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Review

# MASLD and Liver Transplantation: Clinical Challenges, Systemic Complications, and Emerging Role of GLP-1 Receptor Agonists

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**Abstract**

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease worldwide, affecting approximately 30% of the global population, with prevalence reaching up to 50% in certain regions. Its burden is expected to rise in the coming years, primarily due to its potential to progress to liver cirrhosis and ultimately lead to liver transplantation. MASLD has emerged as one of the leading indications for liver transplantation globally, placing its management at the forefront of liver transplant care. Encouraging results from ongoing clinical trials suggest the potential to mitigate the global impact of MASLD in the near future. Glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated promising efficacy in the management of MASLD and are likely to receive approval for its direct treatment. Their beneficial effects on adiposity, along with their ability to reduce cardiovascular and renal burden, further enhance their therapeutic value. Additionally, their potential application in liver transplant settings is gaining increasing attention. In this narrative review, we explore the rising impact of MASLD within transplant medicine, its interplay with metabolic comorbidities, and the emerging utility of GLP-1 receptor agonists in liver transplantation care.

**Keywords:** MASLD, MASH, cirrhosis, fibrosis, liver transplantation, GLP-1

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most prevalent chronic liver disease worldwide, affecting an estimated 30% of the global population.[1] In the Middle East, the prevalence of MASLD is notably elevated, with rates reaching as high as 40%.[2] In Türkiye, prevalence rates as high as 50% have been previously reported in the general population, with a tendency to increase over the years.[3,4] In Germany, the prevalence of MASLD is currently estimated at around 23%; however, it is projected to double by 2030.[5] Moreover, the economic burden of MASLD continues to grow, largely driven by increasing rates of liver-related complications.[6] It should be noted that in patients with MASLD, cirrhosis is not a prerequisite for the development of hepatocellular carcinoma.[7] Despite this, the disease remains underdiagnosed in countries like Germany, highlighting the urgent need for improved early detection strategies and timely intervention to mitigate associated risks.[6] Moreover, since compensated cirrhosis can remain asymptomatic until decompensation occurs, timely detection of the disease and

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management of it are crucial. A German study from 2023 reported that 16% of patients with cirrhosis experienced decompensation within three years, leading to increased healthcare resource utilization and costs. However, only a small proportion of these patients received definitive treatments such as liver transplantation or transjugular intrahepatic portosystemic shunt.[8]

Beyond its rising prevalence, the burden of MASLD is also increasing. According to the U.S. liver transplantation registry, MASLD is now the leading indication for liver transplantation among patients with hepatocellular carcinoma who are on the waiting list.[9] According to recent analyses, MASLD and alcoholic liver disease have become the predominant indications for liver transplantation in both Europe and the United States, reflecting a rising trend in both regions.[10] Likewise, the number of patients with decompensated cirrhosis due to hepatitis B virus (HBV) on liver transplantation waiting lists is declining, thanks to effective antiviral therapies that achieve sustained viral suppression. In contrast, the number of patients listed for transplantation due to decompensated cirrhosis from MASLD is steadily increasing.[11] In Türkiye, although chronic viral hepatitis remains the leading indication for liver transplantation, the impact of MASLD is steadily increasing, mirroring trends observed in other countries.[12]

Despite the increasing burden of MASLD, until 2024 the only approved therapy was lifestyle intervention aimed at achieving a minimum weight loss of 5% of total body weight. This approach has also been shown to be effective in lean individuals affected by MASLD. However, in the long term, many patients tend to regain weight, raising concerns about the sustainability of lifestyle interventions.[13,14] In 2024, resmetirom was conditionally approved in the USA following the positive results in the MAESTRO-NASH trial.[15] Recently, the ESSENCE trial was published, demonstrating promising results for semaglutide, a glucagon like peptide-1 (GLP-1) agonist, showing beneficial effects on MASLD—partially independent of weight loss—particularly in reducing metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis.[16] In addition, dual agonists such as survodutide are gaining increasing interest due to their combined activity as GLP-1 and glucagon receptor agonists, offering enhanced benefits for liver health.[17] These emerging therapeutic options have the potential to significantly transform clinical practice and improve patient outcomes. However, their effects within the context of liver transplantation remain largely unexplored.

In this review, we aim to discuss the comorbidities associated with MASLD and their impact in the context of liver transplantation. Additionally, we will explore the role of GLP-1 receptor agonists in the management of MASLD, focusing on their potential in preventing chronic liver disease progression and their therapeutic implications within liver transplantation settings.

