and quality of life in cirrhotic patients [76].

Overall, current studies suggest a positive impact of supervised PA including high or medium aerobic intensity along with resistance training in patients with T2D and MASLD. However, more RCTs with well-defined therapeutic exercise programs, over a longer period, are needed to assess the long-term results and the potential impact on liver fibrosis [77].

4.3. Multidisciplinary nutritional management

Managing MASLD in T2D patients requires a multidisciplinary approach, involving the primary care physician, hepatologist, diabetologist, dietitian, and ideally a PA educator. To support long-term lifestyle changes, cognitive-behavioral therapy can help address eating behaviors. A pilot RCT showed that cognitive-behavioral therapy improved weight loss and MASH resolution [78], while another trial demonstrated better long-term weight maintenance [79]. Web-based programs may also support adherence [55]. Despite the importance of non-pharmacological strategies, real-world effectiveness is often limited and short-lived [80]. Therefore, several pharmacological therapies for MASLD/MASH are under development or in validation.

5. Glucose-lowering drugs approved in T2D and impact on MASLD

- Metformin and DPP4-inhibitors are neutral on liver steatosis and fibrosis; however, metformin may be associated with lower mortality in patients with cirrhosis and lower incidence of HCC.
- Sulfonylureas and glinides are neutral on liver steatosis and fibrosis but could induce severe hypoglycemia, especially in patients with impaired liver function.
- Pioglitazone improves liver steatosis and MASH and may improve liver fibrosis.
- SGLT2 inhibitors improve liver steatosis, may have an effect on MASH resolution and liver fibrosis improvement and are associated with lower incidence of liver-related outcomes in retrospective cohort-based studies.
- GLP1-RAs at doses used in T2D improve liver steatosis and are associated with lower incidence of liver-related outcomes in retrospective studies.
- At higher doses, weekly GLP1-RAs such as semaglutide 2.4 mg showed further benefits on MASH resolution and fibrosis improvement.
- Dual GIP/GLP1-RA tirzepatide improves liver steatosis and MASH, and may improve liver fibrosis.

At least two aspects should be considered when prescribing antidiabetic medications in patients with MASLD [81]: *i*) their possible additional benefit on liver histology, and *ii*) safety concerns in particular in patients with advanced chronic liver disease (aCLD).

Due to dysregulated glucose metabolism, susceptibility to hypoglycemia is increased in patients with both T2D and cirrhosis. Additionally, recent data suggest that MASLD itself may be considered as a risk factor for hypoglycemia because of a potential downregulation of liver glucagon receptors [82]. Based on the current level of evidence, several drugs are strongly recommended in patients with T2D and MASLD while other are discouraged, in particular in cirrhotic patients because of safety concerns. The effects of the different pharmacological T2D treatments on MASLD progression are summarized in Fig. 3.

5.1. Glucose-lowering drugs with no benefit on MASLD

5.1.1. Metformin

Metformin is the first-line treatment for T2D and its mechanisms of action involves improvement in hepatic insulin sensitivity. However, metformin did not demonstrate any benefit on hepatic steatosis, circulating liver enzymes or histological inflammation and fibrosis [83]. Metformin is therefore considered neutral on MASLD. Some observational studies reported that its use was associated with less mortality, including a lower rate of HCC in patients with MASLD-related cirrhosis [84]. However, a recent meta-analysis did not confirm the association between metformin use and reduction in the risk of HCC, independently of the potential associated consumption of statin and aspirin [85]. No pharmacokinetic data concerning the use of metformin are available in patients with chronic liver disease, but several cases of metformin-associated metabolic acidosis have been reported in this population. Thus, the use of metformin is possible in patients with cirrhosis and preserved or slightly impaired liver function (Child A) but not in those with moderate or severe impaired liver function (Child B-C) [21].

5.1.2. Sulfonylureas

The use of sulfonylureas in T2D is currently decreasing, mainly because of the risk of hypoglycemia, but also because of the lack of cardiovascular and renal benefits compared with newest medications.

Concerning MASLD, previous studies have described an increase in visceral fat content and worsening of hepatic steatosis in sulfonylurea users [86], as well as progression from steatosis to MASH, and emergence of severe outcomes such as HCC [87,88]. This could be due to increased insulin secretion, promoting weight gain and fat mass accumulation through SREBP-1c-mediated lipogenesis [89,90].

Conversely, other studies have reported steatosis regression in people using sulfonylureas, nevertheless less marked than for other antidiabetes treatments, while others reported no effect on steatosis and liver fibrosis [87,91]. Data are then inconsistent, making sulfonylureas unlikely to have a real favorable impact on liver steatosis or liver fibrosis.

The risk of hypoglycemia associated with sulfonylureas is enhanced in patients with impaired liver function, with different degrees of severity depending on the molecule used [21]. Therefore, sulfonylureas should be used carefully in patients with cirrhosis and slightly impaired liver function, and should not be used in patients with cirrhosis and moderately/severely impaired liver function [21].

