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Metabolism and Target Organ Damage

Review

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Metabolic dysfunction-associated steatotic liver disease throughout the liver transplant cycle: a comprehensive review

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing in global prevalence and becoming a leading indication for liver transplantation (LT). The management of MASLD has been well-studied in the pre-LT setting, and we are entering into a golden era of pharmacologic options designed to resolve steatohepatitis and reverse fibrosis. However, the implications of MASLD on organ allocation, risk of post-LT recurrence, and optimal post-LT management remain topics of ongoing investigation. One such unique challenge is the growing necessity to use steatotic organs to address the shortage of available organs for all waitlisted patients, while ensuring acceptable outcomes through careful case selection. Additionally, how best to screen, diagnose, and manage post-LT graft steatosis remains an ongoing topic of debate, given the high rates of recurrence or *de novo* occurrence in patients transplanted for non-MASLD-related etiologies of liver disease. This comprehensive review explores the impact of MASLD across the disease continuum, given it is a chronic illness with a complex pathophysiology and is influenced by other comorbidities and certain medications.

Keywords: MASLD, MASH, liver transplant, graft steatosis

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its more inflammatory and sinister

form metabolic dysfunction-associated steatohepatitis (MASH) are increasingly common etiologies of liver disease worldwide[1]. First reported in 1980[2], the diseases were originally termed non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). While previously a diagnosis of exclusion, its complex pathophysiology and association with the metabolic syndrome [MetS, including obesity, diabetes, hypertension, and/or hyperlipidemia (HLD)] have prompted a shift in nomenclature that more aptly describes the disease and is less stigmatizing to patients[3,4].

While an extensive discussion of biochemical processes underlying MASLD is beyond the scope of this review, the disease is an important example of ectopic fat deposition related to excessive free fatty acids (FFA). These FFAs can be metabolized to lipotoxic products, which create oxidative and inflammatory stress in hepatocytes, leading to steatohepatitis, fibrogenesis, and DNA damage with potential carcinogenesis. Ultimately, patients are at risk of developing cirrhosis and sequelae of portal hypertension, as well as hepatocellular carcinoma (HCC). Liver transplantation (LT) may become necessary for many patients and MASH has become a leading indication[5], particularly with declining rates of hepatitis C[6].

Given its commonality, clinicians should understand the management and implications of MASLD both pre- and post-transplantation. This review provides a comprehensive framework to highlight current challenges and future opportunities to optimize patient care throughout the disease lifecycle.

PREVENTION OF FIBROSIS IN PRE-TRANSPLANT MASLD

Fibrosis and its prognostic implications

Fibrosis is the principal driver of adverse outcomes in MASLD[7,8]. In particular, patients with MASH and at least stage 2 fibrosis are referred to as the "at-risk" group, given they develop higher rates of liver-related morbidity and mortality[8,9]. Rates of fibrosis progression are variable and influenced by underlying genetic factors and comorbid disease control. Prior meta-analysis has shown that MASH progressed one stage per 7 years, while MASLD progressed only one stage per 14 years[10]. However, a more recent Swedish cohort using paired biopsies showed that over a median of 3.4 years, 30.4% of patients had progression of disease[11]. Concerningly, there is a subset of approximately 20% of MASLD patients who rapidly progress from an absence of fibrosis to advanced fibrosis within 5-6 years or develop cirrhosis from bridging fibrosis within a year[10,12]. While identification of this subset of patients is paramount, predictive tools have remained elusive. However, a recent study utilizing machine learning built a model with commonly available clinical data to predict patients at risk for fast progression[13]. Whether this can be commercially deployed to improve clinician identification and management of these high-risk patients remains unclear at this time.

Key points:

- Patients with MASH and ≥ F2s are "at risk" for liver-related morbidity and mortality

- Progression of fibrosis is variable; identifying rapid progressors is an unmet need

Non-pharmaceutical therapeutic options

An initial absence of effective pharmaceutical options for MASLD led to an emphasis on weight loss, physical activity, and optimization of risk factors to improve outcomes [Figure 1]. Patients with MASLD benefit from even small amounts of weight loss. Steatosis improves with a 3%-5% weight reduction, but at least 10% weight loss is generally required to improve steatohepatitis and fibrosis[14-17]. Even with lifestyle modification or dietary interventions, achieving these goals remains a challenge as only about 1/3 of patients achieve ≥ 5% weight loss[18]. Furthermore, maintenance of weight loss is difficult for some patients, as 21% of

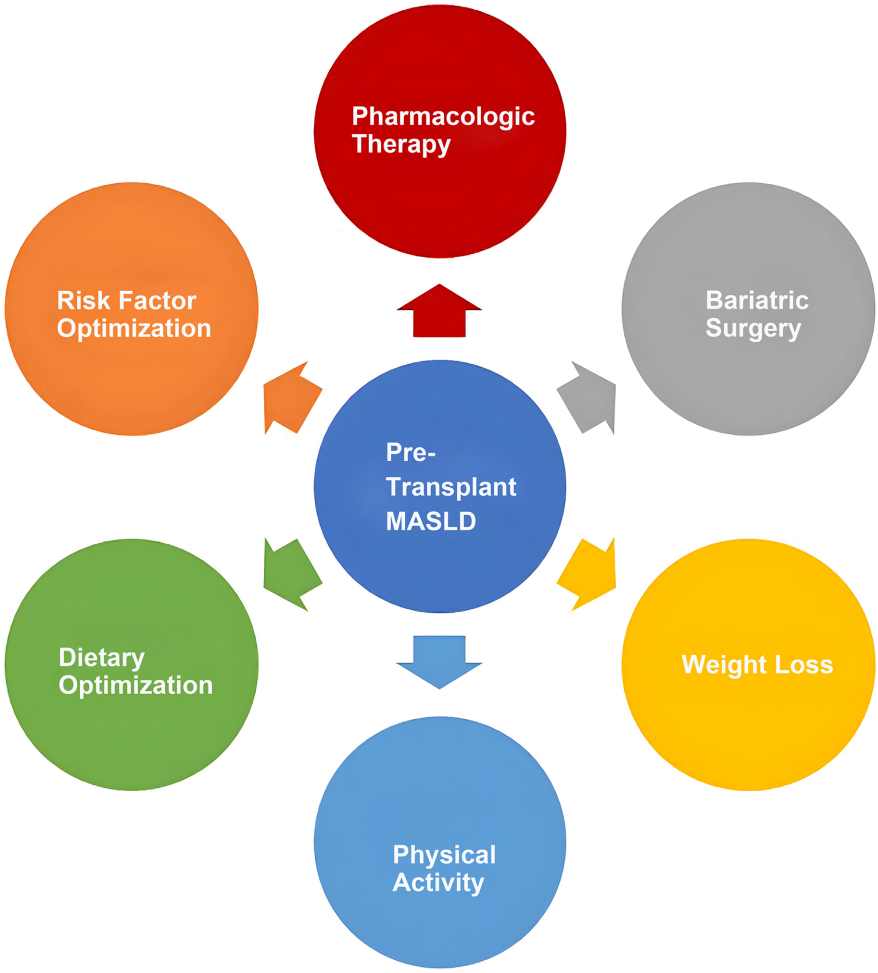

Figure 1. Multifactorial treatment of pre-transplant MASLD. Increased physical activity and optimization of both diet and medical comorbidities are universally recommended. Patients with non-lean MASLD should aim for at least 5%-10% weight loss. Pharmacologic therapeutic options are continuing to expand with the recent approval of a MASH-specific option (resmetirom). Endoscopic bariatric therapies and bariatric surgery represent invasive but effective modalities to achieve significant weight loss and improve metabolic comorbidities. MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis.

patients regain the weight up to nearly 3 years later[18]. Physical exercise is also recommended as a therapeutic modality for MASLD, with at least moderate intensity exercise being shown efficacious in preventing its occurrence or reducing hepatic fat[19,20]. However, higher-intensity exercise may be necessary to reduce fibrosis[21]. For patients with impaired cardiorespiratory fitness, significant arthritis, or orthopedic limitations, resistance exercise has been shown to be similarly effective at reducing hepatic steatosis as aerobic exercise[22].

