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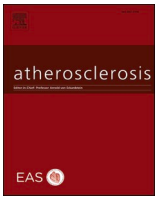

Metabolic dysfunction-associated steatotic liver disease: An opportunity for collaboration between cardiology and hepatology

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ABSTRACT

Altered metabolic function has many detrimental effects on the body that can manifest as cardiovascular and liver diseases. Traditional approaches to understanding and treating metabolic dysfunction-associated disorders have been organ-centered, leading to silo-type disease care. However, given the broad impact that systemic metabolic dysfunction has on the human body, approaches that simultaneously involve multiple medical specialists need to be developed and encouraged to optimize patient outcomes. In this review, we highlight how several of the treatments developed for cardiac care may have a beneficial effect on the liver and *vice versa*, suggesting that there is a need to target the disease process, rather than specifically target the cardiovascular or liver specific sequelae of metabolic dysfunction.

1. Introduction

Cardio-metabolic diseases are the optimal setting to explore the crosstalk between the heart and liver, and the meeting point for multidisciplinary evaluations where cardiologists and hepatologists can find common ground for collaboration. Recent research advances pave the way to a better understanding of the complex pathogenic mechanisms underlying cardiometabolic conditions and their association with cardiovascular disease. The liver is at "the core" of several metabolic disorders and the related histopathological changes range from steatosis, or non-alcoholic fatty liver disease (NAFLD), to steatohepatitis (NASH), to cirrhosis. These states are all associated with various cardiovascular ailments.

Recently, experts in the field raised concerns that the nomenclature currently in use (NAFLD) highlights what is not the root-cause of the liver ailment, rather than stressing the dysmetabolic diseases underlying this condition [1–3]. This led to an effort by multiple stakeholders to reach a consensus on changing the nomenclature and the diagnostic criteria for fatty liver infiltration. In 2023, an international working group proposed to replace NAFLD with the term metabolic dysfunction–associated steatotic liver disease (MASLD) [4]. The new definition highlights the dependence of hepatic steatosis on the presence of dysmetabolic conditions such as the metabolic syndrome, diabetes mellitus, obesity, with and without hypertension. For patients consuming more than 140–350 g/week of alcohol for women, and 210–420 g/week for men, a new nomenclature was also introduced: metabolic and alcohol related/associated liver disease (MetALD) (Fig. 1). The new nomenclature and diagnostic criteria received wide support as they do not carry the stigma attached to the word "fatty", and have important implications for patient advocacy and public health [5].

The connection among MASLD, diabetes mellitus, obesity, and cardiovascular disease lies in a pathophysiological pathway intricately entwining lipid and glucose metabolism. This interplay culminates in a prolonged systemic inflammatory state known as meta-inflammation

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(Fig. 2) [6]. The liver plays a pivotal role in preserving evolutionary interactions between immune responses and metabolism. Safeguarding this delicate equilibrium is paramount for overall health, carrying significant implications for numerous chronic non-communicable diseases.

Recently, several drugs initially designed to target specific cardiac or metabolic disorders were shown through post-marketing surveillance studies to exhibit pleiotropic effects on the liver and the heart. The discovery that these drugs may positively affect a non-target organ offered a new perspective into drug development, that in the future will likely shift towards addressing common pathogenetic mechanisms in patients with multiple comorbidities.

The aim of this narrative review is to highlight drugs that demonstrate a favorable cardiometabolic profile and discuss their potential to foster an interdisciplinary dialogue between cardiologists and hepatologists (Fig. 3). Such a collaboration holds the promise of enhancing outcomes in patients with MASLD. We will discuss which drugs cardiologists use that may enhance liver health and which drugs hepatologists use that may benefit the heart.

In view of the updated terminology and to avoid confusion induced by using too many acronyms, this review will rename the initial labeling used by the authors of manuscripts on steatotic liver disease from NAFLD, NASH and metabolic associated fatty liver disease (MAFLD), to MASLD and MASH (metabolic dysfunction-associated steatohepatitis). This choice is supported by the convincing evidence that the overlap between NAFLD and MASLD is over 95% [4,7,8].

2. What can cardiology offer hepatology?

Table 1 provides an overview of the potential impact that drugs primarily used in the cardiovascular setting can have on liver health.

2.1. Statins and bempedoic acid

Statins are at “the core” of cardiovascular disease prevention and treatment. The American Heart Association advises their use in a public health approach in all people with high cardiovascular risk [9]. Animal studies have provided some evidence that statins may improve MASLD/MASH [10–12]. Statins do not appear to reduce liver fat *per se*, but might mitigate the risk linked with MASLD through their lipid lowering, anti-inflammatory, antioxidant and anti-fibrotic effects [13,14]. In a randomized clinical trial (RCT) of 613 military personnel with MASLD/MASH randomized to either diet and exercise or one of 3 statins (atorvastatin, rosuvastatin and pitavastatin) for 1 year, treatment with statins improved both liver steatosis (measured via the MASLD activity score: NAS) and liver fibrosis (estimated with the FIB-4 score) [15]. In a Korean population study of 11,539,409 people followed for up to 6 years, treatment with statins was associated with a lower incidence of MASLD and lower progression to liver fibrosis in people who developed MASLD during follow-up [16]. It is important to note that both of these studies used non-invasive scores derived from biochemical parameters to diagnose MASLD and liver fibrosis, but no histological or imaging techniques. However, in a RCT including 1005 patients, a combination of atorvastatin 20 mg with 1 g vitamin C and 1000 IU vitamin E daily was associated with a 71% reduction in risk of hepatic steatosis compared to placebo as diagnosed by liver CT imaging [17]. Finally, among 1201 patients submitted to liver biopsy for suspected MASH, the 107 subjects receiving statins showed a dose-dependent lower risk of developing liver steatosis, steatohepatitis and liver fibrosis compared to statin naïve patients [18]. Of note, statins have been reported to reduce portal hypertension and mortality in patients with chronic liver disease [19], as well as the risk of liver cancer in patients with MASLD [20].