5.1.3. Glinides

Very few data are available concerning the effect of glinides on MASLD. Glinides, such as sulfonylureas, promote insulin secretion in a glucose-independent manner, and can thus result in severe hypoglycemia and weight gain. As glinides have a liver-related metabolism through CYP450, repaglinide must not be used in case of hepatic impairment and nateglinide should be used carefully in patients with cirrhosis and impaired liver function, to avoid hypoglycemia [21].

5.1.4. Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors enhance the action of endogenous incretin hormones through inhibition of their degradation. These molecules exert moderate glucose-lowering effects and are neutral in terms of cardiovascular risk [92]. Several studies including two RCTs showed no significant improvement associated with sitagliptin treatment in liver steatosis or fibrosis [93], and DPP-4 inhibitors are therefore no longer considered for the treatment of MASLD. Apart from vildagliptin, DPP-4 inhibitors appear to be safe in patients with cirrhosis and mild-to-moderate hepatic impairment but are not recommended in case of severely impaired liver function [21].

5.1.5. Insulin

Insulin therapy results in a state of hyperinsulinism in patients with T2D, leading to an unfavorable metabolic milieu in MASLD. Thus, insulin effect on MASLD is unclear, with some studies reporting no improvement in liver steatosis, while others showed a decrease of liver fat content measured by MRI after insulin therapy initiation [94–96]. Because of impaired neoglucogenesis, insulin therapy increases the risk

T2DM treatment	Steatosis	MASH	Fibrosis	MALO	MACE	MARE
Metformin	Neutral	Neutral	Neutral	Improve** (in F3/F4)	Neutral	Neutral
Sulfonylureas	Not studied	Not studied	Not studied	Neutral	Neutral	Neutral
DPP-4 inhibitors	Neutral	Not studied	Not studied	Neutral	Neutral	Neutral
Pioglitazone	Improve	Improve	Neutral/ improve (F3/F4)	Neutral	Improve	Neutral
SGLT2-i	Improve	Neutral/ improve	Neutral/ improve	Improve**	Improve	Improve
GLP-1 RA	Improve	Improve*	Improve*	Improve**	Improve	Improve
Dual GIP/GLP-1 RA	Improve	Improve***	Improve***	Not studied	Improve***	Improve***
Insulin	Neutral/ improve	Neutral	Neutral	Neutral	Neutral	Neutral

Fig. 3. Effects of the different pharmacological T2D treatments on MASLD progression. SGLT2is have demonstrated a positive effect on liver fat content, but their effect on liver fibrosis is still unclear. However, retrospective data reported a significant reduction of MALO, as for GLP1-RAs, if administered in patients with T2D. *Only semaglutide administered at higher doses than the usual dose for T2D treatment demonstrated these effects. **These results are derived from population-based retrospective cohorts and need to be validated in dedicated prospective RCTs. ***Tirzepatide only. Regarding liver fibrosis regression, tirzepatide demonstrated an important effect in a phase II study, but no statistical analysis was presented since multiple comparisons were not included in the initial protocol. Abbreviations: DPP-4: dipeptidyl peptidase-4, GLP1-RA: glucagon-like peptide-1 receptor agonist, MACE: major adverse cardiovascular events, MALO: major adverse liver outcomes, MASH: metabolic dysfunction-associated liver steatohepatitis, MARE: major adverse renal events, RA: receptor agonist, RCT: randomized controlled trial, SGLT2i: sodium-glucose cotransporter 2 inhibitor, T2D: type 2 diabetes.

of hypoglycemia, particularly in patients with cirrhosis, and thus requires careful dose adjustment, but it can be otherwise safely administered even in decompensated patients [21].

5.2. Glucose lowering drugs with evidence for benefit on MASLD

5.2.1. Sodium-glucose transport protein 2 (SGLT2) inhibitors

SGLT2 inhibitors (SGLT2is) reduce blood glucose level in people with T2D by reducing renal glucose reabsorption and thereby increasing urinary glucose excretion. Moreover, SGLT2is improve cardiovascular and renal prognosis [97,98]. They are increasingly prescribed in patients with T2D, especially in those with high cardiovascular risk, heart failure and/or CKD [99]. Numerous studies indicate an improvement in hepatic steatosis and in plasma liver enzymes in subjects with MASLD with most of approved SGLT2is [33,100]. Nevertheless, canagliflozin treatment did not show any effect on liver fat content compared with placebo [101]. Hepatic steatosis reduction was correlated with the extent of weight loss, which may partly explain the heterogeneity of the results. A meta-analysis of 12 RCTs showed that SGLT2is reduced the level of liver enzymes and liver fat content measured by MRI in patients with MASLD, associated with T2D in 90 % of cases [102]. Apart from a few open trials with a small number of participants, suggesting a beneficial effect of SGLT2is on fibrosis [103–105], there is still no strong evidence of a direct effect of SGLT2is on histological markers of MASH. Several RCTs with liver histological endpoints are ongoing. However, recently, numerous population-based cohort studies suggested that administration of SGLT2is was associated with significant reduction in liver stiffness progression [106], major adverse liver outcomes (MALO) (including HCC and cirrhosis), MACE, CKD and extra-hepatic cancers in patients with T2D, and MASLD [91,106–108]. The protective effect of SGLT2is was even more pronounced when metformin was administered concomitantly [108].