In the clinic, patients often ask about optimal dietary composition to help achieve weight loss and improve liver health in MASLD. As detailed in Table 1, certain foods have been studied explicitly in association with MASLD. Overall, black coffee and nuts have beneficial effects, whereas excessive red meat, fructose-containing products, and processed foods are harmful[23-35]. A Mediterranean-style diet encompasses many of these principles, promoting a predominantly plant-based diet (with fish as an additional source of protein), including fruits and vegetables, whole grains, and unsaturated fats. Following a Mediterranean diet has been shown to improve MASLD-related steatosis and fibrosis as well as decrease risks of HCC and liver-

Table 1. Dietary therapy for MASLD

Food/Diet	Benefits	Risks/Caveats	Societal concordance?	References
Coffee	Lowers the risk of MASLD, fibrosis/cirrhosis, HCC	Unknown effects of milk (cow or non-dairy variants), creamers (natural or artificially sweetened)	Yes	[23-28,34]
Nuts	Lower the risk of MASLD	-	Not addressed	[29-31]
Red meat	-	Increased risk of MASLD, increased risk of liver cancer and liver-related mortality, development of insulin resistance	Only addressed by EASL guidelines	[32,34]
Fructose-containing beverages and foods	-	Increased risk of MASLD, fibrosis	Yes	[33,34]
Processed foods	-	Increased risk of MASLD	Yes*	[34,35]
Alcohol	None†	Recent studies suggest increased fibrosis and progression to advanced liver disease	Yes‡	[34,35,38-46]

*Not addressed by AASLD or ESPEN; †Recent evidence suggests no safe amount as there is a dose-dependent increase in fibrosis and at-risk MASH; ‡No safe amount is recommended. ESPEN and APASL espouse abstinence in all patients, whereas AASLD and EASL have the strongest recommendation in patients with baseline moderate to heavy use and in those with at least significant fibrosis. MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; HCC: hepatocellular carcinoma; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; ESPEN: European Society for Clinical Nutrition and Metabolism; APASL: Asian Pacific Association for the Study of the Liver.

related death[36]. A drawback, though, is that there is significant socioeconomic variability with access to and affordability of fresh and healthy foods[37]. To counter this, providers should partner with nutrition experts to help patients find local sources and cost-conscious shopping lists and recipes to promote dietary adherence. Popular commercialized diets such as high-protein diets, high-carbohydrate/low-fat diets, low-carbohydrate/high-fat diets, and intermittent calorie restriction have shown short-term success in limited studies in MASLD patients[36]. However, their long-term liver-related benefits, safety, and sustainability remain unproven, and thus, they are not currently recommended in clinical guidelines.

The effects of light to moderate alcohol use in MASLD have been debated over time[38-45]. Recent evidence, though, including a large international study, suggests any amount of alcohol is harmful and is associated with worsened fibrosis and progression to advanced liver disease[46]. Multiple societal guidelines generally advise against alcohol use in all patients with MASLD, but with particular emphasis on those with moderate to heavy use and/or significant fibrosis (defined as Stage 2 or higher)[34,35,47,48].

Key points:

· Weight loss of at least 3%-5% is beneficial but challenging for many patients to achieve and maintain

· Patients should be encouraged to minimize consumption of processed and fructose-containing foods

· A diet low in carbohydrates and saturated fats, with intake of fiber and unsaturated fats, should be instituted with dietician assistance to ensure practical implementation

Pharmaceutical therapeutic options

Initial options for MASLD were limited and several novel agents studied in clinical trials over the past decade produced disappointing results. However, multiple off-label therapies have literature to support their use in MASLD/MASH and are included in various societal guideline recommendations [Table 2]. An over-the-counter option is vitamin E, which is supported by data from a randomized controlled trial (RCT; PIVENS trial) suggesting that 800 international units daily in non-diabetic patients improved steatosis, inflammation, and hepatic ballooning, as well as induced MASH resolution in an additional 15% of patients

Table 2. Assessment of pharmacologic therapy for MASLD

Agent	Mechanism of action	Pros	Cons	Societal endorsement?	FDA approved[*] ?	References
Vitamin E	Antioxidant	Improves steatosis, inflammation, MASH resolution rate *vs.* placebo Reduces risk of death or transplant and hepatic decompensation in ≥ F3 MASH Cheap, OTC	RCT excluded patients with diabetes Long-term outcome study was single-center and retrospective Lack of antifibrotic effect Possible increase in mortality, hemorrhagic stroke, prostate cancer	Yes: ESPEN Equivocal: AASLD, APASL, EASL	No	[49-53]
Metformin	Insulin sensitizer, decreased hepatic glucose production	Possible benefit in patients with T2DM and MASLD - reducing HCC risk and prolonging HCC survival	Does not improve histology	Yes: APASL (T2DM, MASLD, and HCC) No: AASLD, EASL	No	[54,55]
Pioglitazone	PPARγ agonist	Improves histology and insulin resistance Possible antifibrotic effect CV risk reduction	Unfavorable side effects - weight gain, edema, osteoporosis, heart failure exacerbation	Yes: AASLD (T2DM) Equivocal: EASL	No	[49,56-58]
Liraglutide	GLP-1 receptor agonist	Improves steatosis, insulin sensitivity, weight loss CV risk reduction Slows renal disease	GI side effects, gallstones, pancreatitis Lack of antifibrotic effect	Not explicitly addressed	No	[59]
Semaglutide	GLP-1 receptor agonist	Improves steatosis, inflammation, insulin sensitivity, weight loss, increases MASH resolution CV risk reduction Slows renal disease	GI side effects, gallstones, pancreatitis Unconfirmed antifibrotic effect[†]	Yes: AASLD (T2DM, obesity)	No	[60-64,66]
Tirzepatide	GLP-1 receptor agonist + GIP receptor agonist	Improves steatosis, insulin sensitivity, weight loss	GI side effects, gallstones, pancreatitis	Not explicitly addressed	No	[65]
Resmetirom	β-selective thyroid hormone receptor agonist	Increased MASH resolution, antifibrotic effect Improves LDL levels	GI side effects Less clinical experience, expensive	Not explicitly addressed	Yes	[68]

[*]Approved indication specifically for patients with MASLD/MASH; [†]Await published data from ESSENCE phase 3 trial. CV: Cardiovascular; F3: stage 3 fibrosis; GLP-1: glucose-like peptide-1; GI: gastrointestinal; GIP: glucose-dependent insulinotropic polypeptide; HCC: hepatocellular carcinoma; LDL: low-density lipoprotein; OTC: over-the-counter; PPAR: peroxisome proliferator-activated receptor; T2DM: type 2 diabetes mellitus; MASLD: metabolic dysfunction-associated steatotic liver disease; FDA: Food and Drug Administration; RCT: randomized controlled trial; EASL: European Association for the Study of the Liver; MASH: metabolic dysfunction-associated steatohepatitis; AASLD: American Association for the Study of Liver Diseases; ESPEN: European Society for Clinical Nutrition and Metabolism; APASL: Asian Pacific Association for the Study of the Liver.

compared to placebo[49]. Additionally, a retrospective, single-center study demonstrated a long-term reduction in the risk of death or transplant and hepatic decompensation in patients with MASH and advanced fibrosis or cirrhosis[50]. Given no proven antifibrotic effect and some long-term safety concerns regarding increased mortality, hemorrhagic stroke, and prostate cancers in males[51-53], it is important to counsel patients on the risks and benefits of vitamin E.

