Glucagon-Like Peptide-1 Receptor Agonist Use Before and After Liver Transplant

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Abstract: Metabolic dysfunction, manifesting as obesity, type 2 diabetes mellitus (T2DM), and related cardiometabolic comorbidities, has emerged as a major driver of morbidity among patients with advanced liver disease and liver transplant (LT) recipients. These conditions influence disease progression, transplant candidacy, perioperative risk, and long-term graft and patient outcomes. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become cornerstone treatments for obesity and T2DM, with benefits extending beyond glycemic control to include sustained weight loss, improved insulin sensitivity, and reduction in cardiovascular risk. These pleiotropic metabolic effects are highly relevant across the LT continuum, where metabolic disease frequently complicates management both before and after transplant. Historically, adoption of GLP-1RA–based therapies in patients with cirrhosis and in LT recipients has been limited by concerns regarding gastrointestinal tolerability, nutritional status, frailty, and potential interactions with immunosuppressive medications. Emerging observational studies suggest that GLP-1RAs may safely improve glycemic control and support weight management before and after LT, although prospective transplant-specific trials remain needed. This article summarizes the mechanistic rationale, current clinical evidence, and practical considerations for GLP-1RA use in patients with advanced liver disease and LT recipients and highlights key knowledge gaps as well as future research priorities in transplant hepatology.

Keywords
Glucagon-like peptide-1 receptor agonists, liver transplant, metabolic dysfunction, cirrhosis, posttransplant diabetes mellitus, obesity

Metabolic dysfunction disorders, including obesity, type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH), have become major drivers of liver-related morbidity and leading indications for liver transplant (LT) in the United States.[1-4] These conditions accelerate progression to cirrhosis and hepatic decompensation while simultaneously complicating transplant candidacy for those with or without MASH-related cirrhosis, as well as worsening posttransplant outcomes. Management is particularly

challenging in advanced liver disease, where therapeutic options are constrained by concerns regarding safety, tolerability, sarcopenia, frailty, and nutritional status. Glucagon-like peptide-1 receptor agonist (GLP-1RA)–based therapies are now cornerstone treatments for obesity and T2DM, with benefits extending beyond glycemic control and sustained weight loss to include cardiovascular risk reduction and improvements in hepatic steatosis and fibrosis.[5-12] These pleiotropic effects are highly relevant across the LT continuum, where metabolic disease influences transplant eligibility, perioperative risk, and long-term graft and patient survival. However, adoption of GLP-1RA–based therapies in patients with cirrhosis and LT recipients has historically been limited by sparse prospective data, concerns regarding tolerability in advanced liver disease, effects on frailty, and uncertainty surrounding interactions with immunosuppressive regimens.

This article examines the evolving role of GLP-1RA–based therapies across the LT continuum, summarizing available evidence for pre-LT and post-LT use, key safety considerations, and remaining clinical and research priorities relevant to transplant hepatology practice. Detailed mechanistic and cardiovascular effects are discussed in the following section, with subsequent sections focusing on transplant-specific clinical application.

Mechanistic Insights

GLP-1RAs exert metabolic effects beyond glucose lowering. As incretin-based therapies, they enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and regulate appetite. At the pancreatic β-cell, GLP-1 receptor activation enhances glucose-stimulated insulin secretion in a glucose-dependent manner, resulting in a low intrinsic risk of hypoglycemia (with severe events occurring in <1 per 100 patient-years) when GLP-1RAs are used without insulin or sulfonylureas.[13,14] Together, these effects translate into reduced caloric intake, weight loss, and improved insulin sensitivity—key drivers of metabolic liver disease. First-generation GLP-1RAs such as liraglutide produce approximately 5% to 10% weight loss, whereas higher-dose semaglutide (Wegovy and Ozempic, Novo Nordisk) and dual incretin GLP-1 and glucose-dependent insulinotropic peptide (GIP) agonists such as tirzepatide (Zepbound and Mounjaro, Lilly) achieve substantially greater reductions, often exceeding 15%. These agents also improve insulin resistance and ectopic fat deposition, positioning them as potent modulators of metabolic dysfunction.[15-18]

Hepatic benefits are thought to be largely indirect, as GLP-1 receptor expression in hepatocytes is limited.[19-21] Mechanistic studies demonstrate that GLP-1RAs improve adipose insulin sensitivity and reduce free fatty acid flux to the liver, thereby decreasing hepatic triglyceride accumulation.[22,23] They also exhibit anti-inflammatory effects, including reductions in circulating proinflammatory cytokines such as tumor necrosis factor alpha and interleukin 6, as well as reductions in markers of oxidative stress and macrophage activation in both clinical and translational studies.[24-27] These effects provide biologic plausibility for observed improvements in hepatic necroinflammation and fibrosis-related biomarkers.