Concerning SGLT2is safety in patients with cirrhosis, there is no evidence that SGLT2is could cause hepatotoxicity. However, their long-term safety profile and efficacy have not been studied specifically in patients with cirrhosis [21].

5.2.2. Peroxisome proliferator-activated receptors agonists

Thiazolinediones (glitazones) are agonists of peroxisome proliferator-activated receptors γ (PPARγ) that promote lipid uptake and triglyceride storage in adipose tissue [109]. Consequently, these molecules prevent the ectopic storage of fat in the liver and muscles, preventing insulin resistance caused by lipotoxicity. In addition, glitazones induce the secretion of adiponectin, an adipokine that improves insulin sensitivity. Besides protective effects from steatosis, pioglitazone promotes MASH resolution and improvement in liver fibrosis, as demonstrated by two meta-analyses of RCTs with biopsy-proven MASH [110,111]. However, safety concerns (weight gain, worsening of heart failure, osteoporosis and doubts about an increased risk of bladder cancer) led to strong limitation in the use of pioglitazone, withdrawn from the market in some countries [112]. As pioglitazone is mainly metabolized in the liver by CYPC28, it can be used in patients with cirrhosis and preserved liver function but should be avoided in patients with decompensated cirrhosis [21].

5.2.3. GLP1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP1-RAs) improve glucose control and promote body weight loss through their combined actions on different organs including the pancreas and the central nervous system. In the joint EASD-ADA recommendations [99], GLP1-RAs are positioned as first-line drugs in the case of established or high-risk of atherosclerotic cardiovascular disease due to their proven benefits in terms of cardiovascular prevention. Regarding their mechanism of action, it seems that GLP1-receptors are not expressed in the liver [113]. Their hepatic effects are thus mainly indirect, but may lead to decreased hepatic glucose production, increased hepatic insulin sensitivity, and decreased de novo lipogenesis [114].

Several GLP1-RAs have been approved for the treatment of T2D and more recently for obesity management at higher doses. Beneficial effects on the liver were also suggested for some of them in patients with MASH [114]. Among the different compounds, semaglutide showed the most promising results, at least for MASH resolution without worsening of fibrosis in a phase IIb trial [115]. The phase III trial on semaglutide (ESSENCE) further demonstrated the improvement in liver fibrosis at 72 weeks, concomitantly with significant greater weight loss compared to placebo (difference of -8.5 % [95 %CI -9.6;7.4 %]) [116]. This led to conditional approval as an anti-MASH therapy by the FDA in 2025. However, doses used in phase III trial were those used for obesity

treatment (2.4 mg per week), and not for T2D treatment, not allowing these results to be transferred to a T2D population treated with lower doses of semaglutide. Adverse events were mostly gastrointestinal events (36.2 % of patients reporting nausea, 26.9 % diarrhea and 22.2 % constipation). Recently, the SELECT trial demonstrated a significant reduction of MACE in a large prospective RCT enrolling over 17,500 participants with BMI $\geq$ 27 kg/m^2, no T2D, and established cardiovascular disease [117].

An important remaining question is whether such a beneficial effect of GLP1-RAs on the liver is independent or not of the weight loss induced by these treatments. A recent post-hoc analysis from the phase II RCT reported that weight loss associated with semaglutide 0.4 mg daily accounted for 69.3 % of the total effect for MASH resolution [118]. Hence, other potential mechanisms partially independent of weight loss may reduce liver inflammation according to preclinical data [119–121].

Regarding potential hepatic benefits of GLP1-RAs on cirrhosis, in a phase II trial involving patients with MASH and compensated cirrhosis, once weekly injection of semaglutide 2.4 mg did not significantly improve fibrosis or achieve MASH resolution despite improvements in cardiometabolic parameters and non-invasive markers of liver injury [122].

GLP1-RAs are however strongly preferred in patients with cirrhosis as they are not metabolized in the liver and are not associated with an increased risk of hypoglycemia. A small pilot study reported that semaglutide can be safely administered without dose adjustment in patients with cirrhosis and mild-to-moderate liver dysfunction [123]. These preliminary data related to safety concerns have been confirmed by a subsequent phase II RCT in cirrhotic patients [122]. However, the nutritional status should be carefully monitored in cirrhotic patients taking GLP1-RAs in order to avoid malnutrition in these particularly at-risk patients [21].