Insulin sensitizers are commonly utilized in patients with MASLD. Metformin is a first-line oral diabetic agent, but it lacks efficacy in improving hepatic histology. However, it may provide a survival benefit, reduce decompensating events, and prevent HCC in certain patients[54,55]. In contrast, the thiazolidinedione pioglitazone has demonstrated benefits in improving MASH histology and insulin resistance, as well as possibly fibrosis, but its use is limited by unfavorable side effects[49,56-58].

Glucagon-like peptide 1 receptor agonists (GLP1-RAs) are increasingly popular agents for patients with metabolic disease, given their glycemic benefits, induction of weight loss, and improvements in cardiovascular outcomes. Though not presently approved by the Food and Drug Administration (FDA) for MASLD and MASH, there is growing clinical experience and outcome data to support their efficacy in non-cirrhotic patients. Liraglutide was shown in a RCT with MASH to induce a 30% absolute improvement in the rate of MASH resolution, with improvement in some metabolic parameters, including weight loss and hemoglobin A1c[59]. Compared to liraglutide, the GLP1-RA agonist semaglutide has more potent metabolic effects in patients with obesity and type 2 diabetes mellitus (T2DM)[60,61], and also has been studied in patients with MASH. Semaglutide improves steatosis, induces weight loss (up to 12.5%), and appears to induce MASH resolution at rates far superior to placebo. However, its antifibrotic and antilipidemic effects have previously been reported to be modest[62,63]. A confirmatory Phase 3 trial (ESSENCE) is investigating the effect of semaglutide 2.4 mg once weekly (*vs.* placebo) in patients with "at-risk" MASH[64]. While final results are unpublished, preliminary data for semaglutide appear favorable with regard to reduction in MASH and fibrosis and submission for FDA approval is anticipated in 2025. Finally, the newer agent tirzepatide, which is a combination GLP1-RA and glucose-dependent insulinotropic polypeptide (GIP) agonist, was recently shown in a phase 2 RCT to improve MASH resolution rates compared to placebo and was generally well tolerated without significant discontinuation rates[65]. Tirzepatide also appeared to have some antifibrotic effect, although the study was not powered to formally assess this outcome. While promising, further study is required to confirm tirzepatide as an efficacious therapeutic option for MASH.

While GLP1-RAs may provide metabolic benefits in patients with compensated MASH cirrhosis, their efficacy for key endpoints including resolution of histologic inflammation and reduction of fibrosis is presently unproven[66]. Clinicians should exercise caution with GLP1-RAs in cirrhosis, as excessive weight loss may predispose to decompensation and/or exacerbate malnutrition[67]. It is advisable to discontinue GLP1-RA use if decompensation occurs.

Most recently, the β-selective thyroid hormone agonist resmetirom received FDA approval in March 2024 for patients with MASH and moderate to advanced fibrosis. Its approval was based on a phase 3 study demonstrating a 2-3-fold improvement in MASH resolution and 10% absolute improvement in rates of fibrosis improvement by at least one stage. Resmetirom improved low-density lipoprotein levels and was generally well-tolerated[68]. Long-term studies remain ongoing to demonstrate sustained efficacy and reduce liver-related adverse events.

The pharmacologic landscape for MASH is likely to change over the next several years. Numerous novel agents targeting various inflammatory and fibrinogenic pathways have been investigated in both phase 2 and 3 studies, with the anticipated approval of several agents over the next few years[69]. Nonetheless, approval of therapies has historically been difficult given the need to demonstrate improvements in surrogate outcomes for conditional approval and show evidence of long-term clinical outcome benefits for final approval[69]. A summary of the near-term MASH drug pipeline is summarized in Table 3. While exciting, significant therapeutic costs are a concern and need to be carefully evaluated in the context of expected benefits[70].

Key points:

· Many off-label therapies have been studied in MASLD/MASH, although robust antifibrotic effects are limited

Table 3. Near-term MASH drug pipeline

Mechanism of action	Drug	Route of administration	Current trial phase	Clinical endpoints
THR-β agonist	Resmetirom	Oral	FDA Approved (conditional); LTO trial ongoing	MASH resolution or fibrosis improvement
FXR agonist	Obeticholic acid	Oral	Rejected by FDA	MASH resolution or fibrosis improvement
Pan-PPAR agonist	Lanifibranor	Oral	Phase 3, LTO trial ongoing	MASH resolution and fibrosis improvement
GLP-1 receptor agonist	Semaglutide	Subcutaneous	Phase 3, LTO trial ongoing	MASH resolution or fibrosis improvement
FGF21	Efruxifermin Pegozafermin	Subcutaneous Subcutaneous	Phase 3, starting soon (both agents)	MASH resolution or fibrosis improvement (both)
SCD-1 inhibitor	Aramchol	Oral	Phase 3, on hold	NASH resolution or fibrosis improvement

FDA: Food and Drug Administration; FGF21: fibroblast growth factor 21; FXR: farnesoid X receptor; GLP-1: glucagon-like peptide 1; LTO: long-term outcome; MASH: metabolic dysfunction-associated steatohepatitis; PPAR: peroxisome proliferator-activated receptor; SCD-1: stearoyl-coenzyme A desaturase 1; THR-β: thyroid hormone receptor beta; NASH: non-alcoholic steatohepatitis.

· GLP1-RA use in patients with obesity or T2DM and non-cirrhotic MASH appears favorable, although its effect on reducing MALO is unclear

· Resmetirom, a β-selective thyroid hormone agonist, is the first FDA-approved therapy for patients with F2-F3 MASH; longitudinal studies are ongoing to confirm the long-term benefit

BARIATRIC SURGERY IN PRE-TRANSPLANT MASLD

Lifestyle optimization and medical therapy for MASLD play a central role in its management but may be inadequate to prevent disease progression in certain patients. Bariatric surgery is an effective management option for patients with excess body weight and diabetes[71-78]. Given many bariatric patients have concurrent MASLD, there is increasing interest in the effects of surgical weight loss on liver histology and disease progression. Two procedures dominate the current bariatric surgery landscape: sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). The former is a restrictive procedure aimed at reducing gastric capacity and reducing ghrelin secretion, an appetite-stimulating hormone[79]. In contrast, RYGB enables unimpeded delivery of nutrients to the hindgut, bypassing foregut metabolism and thus reducing insulin resistance, modulating gut hormonal pathways, and altering the microbiome[79].

As seen in Table 4, several studies have investigated the effect of various bariatric surgery modalities on MASH resolution and fibrosis regression[80-82]. Overall, bariatric surgery is highly effective at inducing the resolution of MASH and at least moderately effective at improving (or resolving) fibrosis. However, each of these studies has limitations, and unanswered questions include the optimal surgical technique, relative efficacy and safety compared to medical therapies (particularly the GLP1-RAs), and their effect in reducing MALO in the long term.