GLP-1RAs and related incretin-based therapies have emerged as central agents in the management of MASH because of their benefits, which, as mentioned, include not only glycemic control and weight reduction but also meaningful hepatic and cardiovascular effects. Meta-analyses of randomized controlled trials (RCTs) in metabolic liver disease demonstrate 30% to 45% relative reductions in liver fat measured by magnetic resonance imaging–proton density fat fraction, mean alanine aminotransferase reductions of 10 to 20 U/L, and favorable changes in noninvasive fibrosis markers with GLP-1RA–based therapies.[28-32] In the LEAN trial, liraglutide achieved resolution of steatohepatitis in 39% of patients vs 9% with placebo and reduced fibrosis progression by 66% over 48 weeks.[33] The phase 3 ESSENCE trial demonstrated that semaglutide 2.4 mg weekly achieved MASH resolution without worsening of fibrosis (62.9% vs 34.3% with placebo) and improvement in fibrosis stage without worsening of MASH (36.8% vs 22.4% with placebo), leading to US Food and Drug Administration (FDA) approval for treatment of noncirrhotic MASH with moderate to advanced fibrosis.[5] Dual incretin agonism has also shown promising results, with tirzepatide demonstrating substantial reductions in hepatic steatosis and favorable effects on fibrosis-related endpoints in phase 2 trials.[34,35]

Beyond single- and dual-receptor agonism, newer multireceptor agents have demonstrated even greater effects on hepatic steatosis. Survodutide, a dual GLP-1/glucagon RA, achieved at least a 30% liver fat reduction in 84.2% of patients at 48 weeks in a phase 3 trial, alongside clinically meaningful weight loss, and has shown histologic improvement in MASH without fibrosis worsening in earlier studies.[36] Retatrutide, a triple GLP-1/GIP/glucagon RA, has produced the most pronounced reductions in liver fat to date, with relative decreases of up to approximately 80% and normalization of liver fat (<5%) in the majority of patients at higher doses in phase 2 studies, effects closely linked to weight loss and improvements in insulin sensitivity and lipid metabolism.[37] Although histologic outcomes for triple agonists remain under investigation, the magnitude of hepatic fat reduction suggests substantial disease-modifying potential.

Importantly, these therapies also address the broader cardiometabolic risk profile that drives morbidity and

Table 1. Key Studies of GLP-1RAs Across the LT Continuum[a]