Finally, retrospective population-based studies suggest that GLP1-RA therapy in T2D is associated with reduced risk of MALO, including HCC, liver transplantation, and hepatic decompensation in patients with MASH-cirrhosis, compared to non-GLP1-RA therapies [124]. GLP1-RAs were also linked to lower cirrhosis progression risk versus DPP-4 inhibitors [125], with no significant difference in hepatic decompensation compared to SGLT2is [126].

5.2.4. Dual and triple agonists – glucose-dependent insulinotropic peptide (GIP)/glucagon/ GLP1-receptor agonist

Twincretins, either glucagon or GIP/GLP1-RAs, potentiate the effect of a single GLP1-RA and are very promising agents for both obesity and T2D but also for MASLD.

Tirzepatide, a novel dual GIP and GLP1 receptor agonist, was associated with a decrease in biological markers of MASH, such as K-18, PRO-C3 and adiponectin in a population of patients with T2D [127]. In a sub-study of the randomized, open-label, parallel-group, phase III SURPASS-3 trial, tirzepatide significantly reduced liver fat content measured by MRI-PDFF, accounting for a relative change of 47 % in the 10 mg tirzepatide arm vs. 11 % in the control arm [128]. Recently, a large RCT assessing the impact of tirzepatide vs. dulaglutide in cardiovascular outcomes in patients with T2D and cardiovascular disease (NCT04255433, [76]) demonstrated non-inferiority compared to the known beneficial effect of dulaglutide, with an 8 % (95 %CI 0.83;1.01) reduction in MACE.

Tirzepatide also demonstrated in a phase II study (SYNERGY-NASH) a significantly higher percentage of MASH resolution without progression of liver fibrosis, and a higher percentage of liver fibrosis regression without worsening of MASH, at 5 mg, 10 mg or 15 mg compared to placebo although no adjustment was made for multiple comparisons [129]. The mean percentage change in body weight was -10.7 %, −13.3 %, and −15.6 % in the 5 mg, 10 mg, and 15 mg tirzepatide groups, compared with −0.8 % in the placebo group.

Glucagon secretion increases gluconeogenesis, mitochondrial function and turn-over, and decreases oxidative stress and lipogenesis with beneficial effect on the liver: reduced steatosis, inflammation, stellate cell activation and fibrosis [130,131]. In a phase IIb RCT in overweight and obese patients with T2D, cotadutide, a dual GLP1/glucagon RA demonstrated a significant improvement in lipid profile, AST and ALT levels, PRO-C3 level, FIB-4, and nonalcoholic fatty liver disease fibrosis score [132]. Unexpectedly, the pharmaceutical company has decided to stop developing cotadutide to focus on treatments for obesity and T2D. Other dual GLP1/glucagon RAs like pemvidutide and efinopegdutide have shown very positive results in reducing liver fat content (70 % of patients achieved $\geq$ 50 % reduction in liver fat content at week 24 [133]. Retatrutide, a triple GLP1/Glucagon/GIP-RA was associated with 24 % weight loss in patients with obesity [134], a significant improvement in glycemic control in patients with T2D [135] and a very strong defatting effect on the liver (mean reduction in liver fat content of 80 %) in patients with MASLD.

6. MASH-specific therapy

Resmetirom is an oral specific thyroid hormone receptor (THR) β agonist, which was approved by FDA in 2024 and by EMA in 2025 for the treatment of patients with MASH and fibrosis stage F2-F3, including a large proportion of diabetic patients. Resmetirom has no deleterious effect on glucose level. In the MAESTRO trial, the use of resmetirom was not associated with worsening of diabetes biomarkers or cardiac safety signal, suggesting that resmetirom could be used safely in patients with T2D [136]. The administration of resmetirom is therefore recommended in the USA for all MASLD patients with suspected fibrotic MASH (F2-F3) excluding cirrhosis stage (expert opinion, [137]).

7. Adapting glucose-lowering therapy in patients with MASLD

As liver assessment is now widely recommended in patients with T2D, and given the known benefits of some glucose-lowering therapies in improving MASLD, the liver status (presence of MASLD, suspicion of fibrotic MASH) should influence the choice of glucose-lowering therapies in patients with T2D. The algorithm for adapting treatment in patients with T2D according to the severity of MASLD is shown in Fig. 4, to support clinical-decision making.

In patients with T2D and MASLD with:

- Low risk of fibrotic MASH (FIB-4 $<$ 1.30 or LSM $<$ 8 kPa): adaptation of glucose-lowering therapy should be based upon standard of care including consideration of cardio-renal and weight status [33,99].
- Intermediate-to-high risk of fibrotic MASH (LSM $\geq$ 8 kPa) and compensated cirrhosis: a GLP-1-RA or dual GIP-GLP-1-RA should be administered regardless of HbA1c. In case of contraindication or intolerance of GLP1-RAs, SGLT2is or pioglitazone should be alternatively preferred.