## Liver Transplantation in MASLD

The first liver transplantation was performed in 1963 by Starzl in Denver (Colorado) and is now considered the curative treatment for end-stage liver disease and chronic liver disease complications like hepatic decompensation and HCC. Since then, advancements in areas such as surgical techniques and immunosuppression have led to an increase in liver transplantations since the 1980s.[18,19] Due to that, also long-term outcomes, such as 1-year-survival rates, have improved enormously after transplantation.[20] To date, approximately 34,000 liver transplantations are performed annually worldwide.[21] The number of liver transplants had stagnated due to the limited availability of donor organs. To address this, donation criteria were expanded to include higher-risk donors, such as older individuals or those with comorbidities. However, despite these efforts, the waiting list for liver transplantation remains long, and approximately 15% of patients die while awaiting a new liver. Therefore, indications for liver transplantation must be guided by the need to use the limited supply of donor organs as efficiently as possible.[22]

As previously noted, MASLD is now the leading indication for liver transplantation among patients with hepatocellular carcinoma on transplant waiting lists in both Europe and the United States, reflecting a rising trend across both regions.[9,23] This specific patient group requires particularly cautious management. Careful selection of liver transplant recipients is essential, as patients with MASLD are typically older and frequently present with metabolic risk factors such as obesity, type 2 diabetes, hypertension, and cardiovascular disease — all of which significantly increase perioperative risk. Therefore, the management of MASLD-related liver transplantation must also address a range of cardiometabolic comorbidities, requiring a multidisciplinary approach tailored to this complex patient population.[24]

## Comorbidities Associated with MASLD and Their Implications for Liver Transplantation

MASLD is linked to cardiovascular-kidney-metabolic disease, i.e. to metabolic risk factors such as diabetes mellitus, chronic kidney disease, and cardiovascular disease.[25,26] These comorbidities warrant particular attention, especially in the context of risk stratification prior to liver transplan-

tation. Post-transplant, the risk of cardiovascular events and metabolic complications may be further exacerbated by the effects of immunosuppressive therapy.[27] In this section of the review, we will mention metabolic comorbidities in association with the context of MASLD-related liver transplantation.

## Impact of Obesity and Type 2 Diabetes Mellitus

Type 2 diabetes mellitus and obesity are the most impactful metabolic comorbidities in MASLD, contributing significantly to its progression to MASH, cirrhosis, and HCC. Indeed, the prevalence of MASLD among patients with type 2 diabetes mellitus is approximately 70%, with MASH occurring in about 66% and advanced fibrosis in 15% of cases, underscoring T2DM as a significant comorbid factor contributing to the severity of MASLD.[28] Moreover, obesity presents a significant clinical challenge in liver transplantation, as more than one-third of liver transplant recipients have been reported to be obese.[36]

Following liver transplantation, the prevalence of type 2 diabetes mellitus (T2DM) ranges from 31% to 38%, while the incidence of new-onset diabetes mellitus within the first three years post-surgery ranges from 13% to 28%.[29] Pre-liver transplantation T2DM is commonly associated with liver diseases such as MASLD, with a reported prevalence ranging from 33% to 66%. Individuals with T2DM prior to liver transplantation are also at increased risk for post-transplant infections, cardiovascular complications, and poorer overall outcomes.[30–32] A study utilizing data from the American Transplant Registry applied a machine learning algorithm to assess the impact of pre- and post-transplant diabetes on outcomes following liver transplantation. The analysis revealed that increasing age (odds ratio [OR]: 1.01), male sex (OR: 1.09), and obesity (OR: 1.13) were significantly associated with the development of new-onset diabetes after transplantation. Notably, patients who developed post-transplant diabetes had significantly lower 10-year survival rates compared to those without diabetes (63.0% vs. 74.9%; $p<0.001$), with survival rates similar to those of patients who had diabetes prior to transplantation (58.9%).[32]

Profound peripheral insulin resistance is a hallmark of liver cirrhosis, occurring in both diabetic and non-diabetic patients, and often emerges in the early stages of liver disease. This might be due to the role of the liver in insulin resistance, which is called hepatogenous diabetes. Interestingly, liver transplantation can potentially resolve type 2 diabetes mellitus by restoring function within the hepato-pancreatic axis.[33] In a large study involving patients with pre-existing type 2 diabetes mellitus who underwent liver transplantation, insulin requirements were found to decrease by 50% within six months post-transplant, highlighting the significant role of the liver in glucose metabolism.[34]