Importantly, bariatric surgery may also be an option for selected patients with compensated cirrhosis, particularly when performed at high-volume centers[83]. A small single-center study noted a loss of nearly 2/3 of excess weight at up to 3-year follow-up. While there was an elevated complication rate of 34.8%, no patient developed hepatic decompensation[84]. Whether pre-transplant bariatric surgery alters post-transplant outcomes is unsettled. Lower body mass index (BMI) at the time of transplant reduces wound complications and recurrent MASH[85]. One small study of cirrhotic patients with a history of bariatric

Table 4. Selected literature on bariatric surgery in MASLD

Study (Ref.)	N	Study design	Intervention	Primary outcome	Findings	Limitations
Lassailly 2020[80]	180	SC, PC	Bariatric surgery	MASH resolution without worsening of fibrosis at 5 years*	84% of patients met the primary outcome 70% of patients had regression of fibrosis - a median of 1.5 stages Patients with AF had less robust response	Variable surgical procedures over time Few patients with cirrhosis Lack of safety data
Pais 2022[81]	66	MC, RC	Bariatric surgery (SG or RYGB)	Not explicitly defined but likely MASH resolution without worsening of fibrosis*	74% had MASH resolution without fibrosis progression 70% had ≥ 1 stage or fibrosis regression AF persisted in 47% of patients	Small cohort - only 66/196 had follow-up biopsy data Variable follow-up Only studied patients with "severe MASH" - AF or high activity
Verrastro 2023[82]	288	MC, RCT	Bariatric surgery (SG or RYGB) *vs.* lifestyle modification/medical care	MASH resolution without worsening of fibrosis at 1 year*	Bariatric surgery superior for the primary outcome (56%-57% *vs.* 16% in ITT; 70% *vs.* 19% in PP) Bariatric surgery induced more fibrosis regression and improved glycemic control, dyslipidemia, and weight loss Low adverse event rate with bariatric surgery	All study patients were Caucasian Non-surgical arm was intensely monitored and liraglutide permitted (semaglutide and tirzepatide not available) Duration of benefits unknown given the short follow-up

*Biopsy-proven. AF: Advanced fibrosis; ITT: intention-to-treat; MC: multicenter; PC: prospective cohort; PP: per-protocol; RC: retrospective cohort; RCT: randomized controlled trial; RYGB: roux-en-y-gastric bypass; SC: single-center; SG: sleeve gastrectomy; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis.

surgery (mean of 11.6 years prior; mean BMI 31 kg/m^2 at transplant) noted a high reoperation rate (36.4%) but similar survival to patients without a history of bariatric surgery[86]. However, a limitation was that long-term post-transplant metabolic outcomes were not measured. In contrast, a matched case-control study found that patients with a history of bariatric surgery (median time of 7 year from surgery to LT, mean loss of 130lbs, the predominant procedure was RYGB) had a higher risk of delisting or waitlist death in the bariatric surgery group[87]. These findings were attributed to malnutrition and sarcopenia. Thus, while bariatric surgery offers potential benefits in carefully selected patients, its effects may become detrimental as patients develop decompensation and require further investigation. Furthermore, the optimal surgical modality (i.e., SG *vs.* RYGB) in the pre-transplant MASLD population has not yet been firmly established, although the discontinuous anatomy (more difficult biliary access) and potential decrease in immunosuppressant absorption that result from RYGB are significant drawbacks[88,89].

Bariatric surgery is typically avoided in patients with decompensated cirrhosis due to significantly longer hospital stays and increased mortality[83]. However, there is growing interest in performing bariatric surgery concurrently with LT. A recent survey of transplant surgeons indicated a preference for this simultaneous approach over performing bariatric surgery prior to LT[89]. An early case report of gastric band placement was successful, with the authors reporting 30 min of additional surgical time, a 45% reduction in excess total body weight, and significant improvement or resolution of multiple metabolic-related comorbidities[90]. In contrast, SG has been the predominant procedure performed as an "add-on" procedure during LT in subsequent literature. While the overall number of patients undergoing simultaneous LT + SG remains small across a few case series and a Mayo Clinic cohort, there appears to be an

improvement in metabolic comorbidities and a reduction in weight loss[91-94]. Interestingly, operative time increased by only 38 min, although adverse events include a staple line leak, excessive weight loss, and severe acid reflux[93,94]. Despite these encouraging results, further experience is required to understand which patients are specifically at increased risk for complications. Additionally, long-term outcome studies demonstrating a decreased risk of recurrent MASH in patients undergoing simultaneous LT + SG are needed.

Key points:

· Bariatric surgery is highly effective at inducing weight loss and MASH resolution; it also has antifibrotic benefits in many patients (particularly if baseline ≤ F2)

· The optimal surgical procedure (SG *vs.* RYGB) for MASH-related outcomes is unclear and should be a mutual patient-physician decision

· Bariatric surgery is reasonable to consider in selected patients with compensated cirrhosis

· Simultaneous LT + SG is an emerging consideration in patients with obesity and/or MASH-related cirrhosis but requires further validation in larger studies

ENDOSCOPIC BARIATRIC MODALITIES IN PRE-TRANSPLANT MASLD

Endoscopic bariatric and metabolic therapies may induce weight loss, alter neurohormonal signaling, and improve insulin resistance[95]. Most widely available are intragastric balloons (IGB), which are space-occupying devices that have been FDA-approved for patients with class I obesity (BMI 30-35 kg/m^2 and at least one related complication or class II obesity (BMI 35-39.9 kg/m^2)[96]. However, endoscopic sleeve gastroplasty (ESG) has gained popularity in recent years and utilizes a proprietary endoscopic suturing system to reduce gastric volume by inducing a tubular shape to the stomach, mimicking that of a laparoscopic SG[97].

Literature on endobariatric modalities in MASLD is growing but not explicitly addressed in current societal guidelines [Table 5][98-102]. There is a consistent induction of total body weight loss (TBWL) > 10% with both the IGB and ESG, which surpasses the established threshold necessary to produce an antifibrotic effect in MASLD. Unfortunately, several studies utilized biomarker-based non-invasive tests (NITs) to assess reductions in steatosis and fibrosis[99-101], which are less reliable than elastography or biopsy. Despite a lack of long-term outcome data and FDA approval specifically for MASLD, endobariatric interventions appear fairly safe and may represent either bridge (IGB) or definitive therapy (ESG) for certain patients. However, practical considerations such as cost, physician reimbursement, access to local expertise, and insurance coverage currently limit widespread use. Further research is required to confirm long-term efficacy and their role as adjunctive therapies to optimize surgical candidacy before LT.

Key points:

· Endobariatric modalities (IGB and ESG) promote > 10% weight loss in most patients and short-term results suggest improvements in metabolic and MASLD parameters

· Long-term outcomes, safety data, and improved access are required before they can be strongly recommended as an alternative to medical and surgical therapies for MASLD

Table 5. Selected literature on endobariatrics in MASLD

Study (Ref.)	N	Study design	Intervention	Primary outcome (s)	Findings	Limitations
Aoko 2024[98]	911	SR/MA	IGB (6 months)	Change in NAS score and liver enzymes	NAS reduction at 6 months (2 studies) Reduction of liver enzymes (16 studies) and A1c (9 studies) Uncertain effect on fibrosis (3 studies)* Induced weight loss (18 studies)	Heterogenous studies Limited assessment of fibrosis Long-term outcomes unknown
Espinet-Coll 2019[99]	30	SC, PC	IGB (1 year) *vs.* ESG	Undefined	Mean TBWL 16% Improved NIT of fibrosis Improved insulin resistance No major adverse events	Small study VCTE or biopsy not utilized Long-term outcomes unknown
Jagtap 2021[100]	26	SC, PC	ESG	Change in ALT, steatosis, and fibrosis at 6 and 12 months*	Improvement in all primary outcomes at both 6 and 12 months Mean TBWL 18%	Small study VCTE or biopsy not utilized Long-term outcomes unknown
Hajifathalian 2021[101]	118	SC, PC	ESG	Change in insulin resistance, steatosis, and fibrosis at 2 year*	Improved insulin resistance, steatosis, and fibrosis* Mean TBWL 16%	Biopsy or VCTE not utilized to confirm reductions in steatosis or fibrosis Longer-term outcomes unknown 16% loss-to-follow-up at 2 year
Bazerbachi 2021[102]	21	SC, PC	IGB	Change in NAS score and fibrosis at 6 months	NAS reduction in 90% Decrease in fibrosis by 1.17 stages in 15% Mean TBWL 12%	Long-term outcomes unknown Homogenous study population