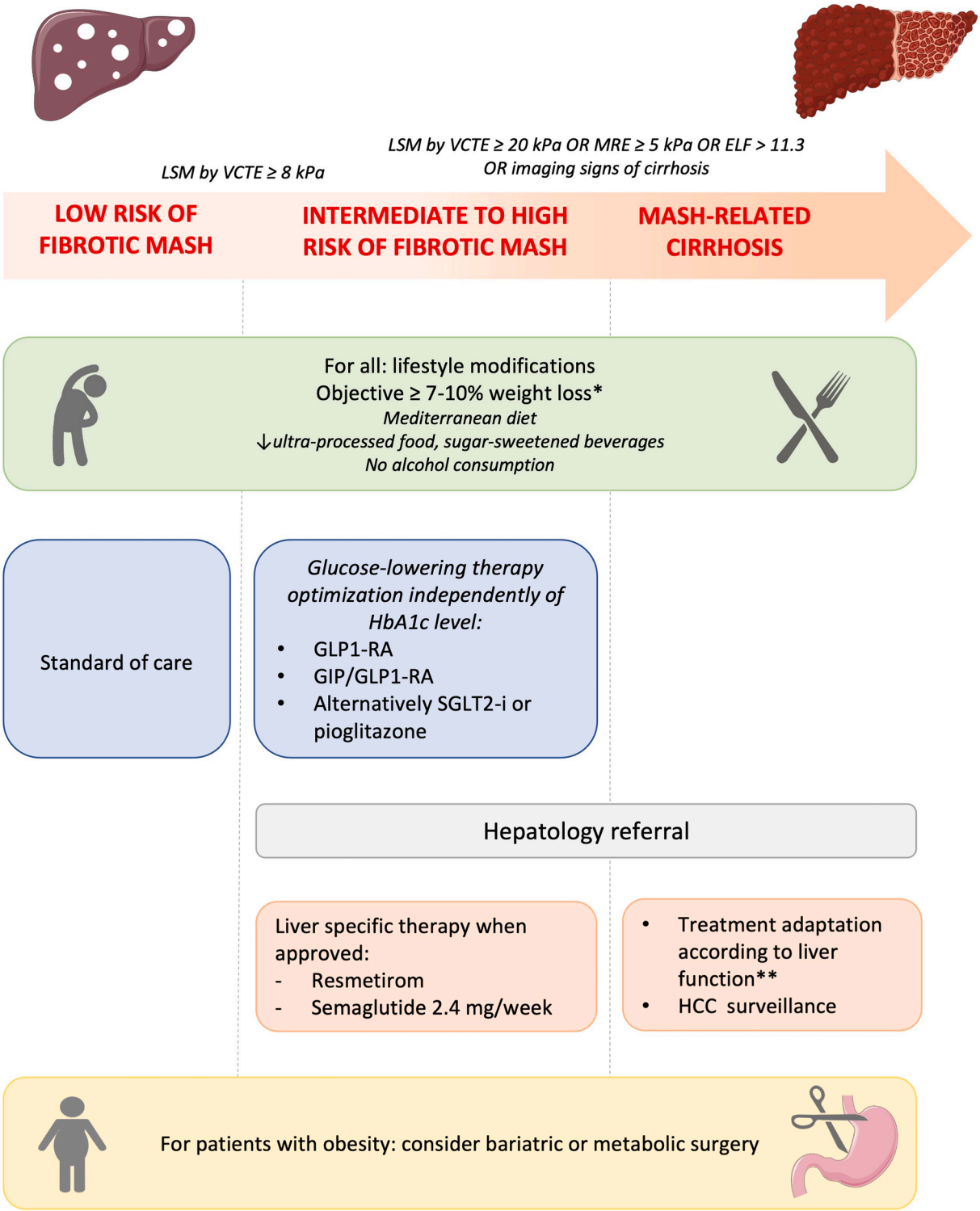

Fig. 4. Adaptation of T2D treatment according to the severity of MASLD. *Lifestyle modifications are recommended for all patients with T2D and MASLD, but weight loss is not recommended in case of cirrhosis with sarcopenia. In case of normal BMI, diet and exercise are still recommended, with no clear consensus on the weight-loss objective. In the case of low risk of AF (LSM < 8 kPa), no specific adjustment of anti-diabetic treatment according to the presence of MASLD can be recommended at present. Cirrhosis diagnosis can be inferred based on the results of different NITs or in case of imaging signs of cirrhosis [137]. In cases of intermediate to high risk of AF, we recommend the introduction of a GLP1-RA or dual GIP-GLP1-RA. In the presence of CKD or heart failure with severely reduced ejection fraction, a SGLT2i should be prescribed in accordance with the approved indications. In patients with MASLD-related cirrhosis, the anti-diabetes therapy should be based upon liver function status (**reviewed in [20]). Physicians should be aware that the risk of LSM false positives increases with BMI, with no clear high threshold established. Abbreviations: BMI: body mass index, ELF: enhanced liver fibrosis, GLP1-RA: glucagon-like peptide-1 receptor agonist, LSM: liver stiffness measurement, MASH: Metabolic dysfunction-associated liver steatohepatitis, MRE: magnetic resonance elastography, RA: receptor agonist, SGLT2-i: Sodium-glucose cotransporter 2 inhibitor, T2D: type 2 diabetes, VCTE: vibration-controlled transient elastography.

8. Potential impact of liver status on the indication for bariatric or metabolic surgery

- Bariatric/metabolic surgery should be proposed to patients living with T2D and MASH and BMI $\geq$ 35 kg/m^2, and considered in patients with BMI between 30–35 kg/m^2.
- Data are insufficient to favor one type of surgical procedure (gastric by-pass, sleeve gastrectomy) for liver improvement.
- Bariatric/metabolic surgery is proven to reduce liver fibrosis over the long term and improve clinical events in MASH.
- Portal hypertension must be rigorously assessed prior to bariatric/metabolic surgery, which is contraindicated in cases of cirrhosis with clinically significant portal hypertension.

Bariatric surgery (BS), also referred to as metabolic surgery (MS), is the most effective treatment leading to significant long-term weight loss concomitant with metabolic improvement. BS/MS should be considered in the context of MASLD, especially in patients with severe obesity.

8.1. Results of bariatric surgery in patients with MASLD

8.1.1. Histological benefits