Study	Population	Design	N	Intervention	Key outcomes	Limitations
MASH[b] (noncirrhotic / F1-F3 fibrosis)						
Armstrong et al[33]	Biopsy-proven MASH F1-F3	Phase 2 RCT (LEAN)	52	Liraglutide 1.8 mg daily vs placebo over 48 weeks	↑ MASH resolution (39% vs 9% placebo) ↓ Fibrosis progression	Small sample
Loomba et al[34]	Biopsy-proven MASH F2-F3	Phase 2 RCT (SYNERGY-NASH)	~190 (157 with evaluable 52-week biopsy)	Tirzepatide 5 mg, 10 mg, or 15 mg weekly vs placebo over 52 weeks	↑ MASH resolution (44%-62% vs 10% placebo) ↑ Fibrosis improvement (51%-55% vs 30% placebo) Dose response	Limited histologic endpoints given missing biopsy data (imputed)
Sanyal et al[5]	Biopsy-proven MASH F2-F3, NAS ≥4, BMI ≥27	Phase 3 RCT (ESSENCE)	~800	Semaglutide 2.4 mg weekly vs placebo over 72 weeks (interim; total 240 planned)	↑ MASH resolution (62.9% vs 34.3% placebo) ↑ Fibrosis improvement (36.8% vs 22.4% placebo)	Not transplant-specific, interim analysis
Kanwal et al[12]	EMR-based MASLD or MASH	Retrospective cohort using administrative claims data	14,606	GLP-1RA vs active comparator DPP-4i with variable follow-up duration	↓ Progression to cirrhosis, complications, mortality	Retrospective, observational, confounding low event rates limiting statistical power, reliance on review of EMR and ICD coding for inclusion
Mantovani et al[29]	MASH/ MASLD (mixed populations)	Meta-analysis (13 RCTs)	1811	GLP-1RAs (class effect)	↑ MASH resolution ↓ LF and enzymes, modest fibrosis benefit	Heterogeneity, few fibrosis-powered studies
Sanyal et al[37]	MASLD defined as MRI-PDFF >10% LF, no biopsy requirement	Phase 2a RCT, (MASLD substudy within obesity trial)	98	Retatrutide (triple GLP-1/GIP/ glucagon RA) 1mg, 4 mg, 8 mg, or 12 mg weekly vs placebo over 48 weeks	↓ LF (MRI-PDFF): ~80% steatosis resolution at highest doses ↓ Blood-based inflammatory markers	Substudy population not enriched for MASH, no histologic endpoints, MASH not formally defined (inferred only), low fibrosis population; surrogate imaging-based outcomes
Kaplan et al[36]	MASLD with evidence of liver inflammation and/or fibrosis (NITs or biopsy-confirmed MASH)	Phase 3 RCT (SYNCHRONIZE-MASLD)	216	Survodutide (dual GLP-1/glucagon RA) 6 mg weekly vs placebo over 48 weeks	↓ LF (MRI-PDFF): 84.2% vs 24.3%	Small sample, not restricted to biopsy-proven F2-F3; broader MASLD population using NITs or biopsy, short duration
Compensated cirrhosis[c]						
Simon et al[51]	MASH Cirrhosis + T2DM	Observational cohort	1431; 1246; 845 matched pairs (to DPP-4i, sulfonylureas, and SGLT2i respectively)	GLP-1RA vs comparators	GLP-1RA reduced decompensation vs DPP-4i and sulfonylureas but not vs SGLT2i	Short follow-up, observational
Loomba et al[59]	MASH-related compensated cirrhosis (F4)	Phase 2 RCT	71	Semaglutide 2.4 mg weekly vs placebo (2:1 randomization) over 48 weeks	No improvement in fibrosis or MASH resolution; improved metabolic parameters	Well-compensated (Child-Pugh A) cirrhosis, potential underpowering for fibrosis endpoints, short duration

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Study	Population	Design	N	Intervention	Key outcomes	Limitations
Compensated cirrhosis[c]						
Kanwal et al[12]	Cirrhosis based on ICD code	Retrospective cohort using administrative claims data	1452	GLP-1RA vs active comparator with DPP-4i	GLP-1RA showed no protective effect against hepatic complications, or mortality once cirrhosis established	Retrospective, residual confounding, low event rates limiting statistical power, reliance on ICD coding
Yen et al[52]	MASH cirrhosis + T2DM in Taiwan	Cohort	467 matched pairs of GLP-1RA users vs nonusers	GLP-1RA users vs nonusers	↓ Risk of mortality, cardiovascular events, decompensated cirrhosis, hepatic encephalopathy, and liver failure	Observational, short-term, unclear generalizability outside Taiwan
Multiple small studies	Compensated MASH cirrhosis	Prospective or retrospective	<100 each	GLP-1RAs	Weight loss ↓ HbA1c No clear safety signal	Underpowered, short follow-up
Posttransplant (LT recipients)						
Grancini et al[72]	LT recipients with T2DM	Prospective single arm cohort	68	GLP-1RA (semaglutide, dulaglutide) as add-on therapy to metformin or insulin over 18 months	↓ HbA1c (~0.4%-0.5%) ↓ Weight, LDL cholesterol ↓ Liver stiffness in first 6 months No immunosuppressant adjustments needed; enabled reduction or discontinuation of insulin therapy in up to 61% of individuals	Small sample, no control
Grancini et al[77]	LT recipients with T2DM	Prospective single arm cohort (interim)	52 (29 completed)	GLP-1RA (semaglutide, dulaglutide) over 52 weeks	↓ HbA1c and glucose Modest weight/body composition changes No changes in elastography Insulin reduction in subset	Interim analysis, small sample
Gordon et al[71]	SOT recipients (including LT) with T2DM	Retrospective, observational matched cohort	70	GLP-1RA vs insulin over 12 months	↓ Insulin dependence, weight ↑ Proportion reached HbA1c goal	Heterogeneous population, observational, small sample
Dotan et al[76]	SOT recipients with T2DM	Cohort	318	GLP-1RA vs nonusers over median follow-up of 3.1 years	↓ MACE (HR, 0.46) ↓ All-cause mortality (HR, 0.39)	Heterogeneous population, observational
Yakubu et al[73]	LT recipients with T2DM	Retrospective, matched cohort	38	GLP-1RA vs matched insulin-treated controls over 12 months	~8% weight loss ↓ Graft steatosis No significant impact on renal function, immunosuppression, or rejection	Small sample, retrospective

[a]Evidence is predominantly observational and heterogeneous, with limited randomized data in cirrhosis and transplant populations. Most studies are underpowered to assess long-term graft outcomes, fibrosis regression, and pharmacokinetic interactions with immunosuppressive agents.