The prevalence of MASLD has increased alongside the rising rates of obesity over the past decade.[35,36] Although BMI is the accepted standard for defining obesity, it has notable limitations, particularly in assessing fat distribution and identifying visceral obesity. Indeed, lean and obese MASLD patients differ in their metabolic profiles and in the prevalence of hypertension, dyslipidemia, insulin resistance, and elevated inflammatory markers. The main consensus indicates that lean MASLD patients have generally a more favorable metabolic profile compared to obese patients.[37,38] On the other hand, evidence suggests that lean MASLD patients may experience worse overall outcomes compared to those with obesity, indicating that alternative pathophysiological mechanisms may be involved. In a recent large-scale study involving 15,155 patients with compensated cirrhosis, obese and non-obese individuals were compared to assess clinical outcomes. The prevalence of type 2 diabetes mellitus (T2DM) was significantly lower among lean patients (47%) compared to their obese counterparts (74%). Interestingly, in multivariable models, lean status was associated with a 64% increased risk of all-cause mortality, despite a lower risk of hepatic decompensation. Moreover, lean individuals exhibited significantly higher rates of cardiovascular-related mortality.[39]

Indeed, pre-transplant obesity is generally considered a risk factor, and many patients are encouraged to lose weight prior to liver transplantation. As a result, obese individuals often remain on the transplant waiting list for longer periods and exhibit a higher model for end stage liver disease (MELD) scores.[40] It has been previously reported that higher BMI and T2DM was associated with adverse post-transplant outcomes.[41] However, paradoxically, some studies have shown that overweight or obese patients may experience lower mortality after transplantation compared to those with normal weight, suggesting the presence of an 'obesity paradox' in this context.[42] Nevertheless, in this single-center study, increased BMI was associated with a significantly higher risk of long-term graft loss. Notably, obese patients did not exhibit longer intensive care unit stays, extended operative times, or increased perioperative complications. However, these findings should be interpreted with caution, as it is likely that obese candidates with the most favorable metabolic profiles were selected for transplantation, potentially contributing to the more favorable short-term outcomes observed.[40] On the other hand, findings on this subject remain conflicting. In another study, obesity was significantly associated with prolonged intensive care unit stays, increased biliary compli-

cations, and a higher incidence of perioperative infections. Moreover, liver transplantation in obese patients is technically more challenging, which may lead some surgeons to be reluctant to operate on this population.[43] Therefore, given the challenges associated with obesity both before and after liver transplantation, it is essential that obesity be appropriately managed within this clinical context.

## Cardiovascular Diseases in Liver Transplantation Setting

Cardiovascular disease is the leading cause of mortality in patients with MASLD, followed by extrahepatic malignancies and liver-related complications, highlighting the multisystemic nature of the condition. Therefore, effective management of cardiovascular comorbidities is critically important in this patient population. In fact, cardiology consultation should be considered essential, particularly for patients at high risk of advanced fibrosis.[44] MASLD is also considered an independent risk factor for cardiovascular disease, including myocardial infarction, coronary artery disease, atrial fibrillation, and stroke. In a meta-analysis involving 34,000 individuals with a follow-up period of seven years, advanced MASLD—characterized by increased liver fibrosis—was associated with a 2.5-fold increase in mortality. These findings underscore that not only the presence of MASLD, but also its severity, significantly contributes to cardiovascular morbidity and mortality.[45] In both pre- and post-transplantation settings, cardiovascular events continue to play a critical role in patients with MASLD, representing a major contributor to increased mortality risk.[46,47] Cardiovascular assessment is a critical component of the pre-transplant evaluation for liver transplantation, as cardiovascular disease remains a leading cause of morbidity and mortality in this population. Coronary angiography is considered the gold standard for diagnosing coronary artery disease in transplant candidates. A study demonstrated that guideline-based management of coronary heart disease prior to transplantation does not adversely impact post-transplant survival, suggesting that appropriately treated cardiovascular comorbidities do not compromise transplant outcomes and may, in fact, help optimize candidate selection.[48] In this study, the prevalence of dyslipidemia following liver transplantation at 1, 3, and 5 years was reported as 32.5% (n=146), 46.8% (n=142), and 55.3% (n=115), respectively. Notably, 70% of cases represented new-onset dyslipidemia, for which statin therapy was initiated. The authors also demonstrated that statin use had a beneficial effect on overall survival, highlighting the importance of managing lipid abnormalities in the post-transplant population.[48]