Although statins are recommended for the prevention of cardiovascular events in patients at risk of MASLD, including those with diabetes mellitus, obesity, and metabolic syndrome, they are under-utilized in this setting. Published evidence suggests that up to 50% of MASLD patients with a clear indication for these drugs, and 33% of those with clinical atherosclerotic cardiovascular disease do not receive statins [21,22]. While available data do not conclusively demonstrate a reduction in cardiovascular disease (CVD) mortality with statins in patients with MASLD, post-hoc analyses of RCTs suggest that the combination of statins and ezetimibe reduced CVD events in these patients [23,24]. In a post-hoc analysis of the GREACE study, that recruited 1600 patients with coronary artery disease, treatment with atorvastatin in patients with suspected MASLD was associated with a 68% relative risk reduction of recurrent CV events compared to patients with suspected MASLD who did not receive atorvastatin [23]. Of interest, patients with MASLD may derive a greater benefit from statins than people without MASLD [23,24].

Bempedoic acid reduces cholesterol levels via downregulation of ATP-citrate lyase and upregulation of AMP-activated protein kinase (AMPK). Its primary effect is the reduction of cholesterol synthesis in the liver. Reduction of gluconeogenesis and plasma levels of C-reactive protein (by AMPK activation) are additional potentially beneficial effects of bempedoic acid [25]. Data from RCTs showed that bempedoic acid can reduce LDL-C about 30% when used alone [26,27], to about 45–55%, when used in combination with ezetimibe [27], or high-intensity statins [26]. In patients with type 2 diabetes mellitus (T2DM), the cholesterol-lowering effect of bhempedoic acid is more pronounced [28]. Animal studies showed that downregulation of ATP-citrate lyase may have a role in reducing fibrosis, and progression

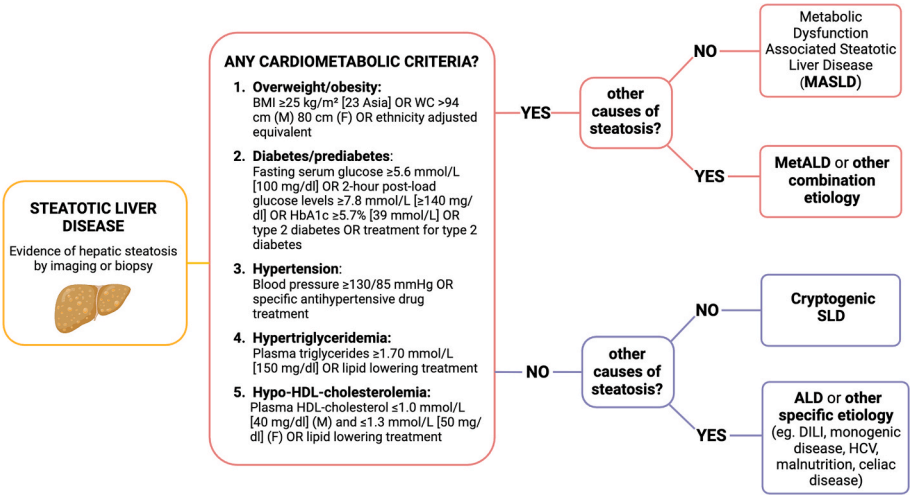

Fig. 1. New nomenclature for fatty liver disease endorsed by the American Association for the study of Liver Disease (Modified from Rinella ME et al. [4]).

of MASLD to MASH through impairment of proliferation and activation of hepatic stellate cells [29,30]. These encouraging preliminary results await confirmatory evidence in human studies [25].

2.2. Ezetimibe

Ezetimibe reduces intestinal absorption of cholesterol [31] and has an additive LDL-C lowering effect when added to statins, with reduction in cardiovascular events [32]. In an early study, ezetimibe in combination with a low-fat diet reduced visceral adipose tissue, intrahepatic triglycerides and serum markers of inflammation in obese patients with insulin resistance and presumed MAFLD [33]. The impact of ezetimibe on MASLD/MASH was explored in a few post-hoc analyses of RCTs. A sub-analysis of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International trial) including 14,819 patients with a recent acute coronary syndrome, examined the effect of the combination of simvastatin + ezetimibe vs. simvastatin alone on liver fibrosis, assessed by NAFLD fibrosis score. The combination was associated with reduced risk of recurrent CV events only in patients with high NAFLD fibrosis scores, implying a protective role of ezetimibe in patients with MASLD/MASH [24]. Two RCTs specifically assessed the effect of ezetimibe in biopsy-proven MASLD/MASH [34,35]. In a trial including 32 patients, treatment with ezetimibe did not improve liver steatosis and lobular inflammation, but it was associated with reduction of liver fibrosis and ballooning [34]. In a double-blind placebo-controlled trial including 50 patients with MASH, ezetimibe was associated with reduced liver steatosis after 24 weeks of treatment, but no significant difference was observed between ezetimibe and placebo [35].