In recent years, several retrospective or prospective cohort studies have demonstrated the efficacy of BS in reducing or even completely reversing steatosis or MASH in patients with obesity, in addition to cardiometabolic benefits. Results from a prospective follow-up BS French cohort showed very high rates of MASH resolution in almost 80 % of patients, both at 1 and 5 years after surgery [138,139]. The resolution of MASH positively correlated with the amount of weight loss while the refractory insulin resistance profile was a negative predictor for histological improvement [139]. Resolution of liver histological damage (including steatosis, inflammation and fibrosis) can be achieved in almost one-third of patients without AF undergoing BS [140]. These benefits are positively associated with the magnitude of weight loss, modification of body composition, remission of T2D, better glycemic control and improved insulin sensitivity [140]. Two meta-analyses confirmed the histological benefits of BS, showing complete MASH resolution up to 69 % of cases [141] and improvements in steatosis, inflammation, ballooning, and fibrosis in 66 %, 50 %, 76 %, and 40 % of patients, respectively [142]. However, the proportion of patients with T2D was not specified. Limited data also suggest that BS may improve hepatic steatosis in children [143].

A recent multicenter randomized study of 288 patients with obesity and MASH (with or without T2D) found that about 55 % of those undergoing BS, either with gastric bypass or sleeve gastrectomy, achieved MASH regression without fibrosis worsening after one year, compared to 16 % in the lifestyle group [144]. Fibrosis improved in around 38 % of BS patients versus 23 % in controls. However, few patients had F3 fibrosis stage, and none had F4 [144]. Other studies suggest that while BS often resolves MASH, fibrosis regression is harder to achieve and may not persist over the long-term, particularly in older patients, those undergoing sleeve gastrectomy, or in those with less metabolic improvement [139,140].

8.1.2. Metabolic and clinical benefits

Overall, BS is associated with improved cardiometabolic outcomes and significantly reduces the mortality rates or the occurrence of MACE [145]. Because MASLD is frequently associated with extra-hepatic comorbidities, we might expect that following BS, these patients have both histological but also cardiometabolic benefits with significant improvement in clinical outcomes. The SPLENDOR study, a retrospective cohort of 1158 patients with biopsy-proven MASH, showed that those who underwent BS had significantly lower 10-year risk of LREs and MACE, with absolute RR of 12.4 % and 13.9 %, respectively [146]. Similarly, a recent large retrospective analysis using the TriNetX database found that BS in obese patients was linked to reduced risks of MACE and all-cause mortality [147]. Very recently, the long-term results of BS with a median follow-up of 10 years have been published [148]. The presence of MASH or significant fibrosis at the time of BS was a significant predictor for overall mortality, but patients with MASH resolution or fibrosis improvement ($<$ F2) one year after surgery recovered the same prognosis as patients without initial MASH/fibrosis, demonstrating the clinical relevance of BS in MASLD. In this cohort, the presence of T2D did not affect histological improvement one year after BS.