## Chronic Kidney Disease in Liver Transplantation Settings

MASLD is known to be associated with an increased risk of chronic kidney disease (CKD), and this risk appears to correlate with disease severity, with more advanced MASLD linked to a higher prevalence of CKD.[49] Even early indicators of CKD, such as microalbuminuria, have been associated with more severe liver histology, suggesting that patients at high risk for MASH should be routinely screened for CKD.[50,51] CKD is also one of the most common post-transplant complications, with reported prevalence rates reaching up to 40% in the post-transplant setting.[52] Moreover, patients with MASLD who undergo combined liver-kidney transplantation have been shown to carry a higher risk of post-transplant renal dysfunction compared to those with other underlying liver diseases, which indicates that MASLD itself can also create a subclinical organ damage on kidney.[24]

## The Utility of GLP-1 Agonists in the Liver Transplant Settings

GLP-1 receptor agonists are currently used in clinical practice for the management of type 2 diabetes mellitus (T2DM) and obesity, primarily due to their beneficial effects on glycemic control and weight reduction. The effects of GLP-1 receptor agonists are summarized in Table 1. In the coming years, they are also expected to gain approval for liver-related indications, largely because of their indirect hepatic benefits. Their weight loss effects are primarily mediated through appetite suppression and delayed gastric emptying. Additionally, GLP-1 receptor agonists improve hepatic insulin sensitivity and enhance fatty acid oxidation in the liver, thereby contributing to improved hepatic fat metabolism.[53] Among the GLP-1 receptor agonists, semaglutide has shown particularly promising effects on liver health. The recently completed ESSENCE trial met its primary endpoints, demonstrating significant rates of MASH resolution without worsening of fibrosis, as well as improvement in fibrosis without worsening of MASH.[16] Moreover, the SWITCH-SEMA 1 trial investigated the effects of transitioning patients with T2DM from liraglutide or dulaglutide to semaglutide. The transition demonstrated additional benefits, particularly in improving the Fatty Liver Index, highlighting semaglutide's superior impact on liver health compared to other GLP-1 receptor agonists.[54]

In the transplant setting, the availability of medications for glycemic control in patients with liver cirrhosis is an important consideration. GLP-1 receptor agonists are becoming increasingly attractive in this context due to their additional cardioprotective and renoprotective effects. Consequently, GLP-1 agonists are often favorably selected for

**Table 1.** Effects of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists on General Metabolic Health

| Organ system | Effect of GLP1-analogs |
|---|---|
| Digestive system (gastrointestinal tract) | Delayed gastric emptying |
| | Appetite inhibition |
| | Increased insulin secretion |
| | Promotion of insulin-dependent glucose uptak |
| Pancreas | Promotion of insulin secretion if blood glucose is elevated |
| | Improved blood glucose control |
| Liver | Inhibition of glucagon release, especially in the fasting phase |
| | Improvement of steatosis, inflammation, possibly fibrosis in MASLD |
| Adipose tissue | Promotion of weight reduction and fat reduction |
| Kidney | Kidney protection |
| | Reduction of the risk of diabetic nephropathy |
| Muscle tissue | Increase in muscle mass and muscle function |
| | Promotion of fat reduction |
| | Improving blood glucose and insulin sensitivity |
| Cardiovascular system | Blood pressure reduction |
| | Promotion of cardiovascular protective mechanisms |
| | Reduction in the risk of cardiovascular events in patients with type 2 diabetes mellitus |
| Central nervous system | Appetite suppression by influencing hypothalamic activity |
| | Potential neuroprotective effects |

patients with type 2 diabetes mellitus, particularly when coexisting cardiovascular or renal comorbidities are present.[55] The strategy for managing MASLD in the context of liver transplantation, including the use of GLP-1 agonists and other medications, is illustrated in Figure 1.