2.3. PCSK9 and its inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors interfere with the activity of PCSK9, a serine protease responsible for the regulation of the LDL-C serum levels. LDL-C binds to the LDL receptor (LDLr) on the hepatocyte membrane and the complex is then internalized in an endosome where the LDLr is normally recycled back to the hepatocyte membrane [36]. By binding to the epidermal growth factor-like repeat A domain of the LDLr, PCSK9 leads to degradation of LDLr in the lysosomes of hepatocytes. Accordingly, PCSK9 inhibition increases the number of available LDLr on the hepatocyte surface leading to a reduction in serum LDL-C level [37]. There are two distinct forms of PCSK9s: one that operates extracellularly and another that functions intracellularly. The intracellular form of this protein may influence liver steatosis by interfering with the metabolism of apolipoprotein B48, apolipoprotein-a, the fatty acid transporter CD36 (cluster of differentiation 36), and the very low-density lipoprotein receptor (VLDLr).

The effect of PCSK9 on liver steatosis and fibrosis was examined in a biopsy study of 201 patients with suspected MASH. Ruscica et al. [38] reported that circulating PCSK9 levels were associated with liver fat accumulation and correlated with the severity of steatosis, necrosis and inflammation, hepatocyte ballooning, and fibrosis stage, independent of other confounders. However, in a study of 64 patients with morbid obesity and MASLD undergoing bariatric surgery, PCSK9 mRNA was not associated with the severity of liver steatosis, lobular inflammation and hepatocellular ballooning [39]. Similarly, conflicting results were reported in other studies with both positive [38,40,41] and negative associations of PCSK9 [42] with liver steatosis.