8.2. Impact of surgical procedures on MASLD improvement

A variety of bariatric procedures are used today, including purely restrictive techniques or both restrictive and malabsorptive ones. Studies on the efficacy of BS in MASLD usually combine results from different procedures [149]. Among BS procedures, gastric by-pass and sleeve gastrectomy lead to greater and longer-lasting weight loss compared to gastric banding and are superior in terms of improving metabolic profile [150]. Gastric by-pass also improves liver and systemic cholesterol homeostasis through the regulation of specific genes in the liver [151]. While gastric bypass may be more effective than sleeve gastrectomy in achieving diabetes remission, evidence for their relative efficiency in improving MASLD is conflicting. Some studies including a head-to-head RCT showed similar resolution of MASH and liver fibrosis with both procedures after one year [144], confirmed by a meta-analysis [152]. Conversely, in a retrospective study, sleeve gastrectomy was found to be an independent predictor of poorer fibrosis regression [140]. Hence, further studies are therefore needed to determine which technique should be preferred for the management of MASLD in T2D.

Finally, endoscopic sleeve gastroplasty has emerged as a new endobariatric procedure with promising results. A meta-analysis suggests that this procedure could improve liver steatosis, liver function and insulin resistance, in addition to enabling 50 % excess weight loss and improvement of at least one cardiometabolic comorbidity in 80 % of the patients [153]. These encouraging data must be confirmed in larger RCTs including histological follow-up.

8.3. Bariatric surgery and cirrhosis

Cirrhosis exposes patients to increased morbidity and mortality after abdominal surgery while cirrhosis regression is associated with significantly improved clinical outcomes [154]. Moreover, obesity is a strong risk factor for cirrhosis decompensation [155]. This raises the question of the relevance and the feasibility of BS in cirrhotic patients, with the need to carefully assess the benefit/risk ratio. A systematic review including 18 studies and 481 cirrhotic patients undergoing BS reported a low rate of post-operative complications and mortality secondary to hepatic decompensation [156]. On the other hand, decompensated cirrhosis is associated with a greater risk of complications than compensated cirrhosis [157]. Accordingly, guidelines on BS and cirrhosis state that surgery may be considered for some patients with compensated cirrhosis (Child-Pugh score A), after careful evaluation of extra-hepatic complications and benefit-risk balance assessment. Decompensated cirrhosis or marked portal hypertension (presence of esophageal varices and/or intra-hepatic gradient $>$ 10 mmHg) are formal contraindications to BS [40,51,158]. However, transjugular intrahepatic portosystemic shunt (TIPS) placement may be discussed in case of BS indication and isolated portal hypertension [159]. No data specifically relating to T2D is currently available. Beyond safety

concerns, the benefits of BS in terms of fibrosis regression or cirrhosis reversal and how this translates into a survival benefit should be further determined.

In conclusion, in addition to incretin-based therapies, BS appears to be an effective therapeutic intervention for the improvement of MASLD in patients with obesity with expected benefits in terms of steatosis and MASH resolution. Although numerous cohorts included patients with T2D, studies specifically dedicated to this population are necessary. Furthermore, since the regression of AF after BS is difficult to obtain, bariatric procedures might be considered in the early stages of the disease. Finally, while decompensated cirrhosis contraindicates BS, compensated cirrhosis should not lead to its systematic rejection if indicated. However, the use of MS in T2D patients has to be balanced against the new therapeutic classes leading to significant weight loss such as GLP1/GIP-RAs.

9. Conclusion and future directions

The prevalence of MASLD and MASLD-related AF has increased significantly over the last decades, in parallel with the rise in T2D. Liver status assessment should be part of the systematic annual check-up of patients with diabetes, and glucose-lowering therapies must be adapted in the presence of MASLD to slow disease progression and potentially reduce the risk of major liver and cardiovascular clinical events.

Therefore, all T2D patients should be monitored regularly for FIB-4, and LSM performed (in hepatology or directly in diabetology) in case of elevated FIB-4 or clinical suspicion of fibrotic MASH.

In addition to lifestyle modification, with the objective of significant weight loss ($\geq$ 7–10 %), we suggest introducing a GLP1-RA or a GIP/glucagon/GLP-1 RA in T2D patients at-risk of fibrotic MASH (LSM $\geq$ 8 kPa), independently from HbA1c level. SGLT2is could also be of interest to decrease the risk of liver complications, and therefore should be considered in their current indications for T2D. GLP-1-RA-based therapies and SGLT2is have the advantage of reducing the risk of cardiovascular and renal adverse events especially in high-risk groups, and may be clinically relevant in patients with T2D and MASLD who exhibit higher risk of cardio-renal complications. BS should be discussed in cases of obesity and fibrotic MASH, since it has demonstrated significant improvement in liver parameters and long-term mortality in these patients.