*Non-invasive testing was used. ESG: Endoscopic sleeve gastroplasty; IGB: intragastric balloon; NAS: NAFLD activity score; PC: prospective cohort; SC: single-center; SR/MA: systematic review/meta-analysis; TBWL: total body weight loss; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: non-alcoholic fatty liver disease NIT: non-invasive test; VCTE: vibration-controlled transient elastography; ALT: alanine aminotransferase.

SARCOPENIA, FRAILTY AND LIVER TRANSPLANT OUTCOMES IN PATIENTS WITH MASH

Sarcopenia, the loss of skeletal muscle mass and function, is part of the natural aging process but is also present at higher rates in patients with obesity, as well as MASLD and MASH[103,104]. Its pathophysiology is complex and detailed discussion is beyond the scope of this review. Nonetheless, the development of sarcopenia is multifactorial, involving contributions from reactive oxygen species, DNA damage, chronic inflammation, decreased protein synthesis and increased degradation, hormonal dysregulation, nutritional deficiency, and physical inactivity[105]. While sarcopenia can be non-invasively assessed through bioimpedance, dual-energy X-ray absorptiometry (DEXA), or cross-sectional imaging[106], there is a lack of consensus definition in the literature. Additionally, only one major societal guideline (ESPEN) provides direct recommendations with regard to sarcopenia and MASLD[47].

A recent study utilizing the National Health and Nutrition Examination Surveys (NHANES) and linked mortality dataset found that patients with MASLD and sarcopenia had a 25% increase in mortality over a mean of 24 years and higher rates of advanced fibrosis[104]. In contrast, a single-center retrospective study found only frailty, but not sarcopenia, predictive of LT waitlist outcomes in patients with MASH[107]. The association between frailty and waitlist mortality was confirmed in a multicentric American cohort[108], although interestingly, this association was independent of the etiology of liver disease[109]. In summary, while sarcopenia can be concurrent or precede the development of frailty, it is the latter that ultimately predicts waitlist mortality. Clinicians should routinely screen for sarcopenia and frailty in patients with MASLD/MASH, particularly in patients under evaluation and listed for transplant [Figure 2]. Early identification and intervention may help optimize patient outcomes.

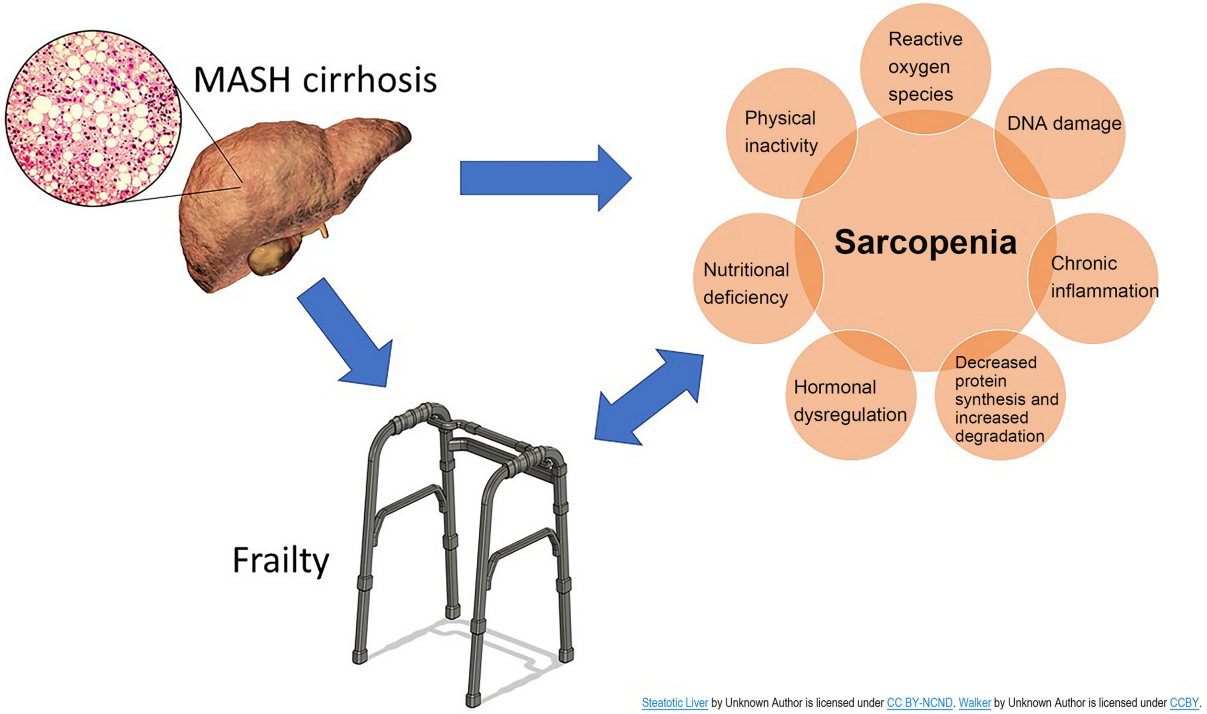

Figure 2. Relationship between MASH cirrhosis, sarcopenia and frailty. Steatotic liver by Unknown Author, licensed under . Walker by Unknown Author, licensed under . MASH: Metabolic dysfunction-associated steatohepatitis.

In patients with MASH who ultimately undergo a transplant, outcomes, fortunately, are comparable to other etiologies across multiple studies[5,110-112]. Additionally, a meta-analysis of 15 studies demonstrated similar post-LT survival between MASH and non-MASH patients, including no increased risk of cardiovascular-related deaths[113]. Higher Model for End-Stage Liver Disease (MELD) scores in MASH patients predicted worse survival, although specific demographic and comorbid conditions were not predictive. This finding requires further investigation but could be interpreted as MASH patients being less tolerant to post-LT complications given their advanced age at transplant and higher risk for renal dysfunction. A separate meta-analysis provides evidence to this theory as higher recipient age and pre-LT T2DM were both independent risk factors for post-LT mortality in MASH patients[114].

Weight at transplant has variable effects on patient outcomes. In a single-center study of > 1,000 LT recipients, a higher BMI (> 35 kg/m^2) increased the risk of wound infections, whereas malnourished patients with a BMI < 16 kg/m^2 had more postoperative infections in general[115]. Another retrospective study did not find an association between BMI and graft survival. However, each 1 kg/m^2 rise in BMI was associated with a 3% increase in biliary complications and a low BMI (< 18.5 kg/m^2) increased the risk of hepatic artery thrombosis[116]. Nonetheless, both studies acknowledge that weight itself may not be the most important factor in influencing LT complications and long-term outcomes. Instead, the degree of sarcopenia and severity of malnutrition likely play a significant role[115,116].