The influence of PCSK9 inhibition on liver steatosis can be inferred

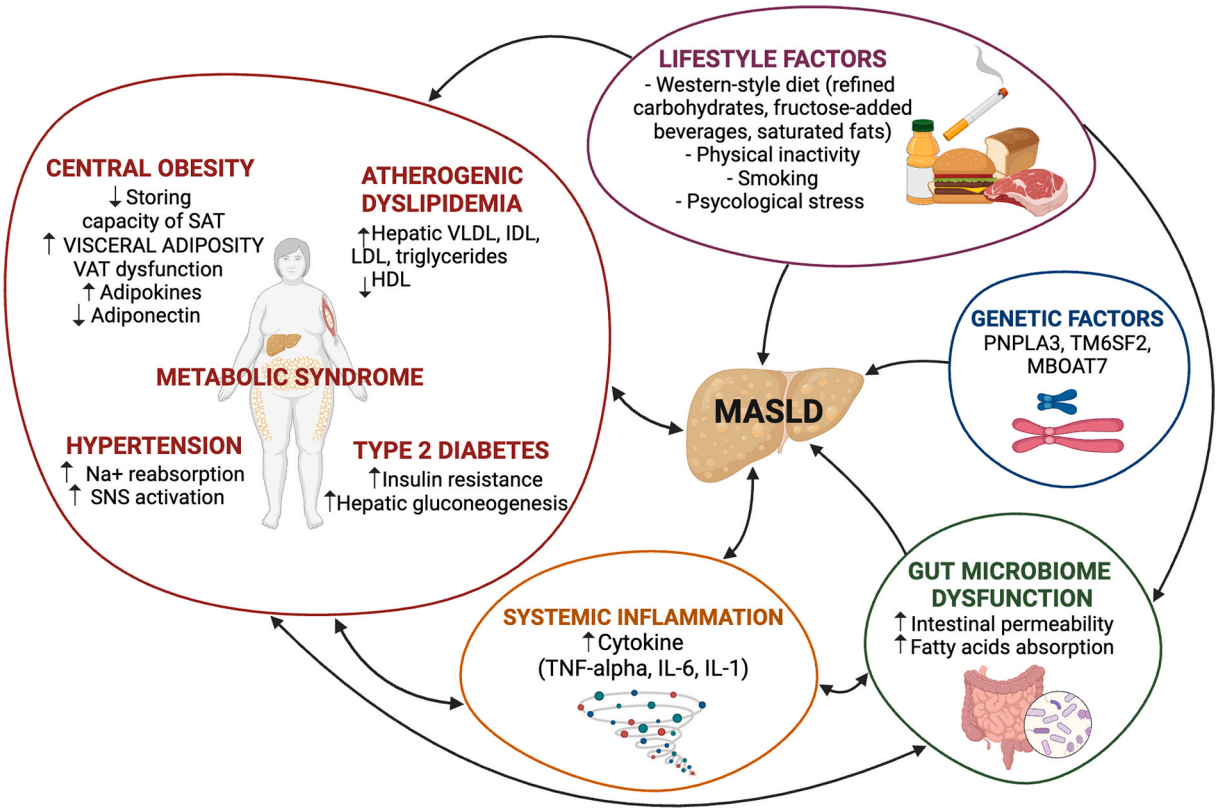

Fig. 2. Pathophysiology of metabolic dysfunction associated steatotic liver disease.
HDL high-density lipoprotein; IDL intermediate density lipoprotein; IL-1, interleukin 1; IL-6 interleukin 6; LDL low-density lipoprotein; MASLD, metabolic dysfunction associated steatotic liver disease; MBOAT7, membrane bound O-acyltransferase domain containing 7; PNPLA3, patatin like phospholipase domain containing 3; SAT, subcutaneous adipose tissue; SNS sympathetic nervous system; TM6SF2, Transmembrane 6 superfamily member 2; TNF-alpha, tumor necrosis factor alpha; VAT, visceral adipose tissue; VLDL very low-density lipoprotein.

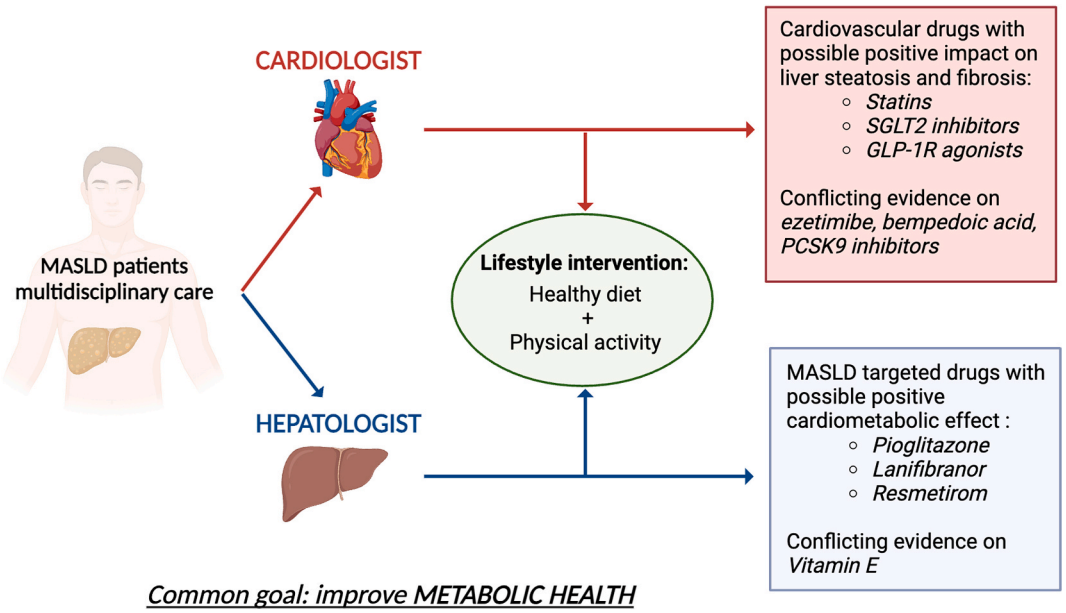

Fig. 3. A proposed shared approach to treatment of metabolic dysfunction associated steatotic liver disease by cardiology and hepatology specialists.

Table 1
Cardiovascular drugs with a potential effect on steatotic liver disease.

Medication	Class, mechanism of action	Indication	Hepatic impact in patients with MASLD/MASH and significant liver fibrosis	Cardiometabolic impact	Potential side effects
Atorvastatin, rosuvastatin, simvastatin, pitavastatin	Statins, hydroxymethylglutaryl-coenzyme A reductase	Primary and secondary cardiovascular prevention; lipid-lowering	Possible beneficial effect on liver steatosis and fibrosis	Primary and secondary prevention of cardiovascular disease, lipid-lowering, decreased incidence of the first and recurrent CV events and mortality	Muscle pain, myopathy, gastrointestinal (mild-to-moderate), flu-like symptoms; insulin resistance (?)
Bempedoic acid	ATP citrate lyase inhibitor	Primary and secondary cardiovascular prevention; lipid-lowering	No sufficient data; possible beneficial effect on liver fibrosis in animal studies	Lipid-lowering, decreased number of CV events in patients with high CV risk	Muscle pain, flu-like symptoms
Ezetimibe	Inhibition of intestinal and biliary cholesterol absorption	Primary and secondary cardiovascular prevention; lipid-lowering	Uncertain effect on liver steatosis; possible reduction of liver fibrosis in long-term use	Lipid-lowering, decreased incidence of the first and recurrent CV events and mortality when in combination with statins	Muscle pain, gastrointestinal, flu-like symptoms
Evolocumab, alirocumab	PCSK9 inhibitors	Primary and secondary cardiovascular prevention; lipid-lowering	Conflicting results on improvement of liver steatosis and liver fibrosis	Lipid-lowering, reduced risk of CV events	Flu-like symptoms, high glucose levels, pain and redness at the injection site
Dapaglifozin, empaglifozin	Sodium-glucose cotransporter 2 inhibitors	Heart failure, diabetes mellitus	May improve liver steatosis, reduction of liver aminotransferase levels	Reduces risk of clinical events in patients with chronic heart failure, regardless of ejection fraction and presence/absence of diabetes	Fatigue, polyuria, polydipsia, frequent urinary tract infections
Semaglutide	GLP-1RA	T2DM, overweight/obesity	Steatosis improvement, MASH resolution, no fibrosis improvement	Weight loss, insulin sensitivity improvement, lipid improvement, reduced MACE in people with T2DM and overweight/obesity	Gastrointestinal (mild to moderate diarrhea, nausea), pancreatitis (rare)