On the other hand, the effects of semaglutide for liver cirrhosis remain controversial. In phase 2 trials involving MASH-related cirrhosis, after 48 weeks of treatment, there was no significant improvement in MASH or fibrosis. Fortunately, no cases of hepatic decompensation or death were reported, although some gastrointestinal

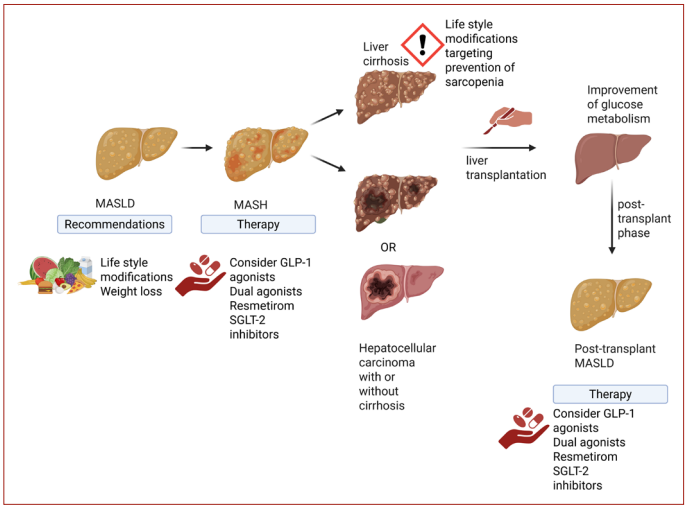


**Figure 1.** The strategy for managing MASLD in the context of liver transplantation (Created with Biorender.com).

side effects were observed.[56] It is important to note that efruxifermin, a fibroblast growth factor 21 (FGF21) agonist, was recently investigated in a 96-week phase 2b trial (SYMMETRY) involving patients with compensated MASH-related cirrhosis. While no significant effect on liver fibrosis was observed at 36 weeks, by 96 weeks the treatment demonstrated a significant improvement, including evidence of regression from cirrhosis to fibrosis. These findings suggest that, in MASH cirrhosis, trial durations should be extended to capture the potentially delayed therapeutic effects of the drugs.[57] Recently, dual agonists have also gained attention, such as survodutide, which targets both GLP-1 and glucagon receptors. These receptors are directly expressed in the liver, and activation has shown beneficial hepatic effects by increasing hepatic energy expenditure.[17] The effects of survodutide are currently being investigated in the LIVERAGE Cirrhosis Trial (NCT06632457).

On the other hand, data on the use of GLP-1 receptor agonists in the liver transplantation setting remain limited. A recent systematic review analyzed 12 studies examining the efficacy and safety of GLP-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors in liver transplant recipients. Overall, these agents were associated with reductions in hemoglobin A1c levels, improved glucose metabolism, weight loss, and decreased insulin requirements. Moreover, their potential to reduce graft steatosis, enhance renal function, and lower the incidence

of major cardiovascular events highlights their emerging relevance in this patient population.[58]

In a retrospective analysis, liver transplant recipients receiving GLP-1 receptor agonists were compared with those undergoing insulin therapy. Patients treated with GLP-1 receptor agonists experienced an average weight loss of approximately 8%, whereas those on insulin therapy gained around 10% of their body weight. Additionally, GLP-1 agonists demonstrated beneficial effects in reducing graft steatosis. Importantly, neither therapy had a significant impact on the incidence of transplant rejection.[59] In another study conducted among various transplant recipients, GLP-1 receptor agonists were found not to significantly affect tacrolimus levels, further supporting their safety in the liver transplantation setting.[60] Moreover, GLP-1 receptor agonists have been associated with a significant reduction in major adverse cardiovascular events. In various transplant settings, including heart and kidney transplantation, the use of GLP-1 receptor agonists has been linked to a more than 50% reduction in the risk of cardiovascular events.[61] In another study, the use of GLP-1 receptor agonists during the first 12 months post-transplant was associated with a 70% reduction in insulin requirements.[62] Overall, the accumulating evidence supports the beneficial effects of GLP-1 receptor agonists in the liver transplant setting not only in terms of liver health but also a general metabolic health. However, prospective studies are still needed to confirm their safety and efficacy in this specific population.

## Conclusion

MASLD represents a significant and growing health burden and is becoming the leading cause of liver transplantation. As a result, the management of MASH cirrhosis, MASH-related liver transplantation, and the post-transplant care of these patients will increasingly become a central focus in liver transplant settings. In this context, GLP-1 receptor agonists appear to be a promising therapeutic option—not only for improving overall metabolic health but also for their potential benefits in reducing graft steatosis. The accumulating evidence supporting the use of GLP-1 receptor agonists in patients with MASH and MASH-related cirrhosis offers promise for more effective disease management in the future. However, further research is needed to clarify the effects and safety of this class of medications in liver transplant recipients.

### Disclosures

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