Key points:

· Sarcopenia is common in patients with MASLD, but pre-LT outcomes are predominantly tied to frailty

· Transplant outcomes in MASH are similar to other etiologies of liver disease; extremes of weight increase postoperative infection risk

IMPACT AND UTILIZATION OF STEATOTIC GRAFTS IN LT

There exists a severe mismatch between organ supply and demand for LT, leading to significant waitlist mortality[117]. Patients with MASH are particularly vulnerable to this disparity. Despite a higher burden of portal hypertension-related complications and lower MELD scores (given disproportionally slower declines in hepatic synthetic function compared to other etiologies of liver disease)[118,119], waitlist mortality is increased in patients with MASH cirrhosis compared to other etiology of liver disease[118,120] The long-term clinical consequences of their comorbid conditions and accumulating frailty may make certain patients "too sick" for transplant. In the absence of a living donor, the current acuity circle-based allocation system in the United States may disadvantage patients with MASH. Whether the revised MELD 3.0 score, which now incorporates serum albumin and patient sex as model variables[121], will ultimately improve transplant equity for this population in the United States is yet unknown. Thus, novel approaches to increase organ access include consideration of steatotic grafts [Figure 3].

Attempts to mitigate the organ shortage include the use of "marginal" deceased donor grafts, which are organs from donors conferring an increased risk of graft and patient survival. One of these risk factors is graft steatosis, which is a frequent finding during procurement, given the rising prevalence of MASLD[122]. Historical data suggest that the presence of any microvesicular steatosis or < 30% macrovesicular steatosis does not affect post-transplant outcomes[123-125]. In contrast, the use of organs with > 30% macrosteatosis may be more susceptible to ischemia and reperfusion injury, conferring a higher risk of primary graft nonfunction[124,125]. About 25% of discarded donor livers are due to significant macrosteatosis[126]. However, macrosteatotic graft utilization has risen over the past two decades by 15%[127]. While a recent Scientific Registry of Transplant Recipients (SRTR) registry study showed a hazard ratio for graft failure of 1.53 for highly steatotic livers, the authors noted that they were being disproportionally discarded relative to the expected risk[128]. Their concern is supported by other literature, which has shown that when other risk factors for graft loss are mitigated (i.e., long cold ischemia time, donor age, *etc.*), outcomes of highly steatotic grafts may be non-inferior to non-steatotic grafts in select individuals[127].

Another strategy with increasing interest and already employed by some transplant centers is normothermic machine perfusion (NMP), which can utilize defatting agents[129]. Although expensive and requiring personnel with expertise in operating the device, NMP helps keep the liver metabolically active to reduce cold ischemia time. This homeostatic mimicry may reduce the risk of ischemia-reperfusion injury. A small case series of 14 grafts demonstrated the potential of NMP to increase recovery rates of steatotic liver grafts, although optimal NMP timing and organ viability assessment remain undefined[130]. More research, experience, and cost reduction are required before this strategy becomes the standard of care in LT.

An additional alternative to the use of a "marginal" deceased donor graft is living donor liver transplant (LDLT). This technique is gaining popularity in the United States but is the predominant modality of LT in several countries, including East Asia[131]. Biliary complications are more common in LDLT (15%-60%) compared to deceased donation after brain death (DBD) donors[131], although long-term outcomes with modern techniques and surgeon experience are now similar to recipients of DBD organs[132]. However, the high prevalence of hepatic steatosis in the general population represents a potential threat to the donor pool. Some transplant centers decline donors with > 10% macrosteatosis, but this may be overly restrictive if other important characteristics associated with outcomes (such as graft to recipient body weight ratio and future liver remnant) are optimized. In well-selected individuals, LD grafts with up to 20% macrosteatosis may

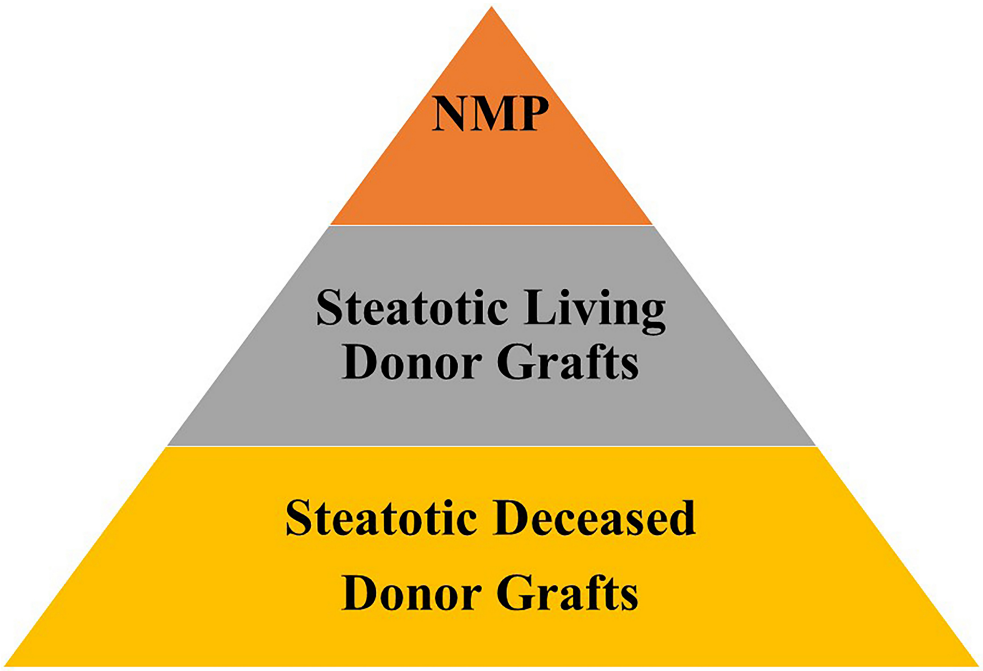

Figure 3. Currently employed strategies to maximize utilization of steatotic liver grafts. NMP: Normothermic regional perfusion.

produce non-inferior outcomes relative to LD grafts with < 10% macrosteatosis[133]. However, further multi-center study is required before considering the widespread adoption of this practice.

A rising concern has also been the standardization of defining macrosteatosis in potential donor livers. The Banff Working Group on Liver Allograft Pathology addressed this problem with consensus recommendations in 2022, seeking to standardize the approach to biopsy evaluation and definition of how to report macrosteatosis (given its relationship to allograft dysfunction)[134]. In addition, evaluation of donor steatosis may rely on some subjective components, including surgeon visual inspection (either direct or review of varying quality photographs) of the graft and consideration of other donor clinical factors such as BMI, comorbid conditions, and history of underlying liver disease, leading to non-utilization of certain grafts[135]. A wider application of the consensus definition of macrosteatosis is needed to ensure uniform practices in organ assessment to improve both discard rates as well as patient outcomes.

Key points:

· Strategies to improve organ access include the use of macrosteatotic liver grafts, machine perfusion, and living donation

· Further research is needed to understand the range of acceptable graft macrosteatosis to increase utilization rates of both deceased and living donor grafts

RECURRENT AND *DE NOVO* MASH IN THE POST-TRANSPLANT SETTING

Incidence

Development of graft steatosis after LT is common and may occur in as little as three weeks[136]. This is particularly concerning, as post-LT steatosis can lead to hepatic fibrosis within 2 years[136]. In patients transplanted for MASH, recurrent steatotic liver disease may occur in 40%-59% of patients at 1 year[137,138]. The overall prevalence of recurrent hepatic steatosis post-LT is increasing with time, with an 11% rise per

decade, and is most problematic in North America compared to Europe or Asia[137]. However, patients transplanted for non-MASH-related etiologies of liver disease can also develop *de novo* graft steatosis. Estimates vary depending on the study and methodology, as well as the subtype of steatosis. Rates of *de novo* MASLD reach nearly 78% by 5 years, with *de novo* MASH occurring in only 17% of patients[138]. At least moderate fibrosis may be present in > 40% of patients[136,139], placing afflicted patients at risk of progressing to cirrhosis of their graft.