CV: cardiovascular. GLP-1RA: glucagon like peptide 1 receptor agonist. MASLD: metabolic dysfunction–associated steatotic liver disease. MASH: metabolic dysfunction–associated steato-hepatitis. PCSK9: Proprotein convertase subtilisin/kexin type 9. T2DM: type 2 diabetes mellitus.

from observations conducted on patients with loss-of function variants in the PCSK9 gene [43]. Grimaudo et al. examined the PCSK9 rs11591147 loss of function variant in a multicenter study of 1874 patients at risk of MASH [43]. Carriers of the mutation presented lower circulating LDL-C levels and were protected against MASLD (OR: 0.42; 95% CI: 0.22–0.81), MASH (OR: 0.48; 95% CI: 0.26–0.87) and fibrosis (OR: 0.55; 95% CI: 0.32–0.94) independent of other clinical, metabolic and genetic factors. PCSK9 hepatic expression was directly correlated with liver steatosis [44]. The PCSK9 loss of function variant described by Welty et al. in patients with hypobetalipoproteinaemia was associated with a lower risk of liver damage [45]. Other PCSK9 loss of function variants were found to be associated with increased hepatic uptake of free fatty acids and hepatic steatosis [43]. Baragetti et al. conducted a study on the loss of function R46L variant, among the 2606 patients enrolled in the PLIC (Progressione Della Lesione Intimale) study. Carriers had a larger total and android fat mass, epicardial fat thickness and a two-fold higher prevalence of hepatic steatosis [46]. However, genetic studies conducted using the UK-Biobank did not confirm that a loss of

function variant for gene PCSK9-p.Arg46Leu is associated with an increased risk of MASLD [47]. Demers et al. offered a potential explanation for these conflicting results [46]. They showed that PCSK9 mediates the degradation of CD36, a hepatocyte receptor involved in the transport of long-chain fatty acids and triglyceride storage, and thus can limit fatty acids uptake and triglyceride accumulation in the liver [48]. Accordingly, inhibition of PCSK9 could potentially increase the risk of MASLD by increasing CD36-mediated liver fat uptake.

Data on the effect of PCSK9 inhibitors in clinical practice are very limited and mainly based on presumed steatotic liver disease using serum biomarkers. Shafiq et al. performed a retrospective chart review on 29 patients treated with PCSK9 inhibitors for a mean duration of 2 years. The ALT levels decreased significantly compared to the pre-treatment period, and 73% of patients who had a radiological diagnosis of hepatic steatosis achieved resolution on imaging during treatment [49]. Scicali et al. reported an improvement of steatosis biomarkers in an observational study of 26 patients with genetically confirmed familial hypercholesterolemia and MASLD treated with a PCSK9 inhibitor [50]. The very limited data available to date do not allow us to conclude that PCSK9 inhibitors are an effective treatment option for MASLD.

2.4. Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) help improve glycemia in T2DM by promoting urinary glucose excretion, and are also beneficial for treatment of heart failure through a number of mechanisms that go beyond osmotic diuresis [51]. Dapaglifozin and empaglifozin are now recommended for the treatment of heart failure with reduced, mildly reduced or preserved ejection fraction [52], and there is a high prevalence of heart failure with preserved ejection fraction among patients with MASLD. Additionally, recent data from meta-analyses of RCTs showed that SGLT2i improve liver function parameters and metabolic outcomes among patients with MASLD and MASH. Mantovani et al. published a meta-analysis of 7 active-controlled and placebo-controlled phase-2 RCTs that employed SGLT2i (empaglifozin, dapaglifozin, canaglifozin) for the treatment of MASLD in patients with T2DM [53,54]. Compared to placebo or standard of care, treatment with SGLT2i (especially empagliflozin and dapagliflozin) was associated with a significant improvement in liver fat content in four RCTs [55–58], along with a significant reduction in body weight (~3.5 kg) and HbA1c level (~0.5%). In all RCTs, treatment with SGLT2i was also associated with a significant reduction in serum aminotransferase levels. In a meta-analysis that included a total of 839 patients with MASLD, dapaglifozin led to a greater reduction in alanine aminotransaminase, aspartate aminotransaminase, gamma-glutamyl transferase, triglycerides, body weight, body mass index, HbA1c, and fasting plasma glucose compared to standard of care [59]. Similar results were reported by Sun et al. [60].