To date, many aspects of the optimal management of these patients remain unknown. Optimizing the care referral pathway between diabetology/primary care and hepatology is critical. Diabetologists and primary care physicians need to be aware of the small but real possibility of false negatives with FIB-4, which can become problematic in populations where the prevalence of AF is high (typically, poorly controlled long-standing diabetes in elderly men). Further studies are needed to investigate whether it would be more appropriate to perform a second-line test straightaway in case of high metabolic burden or diabetic complications. The management and follow-up of T2D patients with intermediate FIB-4 or discordant NITs must be more precisely defined, especially if the risk-benefit ratio of the liver biopsy (recommended in that situation) appears unfavorable.

Regarding therapeutics, the potential synergistic effect between resmetirom and anti-diabetic therapeutics should be assessed, as well as the association of BS/MS and incretin-based therapies. Real-life data of anti-diabetic treatments in patients with cirrhosis could refine in the future the place of the current medications, and new effective drugs should be developed for patients with MASLD-related cirrhosis. The clinical impact of T2D therapeutic adaptation according to MASLD presence and severity needs to be prospectively demonstrated in future years, focusing on both hepatic and cardiovascular events, as well as overall mortality. Notably, the renal and/or cardiovascular benefits of the different molecules administered need to be studied specifically in T2D patients with MASLD.

Altogether, including an assessment of liver status in the annual check-up of patients with T2D will make it possible to integrate liver health profiles alongside the cardio-renal and BMI profiles in the process of therapeutic decision-making, further defining personalized management.

Conflicts of interest

CyC received consulting fees from Gilead, NovoNordisk, AstraZeneca, Lilly, E-scopics, MSD, Bayer, Corcept and Echosens, and grant support from Gilead. LC reports consulting fees from Boehringer Ingelheim, Boston pharmaceutical, Echosens, Gilead, GSK, Madrigal, MSD, Novo Nordisk, Pfizer, Sagimet and Siemens Healthineers, and speaker fees from AstraZeneca, Echosens, Gilead, Inventiva, Madrigal, Novo Nordisk and Siemens Healthineers. BG declares consulting, expert opinions, writing, and proofreading work, participation in phase II, III, and IV clinical studies, speakers at symposia, co-funding or grants for clinical research projects for the following pharmaceutical and industrial companies, healthcare providers, official organizations, and scientific societies: Novo Nordisk, Eli Lilly, Johnson & Johnson, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Sanofi Aventis, GlaxoSmithKline, Novartis, Janssen, Intarcia, Metacure, Insulet, Pfizer, MSD, Roche Diagnostic, Medtronic, Menarini Diagnostic, Ypsomed, Abbott, Dexcom, Lifescan, Vitalaire, Dinno Santé, Ork'yn, Asten, ISIS diabète, CEMKA, SANOIA, SEMEIA, AFSSAPS, CNAMTS, CEPS, ANSM, CNEDIMTS, GMED, EASD, SFD, SFE, NSFA, EASD (EUDF). BC reports consulting fees from MSD, Novo Nordisk, Novartis and Ultragenyx, and speaker fees from Amgen, AstraZeneca, Gilead, Eli Lilly, Novartis, outside the submitted work. PG has received research support or consultant fees, or has served on advisory panels for Abbott, Abbvie, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pfizer, and Sanofi. ClaC reports personal fees from Novo Nordisk, Lilly, Rhythm, Boehringer Ingelheim, Pfizer, Astra Zeneca, Novartis and MSD. RA has received research support from Novartis, Echosens, Mayoli-Spindler. LP reports consulting fees from AbbVie, Gilead, MSD, Novo Nordisk, Ipsen. JBJ has received consulting fees from Sanofi and lecture fees from Eli Lilly, Novo Nordisk, and Sanofi. SS reports speaker fees from Eli Lilly, Novo Nordisk and Sanofi. AG reports speaker fees from Abbvie and Gilead. MG received consulting fees from Novonordisk and Madrigal, and speaker fees from Novonordisk Gilead, Abbvie, IPSEN. TM has received lecture fees from Novonordisk, Gilead, MSD and Siemens, and support from Fresenius Kabi, Elivie, Asten santé, Novonordisk, and Lilly for conference attendance. AR has received support from Sanofi, Eli Lilly, Novonordisk, Amgen, Santélys, Vitalaire, Servier, Ipsen and Abbott for conference attendance. JMP received consultant fees from Gilead, NovoNordisk, Lilly, MSD, and Intercept. JB received consulting fees from Echosens, Intercept, Inventiva, Siemens, Novo Nordisk, Lilly, speaker fees from Abbvie, Gilead, Intercept, Novo Nordisk, Sanofi, Siemens, support for conference attendance from Gilead, research support from Diafir, Echosens, Gilead, Intercept, Inventiva, Ipsen, Siemens and has served on advisory panels for BMS, Intercept, Pfizer, Madrigal, MSD and Novo Nordisk.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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