Key point:

· Steatosis of liver grafts is common and may occur in patients transplanted for MASH at an accelerated rate

Risk factors

Multiple risk factors for recurrent or *de novo* MASLD have been identified and are remarkably similar to those that contribute to pre-LT MASLD. The most consistently reported risk factors include the presence of metabolic comorbidities (diabetes mellitus, hypertension, HLD), elevated BMI, donor graft steatosis, post-LT weight gain, and use of sirolimus for immunosuppression[137-139]. In a single study looking at risk factors for the development of *de novo* MASLD 5 years after LT, male sex, obesity, MetS, and new-onset diabetes mellitus were all independently predictive in multivariate analysis[136]. Pre-transplant MASLD confers a 5-fold risk for post-transplant steatosis, with alcohol-associated liver disease and chronic hepatitis C being associated with only a 2.5-fold and 2-fold risk, respectively[137]. Genetic influences, including specific polymorphisms in the *PNPLA3* gene and *TM6SF2*, confer increased risk if present[137]. For example, the presence of the *PNPLA3 rs738498-G* variant in both the donor and recipient led to a 27-fold increased risk of graft steatosis[140]. Similarly, recipients with the minor allele form of *ADIPOR1 rs10920533* have more severe post-LT MASLD. Conversely, the same study found that donors with the *rs4880-A* polymorphism of *superoxide dismutase-2* led are protective against post-LT steatosis[141]. While interesting from a research perspective, testing for the aforementioned polymorphisms is not routine in clinical practice, given a lack of available gene-modifying therapies.

Another driver of post-LT MASLD is exposure to immunosuppressive agents with unfavorable metabolic consequences, as summarized in Table 6[142]. Of note, corticosteroids promote gluconeogenesis and free-fatty acid uptake, reduce insulin production, and decrease lipoprotein lipase (LPL) activity, leading to impaired triglyceride degradation[142]. However, most patients can be weaned off corticosteroids within 90 days, with a minority of transplant centers practicing steroid-free protocols. In contrast to corticosteroids, however, CNIs are typically the backbone of post-LT immunosuppression, and thus, patients have chronic exposure. These agents increase gluconeogenesis, reduce bile acid synthesis from cholesterol (thus resulting in excessive cholesterol levels), and reduce pancreatic beta cell proliferation and survival[142]. Mammalian target of rapamycin inhibitors (mTORis) represent another class of immunosuppressants, which are sometimes used in post-LT patients for their renoprotective and antitumor effects. While not explicitly diabetogenic, mTORis are strongly associated with HLD related to the downregulation of LPL activity and increased adipose tissue lipase activity[142]. Current American Association for the Study of Liver Diseases (AASLD) and American Society of Transplantation (AST) guidelines do not explicitly recommend a preferred immunosuppression strategy to reduce post-LT MASLD but acknowledge the importance of avoiding excessive weight gain and controlling metabolic comorbidities[143]. Immunosuppression in patients should be routinely reviewed and minimized when possible.

Key points:

· Steroids, CNIs, and mTORis commonly used in LT recipients have negative metabolic consequences

Table 6. Metabolic effects of common immunosuppressants

Medication	Hypertension	Dyslipidemia	Diabetes mellitus	Weight gain
Cyclosporine	↑↑	↑↑	↑	↑
Tacrolimus	↑↑	↑	↑↑	↑
mTORi	-	↑↑↑	↑	-
Mycophenolate	-	-	-	-
Corticosteroids	↑↑	↑↑	↑↑↑	↑

↑: Increases risk; -: no significant effect. mTORi: Mammalian target of rapamycin inhibitor (i.e., sirolimus, everolimus).

· Reduction in immunosuppression over time may improve metabolic health

Diagnosis of post-LT MASLD

While significant graft steatosis can be easily identified using ultrasound or contrast-enhanced cross-sectional imaging, the assessment of fibrosis with these modalities remains limited until advanced disease is present. Accurately staging fibrosis provides vital prognostic information as allograft fibrosis is associated with decreased graft survival and increased need for retransplantation[144]. Elevated liver enzymes are common in the post-LT setting and may be secondary to various inflammatory insults, including (but not limited to) cellular or antibody-mediated rejection, vascular issues, biliary complications, infectious etiologies, toxic exposures (including medications), and recurrence of pre-LT disease. However, their elevation does not necessarily correlate with hepatic fibrosis[144]. Liver biopsy is often performed if the etiology remains unclear or to confirm suspected acute or chronic rejection. Biopsy is favored earlier in the post-LT timeframe when the differential diagnosis is broader, but in patients otherwise doing well, particularly several years out from transplant on stable doses of immunosuppression, the probability of post-LT MASLD rises. Given the high incidence, liver biopsy may not always be necessary or practical despite remaining the gold standard assessment.

When either recurrent or *de novo* MASLD is suspected, it is important to confirm a diagnosis to avoid unnecessary additional workup and an inappropriate empiric increase in immunosuppression. Various modalities have been investigated, but each has its own strengths and weaknesses, as detailed in Table 7. Serum-based NITs are well-validated for MASLD in the pre-LT setting, but their utility post-LT is less well-established[145]. While easy to calculate, the aspartate aminotransferase-to-platelet ratio (APRI) and the fibrosis-4 score (FIB-4) demonstrate modest positive predictive values but high negative predictive values[146-148]. Changes in these scores over time predict graft loss and death[148], although their dependence on platelet levels is a significant drawback. Many patients post-LT continue to have thrombocytopenia despite improvement in portal hypertension, which may lead to an overestimation of fibrosis by these scores[149].

Other NITs have also been investigated in LT recipients. Vibration-controlled transient elastography (VCTE) is widely available and part of the recommended care pathway by AASLD and European Association for the Study of the Liver (EASL) for patients with suspected MASLD[34,48,150]. Its use in post-LT patients is validated and superior to serum-based NITs[145,151], albeit with smaller sample sizes[152]. Shear wave elastography (SWE) is a modality similar to VCTE that utilizes ultrasound technology to estimate fibrosis and is favored by radiologists. While not as widely available as VCTE, SWE demonstrated reasonable performance in ruling out significant fibrosis in a cohort of post-LT patients with corresponding liver biopsy[153]. However, it is important to note that the generalizability of the prior study is limited by a relatively limited number of MASH patients. Magnetic resonance elastography (MRE) has demonstrated utility in diagnosing advanced fibrosis[145,154], but its use is limited by availability, cost, and uncertain ability to detect earlier stages of fibrosis.

Table 7. Comparison of diagnostic modalities for post-LT MASLD

Modality	Availability	Cost	Utility	Limitations	References
Liver-associated enzymes	+++	$	+	(1) Non-specific (2) Poor correlation with fibrosis	[144]
Imaging*	+++	$$-$$$	++	(1) Variable US interpretation (2) Cannot assess for early fibrosis	-
Biomarker-based NITs†	+++	$-$$	+	(3) Platelet levels unreliable (4) FibroSure® and ELF™ not validated in post-LT setting	[145-149]
Elastography‡	++/+++	$$	+++	(1) Invalid in certain patients	[34,45,145,150-153]
MRE	+	$$$	++	(1) Less studied (2) Uncertain diagnostic accuracy for early fibrosis	[145,154]
Biopsy	+++	$$	+++	(1) Sampling error (2) Risk of procedural complications	-

*Includes ultrasound, CT and MRI; †Includes APRI, FIB-4, FibroTest™/FibroSure®, ELF™ test; ‡Includes VCTE and SWE. ELF: Enhanced liver fibrosis; LT: liver transplantation; MRE: magnetic-resonance elastography; NIT: non-invasive test; US: ultrasound; FIB-4: fibrosis-4 score; APRI: aminotransferase-to-platelet ratio; SWE: shear wave elastography; VCTE: vibration-controlled transient elastography; MASLD: metabolic dysfunction-associated steatotic liver disease.