2.5. Glucagon-like peptide-1 receptor agonists

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for treatment of T2DM and for chronic weight management in overweight and obese patients [61,62]. Among all molecules in development for treating MASH, semaglutide stands out with the most robust evidence on cardiovascular outcomes, with 2 RCTs available in patients with T2DM and obesity [63,64]. In the SUSTAIN-6 trial, targeting 2735 people with T2DM, semaglutide treatment was associated with a significant reduction in risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared to standard of care [64]. Similarly, in the recently published SELECT study, semaglutide was superior to placebo in reducing the incidence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in 1704 overweight or obese individuals with a history of cardiovascular disease but no diabetes mellitus, after a mean follow-up of 40 months [63]. Consistent with these results, two RCTs conducted in patients with MASH showed that semaglutide induced significant weight loss, and improved HbA1c, triglycerides, and LDL-C levels [65,66]. Semaglutide may exert its beneficial effects on MASLD via weight loss and increased insulin sensitivity, and the associated reduction in cytosolic lipid overload and inflammation [67]. Preclinical studies suggested a direct effect of semaglutide on liver inflammation independent of weight loss [68]. Despite the positive weight and biochemical effects, the 2 RCTs mentioned above gave conflicting results with reference to hepatic benefits of semaglutide [65,66]. Newsome et al. studied the effect of different doses of daily subcutaneous semaglutide in patients with MASH and stage 2–3 (F2–F3) liver fibrosis [65]. At 72 weeks, semaglutide 0.4 mg/daily induced MASH resolution (defined as no more than mild residual inflammatory cells infiltration and no hepatocyte ballooning) in the absence of fibrosis worsening, in 59% of the patients compared to 17% of patients receiving placebo. In contrast, Loomba et al. [66], could not confirm MASH resolution in a 48-week RCT with once-weekly semaglutide 2.4 mg in patients with cirrhosis secondary to MASH. The failure of semaglutide to achieve a significant fibrosis improvement may have been due by the relatively short duration of follow-up [65,66].

A phase 3 RCT in patients with MASLD and liver fibrosis stage F2–F3 is currently ongoing, with an interim analysis expected in the second quarter of 2024 [69]. The latest guidelines of the American Association for the Study of Liver Diseases state that semaglutide can be considered for treatment of T2DM and obesity in patients with MASH, although the drug has no proven anti-fibrotic effect [70]. Besides semaglutide, other GLP-1RAs have been tested in MASLD including liraglutide, exenatide, lixisenatide, and dulaglutide [71]. However, only liraglutide has been tested in an RCT in the setting of MASH: the LEAN trial [72]. This study, conducted on a small sample of 52 patients with biopsy-proven steatohepatitis, reported significantly greater resolution of inflammation and lower rates of liver fibrosis progression in patients taking liraglutide compared to placebo [72].

2.6. Metformin

In clinical and preclinical studies, metformin has been shown to improve markers of liver steatosis. In animal studies metformin decreased hepatic steatosis and inflammation in diet-induced obesity models [73,74], upregulated hepatic leptin receptors and decreased hepatic triglyceride content [75].

Clinical studies showed that metformin can reduce mean transaminase serum level and improve insulin sensitivity, with some patients experiencing normalization of transaminase levels and a decrease in liver volume [73]. Additionally, metformin has been associated with a decrease in hepatic steatosis index scores in patients with type 2 diabetes mellitus over a 2-year treatment period [76]. Additional preclinical studies showed that metformin can improve liver function, decrease liver collagen deposition, regulate inflammatory and oxidative stress markers in animal models of liver fibrosis [77–80], and induce apoptosis in hepatic stellate cells, that are key effector cells in the fibrogenic process [78,80]. Despite these promising findings from animal and in vitro studies, there is a lack of evidence that metformin improves liver histology in patients with MASLD and MASH. As a consequence, the American Association for the Study of Liver Diseases (AASLD) does not recommend metformin for the treatment of MASH [70].

2.7. Sulfonylureas

There is limited to no evidence linking sulfonylureas to improved liver function in MASLD. A sub-group analysis of the TOSCA.IT trial showed that indices of MASLD did not improve after treatment with sulfonylureas, in contrast to pioglitazone [81]. In a comparative study tofogliflozin led to an overall improvement in liver histology, while glimepiride improved only hepatocellular ballooning [82]. Dai et al.

showed that use of sulfonylurea was associated with an increased risk of liver fibrosis [83]. This suggests that sulfonylureas may not be the optimal choice for glycemic management in patients with MASLD due to their limited effects on liver steatosis and potential association with liver fibrosis. The American Association of Clinical Endocrinology (AACE) and AASLD do not specifically address the impact of sulfonylureas on liver fibrosis [84].

2.8. Omega-3 polyunsaturated fatty acids and fibrates

Despite a large experimental literature showing a positive effect of omega-3 polyunsaturated fatty acids and fibrates on liver enzymes and hepatic triglyceride content [85,86], there is no clinical trial evidence of either of these 2 drugs improving liver histology or outcomes in humans affected by MASL/MASH.

3. What can hepatology offer cardiology?

Lifestyle interventions such as diet and physical activity, although highly effective if sustained, are not sufficient to halt the rising tide of MASLD related morbidity and mortality [87].

3.1. Pharmacological approaches for treating MASLD

To date, there is no officially approved drug to specifically target MASLD. However, vitamin E and pioglitazone have been recommended for treating MASH [88]. In addition, several novel therapeutic molecules have reached phase-3 clinical trial stage for treating MASLD; the most promising are resmetirom, lanifibranor and FGF21 inhibitors [89]. Prioritizing drugs with additional cardiovascular benefits appears to be an important consideration for the MASLD population, where cardiovascular disease is the leading cause of mortality [90]. Table 2 provides an overview of the hepatic and cardiovascular effects of these drugs.

3.2. Vitamin E

Vitamin E is a liposoluble antioxidant that contributes to cellular signaling and regulates gene expression, exhibiting anti-inflammatory and anti-apoptotic properties [91]. In two RCTs, administration of 800 IU of vitamin E daily resulted in greater MASH resolution, defined as reduction in steatohepatitis and inflammation compared to placebo, in both adults and children [88,92]. Similarly, in another clinical trial targeting HIV patients with MASLD, vitamin E treatment decreased liver enzymes and improved hepatic steatosis and hepatocyte apoptosis [93]. However, none of these studies demonstrated a beneficial effect of vitamin E on liver fibrosis, and current hepatology guidelines recommend its use only as a short-term therapeutic option for patients with MASLD and no diabetes, at risk of rapidly progressing disease [70,93,94]. Given the central role of oxidative stress in atherosclerosis, several studies have investigated the antioxidant properties of vitamin E in cardiovascular disease, with mixed results [95]. An association between low vitamin E levels and cardiovascular events was reported in several observational studies [96–98]. Patients supplemented with vitamin E appeared to have a lower incidence of myocardial infarction and angina [99], as well as a reduced risk of all-cause mortality and mortality from coronary artery disease [100]. However, subsequent interventional studies yielded mixed results, with some reporting a protective effect on cardiovascular events [101–104], and others failing to show a significant benefit [105–108]. Along the same lines, a metanalysis on this topic produced inconclusive results [95]. This may reflect the high heterogeneity of the RCTs investigating this drug, in which different doses of vitamin E were administered, no baseline vitamin E levels were obtained, and heterogeneous populations were included. Overall, vitamin E has a good safety profile. Although some authors warned of a possible association between vitamin E and bleeding disorders, particularly hemorrhagic stroke [109], this evidence was not confirmed in a recent metanalysis [110]. Similarly, a possible association with prostate cancer has been suggested but not proven [111].

3.3. Peroxisome proliferator-activated receptors (PPARs) ligands

Pioglitazone is a thiazolidinedione that binds to the peroxisome proliferator-activated receptors gamma (PPARγ) and is approved for the treatment of T2DM [112]. By activating PPARγ, it improves insulin resistance, inflammation, and lipid metabolism [113]. Consistent with its biological mechanisms, initial evidence showed a beneficial effect on MASH histology [114]. However, in the PIVENS trial, targeting 247 patients with MASH with or without T2DM, pioglitazone did not meet the pre-specified primary endpoint, despite some improvement in hepatic steatosis and inflammation [88]. In a subsequent 18-month RCT, pioglitazone achieved ≥2-point reduction in NAS (NAFLD Activity Score: steatosis, inflammation, hepatocyte ballooning), with a trend toward regression of fibrosis compared to placebo [115]. Two recent meta-analyses concluded that pioglitazone is superior to placebo in achieving both MASH resolution and 1-stage improvement in fibrosis [116,117]. Observational studies [118,119], RCTs [120] and metanalyses [121,122], as well as imaging studies [123–125], have supported the beneficial cardiovascular effects of pioglitazone. Despite this promising evidence, pioglitazone is no longer commonly used in diabetes care and is not currently being studied in any phase 3 RCTs. This is likely due to its side effect profile that include weight gain and fluid retention that can lead to heart failure exacerbation, bone loss with increased risk of fractures, and a controversial risk of bladder cancer [126].

Table 2
MASH-targeted drugs and their potential cardiometabolic effect.

Medication	Class, mechanism of action	Indication	Hepatic impact in patients with MASLD/MASH and significant liver fibrosis	Cardiometabolic effect	Potential side effects
Vitamin E	Fat soluble vitamin	NA	Steatosis improvement, MASH resolution, no fibrosis improvement	Conflicting evidence on cardiovascular outcomes	Hemorrhagic stroke? Prostate cancer?
Pioglitazone	PPARγ agonist	T2DM	Steatosis improvement, MASH resolution, fibrosis improvement?	Weight gain, insulin sensitivity improvement, lipid profile improvement, reduced atherosclerosis progression, reduced MACE in people with T2DM	Weight gain, heart failure exacerbation in patients with heart failure, bone loss, bladder cancer?
Lanifibranor	Pan-PPAR agonist	NA	Steatosis improvement, MASH resolution, fibrosis improvement	Lipid profile improvement	Diarrhea, nausea, peripheral edema, anemia
Resmetirom	THR-β agonist	NA	steatosis improvement, fibrosis improvement, MASH resolution	Lipid profile improvement	Gastrointestinal (mild to moderate diarrhea, nausea).

MACE: major adverse cardiovascular event. MASLD: metabolic dysfunction–associated steatotic liver disease. MASH: metabolic dysfunction–associated steatohepatitis. PPAR: peroxisome proliferator-activated receptor ligand. THR-β: beta thyroid hormone receptor. T2DM: type 2 diabetes mellitus.