Key points:

· Diagnosis of post-LT MASLD requires confirmation of graft steatosis and ruling out other causes of elevated liver enzymes, including rejection

· Key limitations of non-invasive testing in the post-LT population include less robust data, difficulty in diagnosing early fibrosis, and overestimation of fibrosis if platelet levels are chronically suppressed

TREATMENT OF THE METS AND MASLD AFTER LIVER TRANSPLANT

Post-transplant MetS is common, with rates of up to 90% rate in patients with prior MASH-associated cirrhosis[155]. In particular, LT recipients are at increased risk for *de novo* hypertension, HLD, and diabetes mellitus[143]. These conditions are associated with early atherosclerotic changes and cardiac dysfunction[156], with a long-term risk of clinically significant coronary heart disease[157]. Initial management is focused on the optimization of metabolic comorbidities, with specific strategies shown in Table 8[89-94,143,158-170].

Given that CNI and mTORi use contribute significantly to the development or exacerbation of MetS and MASLD, reduction in immunosuppression (as tolerated) is generally favored in the long term. Pharmacologic knowledge is also important, particularly with regard to HLD management. Both cyclosporine and certain statins (atorvastatin, fluvastatin, lovastatin, and simvastatin) are heavily metabolized by the cytochrome 450 system, leading to elevated serum statin concentrations and a higher risk of myopathy or elevated liver enzymes[159]. Thus, the selection of a hydrophilic statin (pravastatin or rosuvastatin) and/or the use of tacrolimus or a mTORi is preferable.

The use of GLP1-RAs in the post-LT population is becoming commonplace, although evidence for their benefits is primarily derived from kidney transplant recipients. As a class, GLP1-RAs do not require immunosuppression adjustments[166,167] and are associated with a reduction in the rate of estimated glomerular filtration rate loss as well as cardiovascular events, both of which are major sources of morbidity and mortality in LT recpients[164]. The specific agent dulaglutide has been shown to induce weight loss and decrease exogenous insulin requirement[165]. Further research is needed, including experience specifically in LT recipients, but current extrapolation from kidney transplant populations appears reasonable given similar metabolic profiles and even higher dose immunosuppression regimens.

Table 8. Post-LT metabolic comorbidity management

Metabolic condition	Targets	Preferred agent(s)	Comments	References
Hypertension	BP < 130/80	Amlodipine - counteracts CNI-induced renal vasoconstriction ACEi/ARBs – preferred if DM, CKD, and/or proteinuria present	Good control reduces mortality and CV events	[143,158]
Hyperlipidemia	LDL < 100 TG < 150	Elevated LDL or mixed hyperlipidemia - statins preferred; ezetimibe as adjunctive or monotherapy if statin intolerance Isolated hypertriglyceridemia - fish oil, fibrates*	Reduction of dietary saturated and trans fats, alcohol abstinence recommended Certain statins significantly interact with cyclosporine† Check lipids before starting mTORi	[143,157,159]
Diabetes Mellitus	A1c < 7%	Immediately post-LT - insulin Later - metformin, DPP-4i, SGLT2i, GLP1-RAs	Insulin allows for pancreatic β-islet cell rest	[143,160-167]
Obesity	Patient-specific weight loss goals	Diet, exercise GLP1-RAs Bariatric surgery	GLP1-RA use offers renoprotective and CV benefits‡ The optimal timing of bariatric surgery (simultaneous with LT *vs.* delayed) is unclear. SG preferred over RYGB to avoid malabsorption and preserve conventional biliary access	[89-94,143]

*Requires careful monitoring, given interaction with CNI and increased risk of myopathy when combined with statin; †Statins heavily metabolized by cytochrome 450 system: atorvastatin, fluvastatin, lovastatin, simvastatin; ‡Evidence derived from kidney transplant recipients. ACEi: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; CKD: chronic kidney disease; CV: cardiovascular; DM: diabetes mellitus; DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP1-RA: glucose-like peptide-1 receptor agonist; LDL: low-density lipoprotein; LT: liver transplantation; mTORi: mammalian target of rapamycin inhibitor; RYGB: Roux-en-Y gastric bypass; SG: sleeve gastrectomy; SGLT2i: sodium-glucose cotransporter-2 inhibitor; TG: triglycerides; CNI: calcineurin inhibitor.

Bariatric surgery after LT is also another strategy to address obesity, the MetS and potentially prevent the development of either recurrent or *de novo* MASLD. A small matched case-control study of post-LT patients undergoing SG demonstrated a 44% remission rate of diabetes and similar reductions in hypertension, sleep apnea, and HLD. No difference in immunosuppression pharmacokinetics was detected in the pre- and post-SG periods. However, there was a high incidence of postoperative malnutrition complications (25%) requiring balloon dilatation or gastrostomy tube placement[168]. Though the metabolic effects from this study were encouraging, follow-up duration was variable and there was no investigation into the prevention of recurrent or *de novo* MASH. A small single-center cohort of 15 patients (all but one had pre-LT MASH) who underwent SG a median of > 2 years post-LT also reported excess body weight loss of 51.5% after a year. Patients had improvement in some metabolic parameters, particularly reduced insulin requirement, and only one patient had a complication (surgical site infection). The authors noted an early reduction in tacrolimus levels, but this was attributed more to immediate post-surgical side effects, as the levels improved further over time and no patient developed allograft rejection[169]. Other low-quality evidence for post-LT bariatric surgery includes multiple small case reports or retrospective cohorts utilizing a variety of techniques. The excess body weight loss is comparable to the aforementioned studies, but several studies reported fatalities and specific investigation into rates of post-LT MASH were lacking[170]. In summary, post-LT bariatric surgery may be an efficacious treatment modality for obesity and MetS, but careful patient selection is required to mitigate the increased risk of adverse events compared to the non-transplant population. Furthermore, long-term outcomes of post-LT bariatric surgery on the reduction of MASLD/MASH rates are needed.

Key points:

· Optimization of metabolic comorbidities is key and may require a combination of directed medical therapies and immunosuppression adjustment

· Experience with GLP1-RAs in the post-LT population is increasing and potential benefits appear promising

· Bariatric surgery after LT may offer metabolic and weight loss benefits, although the long-term effects on reducing MASLD/MASH are unknown

CONCLUSION

The prevalence of MASLD is predicted to continue growing, with parallel increases in MASH, advanced fibrosis and cirrhosis. The development of portal hypertension and/or HCC in many patients will necessitate transplant consideration and medical providers will need to be adept at managing MASLD and its associated metabolic comorbidities in both the pre- and post-LT setting. The burgeoning MASLD epidemic also impacts the potential donor pool of organs and strategies designed to optimize organ procurement and minimize reperfusion injury will continue to be an ongoing area of focus in the years to come. Further study into MASLD and its implications throughout the transplant lifecycle is required to address this public health problem to ensure excellent patient outcomes while maintaining financial solvency.

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Authors' contributions

The author contributed solely to the article.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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