Another PPAR agonist, lanifibranor, has shown promising results in MASH trials by simultaneously improving adipogenesis, inflammation and fibrosis [127], and unlike pioglitazone, it has progressed to phase 3 RCTs. Lanifibranor is an oral pan-PPAR agonist that targets PPARα, PPARδ and PPARγ [127]. In the phase 2b NATIVE trial, lanifibranor achieved both MASH resolution and improvement of ≥1 fibrosis stage [127]. In the ongoing phase 3 RCT, NATiV3, 1000 patients with MASH and F2–F3 liver fibrosis will be randomized to lanifibranor versus placebo to assess steatohepatitis resolution and fibrosis improvement [128]. Lanifibranor increases HDL cholesterol levels and reduces triglyceride and HbA1c levels compared to placebo [127]. It also induces a dose-dependent increase in serum adiponectin levels, suggesting a beneficial modulation of adipose tissue function. Despite the reported weight gain, patients taking lanifibranor showed improvement in MASH histology [127]. Of interest, lanifibranor induced weight gain appears to be a result of body fat remodeling, with a shift from visceral to metabolically healthy subcutaneous adipose tissue [127]. This effect, previously observed with pioglitazone [129], aligns with evidence that adipose tissue dysfunction and visceral adiposity, rather than obesity *per se*, play a central role in MASH [130].

3.4. Beta thyroid hormone receptor (THR-β) activators

The beta thyroid hormone receptor (THR-β) is emerging as a promising pharmacological target for the treatment of fibrosis in MASH. Frequently disrupted and downregulated in this condition, THR-β has demonstrated a pivotal role in regulating liver metabolic and fibrogenic pathways [131]. Resmetirom is an oral, liver-targeted, selective THR- β agonist, currently standing as the front runner for FDA approval in MASH therapy. After a successful phase 2 RCT, showing reduction of liver fat content at 12 weeks and the resolution of MASH at 36 weeks in 84 patients with biopsy-proven MASH [132], resmetirom has progressed to four phase 3 RCTs: MAESTRO-NAFLD-1 and its extension MAESTRO-NAFLD-OLE in patients with presumed MASH; MAESTRO-NASH in patients with biopsy-proven MASH and significant fibrosis; and MAESTRO-NASH-OUTCOMES in patients with MASH and biopsy proven compensated cirrhosis [133]. The first 52-week interim analyses of MAESTRO-NAFLD-1 and MAESTRO-NASH trials showed that resmetirom reduced hepatic fat with little effect on liver fibrosis [134] and good MASH resolution with ≥1 stage fibrosis improvement [135]. Notably, in these RCTs resmeritom exhibited a favorable effect on atherogenic particles, with significant reduction in LDL-C, apolipoprotein B, triglycerides, as well as apolipoprotein CIII, lipoprotein(a), remnant-cholesterol, and very low-density lipoprotein cholesterol compared to placebo [134,135]. Resmetirom appears to be safe, with no increase in serious treatment-emergent adverse events [132,134]. The most common side effects reported were diarrhea and nausea of mild to moderate intensity, occurring at the start of treatment and lasting approximately 2 weeks [132,134].

4. Summary

This narrative review discussed emerging and established therapies that may offer a clinical advantage in the management of both cardiac and hepatic diseases. The new classification of steatotic liver disease stresses the importance of metabolic pathways as the etiologic factors underlying the development of fatty liver with untoward cardiovascular outcomes.

In this manuscript we aimed to introduce metabolic health as the goal of therapy. This construct considers the net patients' advantage with regards to multiple metabolic parameters captured by body composition data (BMI, visceral and liver fat accumulation), lipid fractions, glycemia, insulin resistance, kidney function and bone turnover. The pathway to improve metabolic health includes first and foremost lifestyle interventions, followed by the introduction of drugs that may offer pleiotropic activity in different disease states, as is the case for the drugs mentioned in this review. In this scenario, the focus is not the treatment of single morbidities but rather the simultaneous treatment of multiple comorbidities. The drugs discussed likely act on common inflammatory pathways that are at the core of multiple comorbidities and aging. Therapy should also target liver fibrosis, since several studies showed that all-cause mortality (mostly driven by cardiovascular disease) increases proportionally with the increase in liver fibrosis stage [136].

This review suggests that cardiometabolic conditions should be approached with a cascade of care from primary prevention to treatment of advanced disease. Some of the authors of this review are neither cardiologists nor hepatologists, but rather infectious disease experts in HIV disease. People living with HIV often face multiple aging-related morbidities and are affected by frailty, seeking care in specialized clinics designed to facilitate a multidisciplinary holistic approach that addresses their diverse health needs across various dimensions. Metabolic health is not just the absence of metabolic diseases but rather a road map for healthy living. This perspective paves the way to a patient centered model of care in which the goal of treatment is the improvement of health-related quality of life and wellness in general. Such an approach would break down barriers between personalized medicine and the current standard of care.

Primary care providers play a crucial role in increasing awareness and engaging vulnerable individuals in a new care model, fostering collaboration between hospital consultants and general practitioners to achieve shared objectives. This goal can be achieved through various avenues, including: [a] organizing educational meetings that delve into local epidemiology, clinical presentations, and treatment opportunities; [b] utilizing electronic health records accessible to multiple stakeholders to coordinate medical care; and [c] empowering patients to advocate for and adopt healthy living practices. This interdisciplinary dialogue offers an opportunity to deliver comprehensive management of MASLD, considering both the multiple comorbidities and the overall metabolic health of the individual.

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