[b]Please note: Earlier studies defined eligibility using NASH/NAFLD criteria, which are not identical to the current MASH/MASLD definitions following the nomenclature update. For consistency of terminology across this table, all references to NASH/NAFLD have been changed to MASH/MASLD, while the original study inclusion criteria remain as reported by the respective publications.

[c]Decompensated cirrhosis is not mentioned in the table owing to a lack of prospective data.

EMR, electronic medical record; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; HbA1c, hemoglobin A1c; HR, hazard ratio; ICD, International Classification of Diseases; LF, liver fat; LDL, low-density lipoprotein; LT, liver transplant; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NITs, noninvasive tests; RCT, randomized controlled trial; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SOT, solid-organ transplant; T2DM, type 2 diabetes mellitus.

mortality in MASH. Cardiovascular disease remains the leading cause of death in this population, and GLP-1RAs have consistently demonstrated cardiovascular benefit.[38] Meta-analyses of large cardiovascular outcomes trials involving more than 70,000 patients show that long-acting GLP-1RAs reduce major adverse cardiovascular events (MACE) by approximately 14% and all-cause mortality by 12%, in addition to improving blood pressure and atherogenic lipid profiles.[6,9,39-41] These dual hepatic and cardiovascular benefits underscore the paradigm shift toward integrated, metabolism-targeted treatment strategies in MASLD/MASH, with emerging multireceptor agonists representing a particularly promising next generation of therapy.[42-48]

Potential Benefits and Limitations

Recent observational studies, short-term clinical trials, and posttransplant cohort data have begun to clarify the safety profile and potential benefits of GLP-1RA–based therapies in both pre-LT and post-LT settings. Emerging evidence suggests these agents may facilitate metabolic optimization for transplant candidacy, improve posttransplant diabetes and obesity, and potentially mitigate recurrent or de novo MASLD in the graft. However, the current evidence base is largely derived from retrospective and observational studies, which are subject to selection bias and residual confounding (Table 1). Accordingly, findings should be interpreted cautiously, and prospective transplant-specific trials are needed to define efficacy and safety more definitively.

Before Liver Transplant Use

The pretransplant period represents a critical window in which metabolic optimization may influence transplant candidacy, waitlist outcomes, and perioperative risk. Obesity and T2DM are present in 30% to 40% of LT candidates, and MASH is now a leading indication for LT in the United States.[49,50]

GLP-1RAs have been shown to reduce the risk of progression to cirrhosis, liver-related complications, and mortality in patients with MASLD without established cirrhosis, but this benefit is not necessarily observed in patients with established cirrhosis.[51-55] In a large retrospective cohort of 14,606 patients with MASLD and T2DM, GLP-1RAs were associated with a reduced risk of progression to cirrhosis, hepatic complications, and all-cause mortality compared with dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, sitagliptin, linagliptin) after 18 to 24 months of treatment.[12] A 2025 meta-analysis of 13 RCTs (n=1811) demonstrated improved MASH resolution (odds ratio [OR], 3.48; 95% CI, 2.6-4.51) and fibrosis (OR, 1.79; 95% CI, 1.37-2.35), particularly with semaglutide 2.4 mg weekly; however, no benefit was observed in patients with compensated cirrhosis.[29] Notably, GLP-1RAs may also be superior to sodium-glucose cotransporter 2 (SGLT2) inhibitors for liver outcomes. In a propensity-matched cohort (15,176 pairs), GLP-1RAs were associated with a 16% lower risk of major adverse liver outcomes (HR, 0.84; 95% CI, 0.73-0.97), driven largely by fewer decompensation events, and a 16% reduction in all-cause mortality.[53] Evidence outside MASLD/MASH is lacking, and benefits in other non-MASLD liver diseases (eg, viral hepatitis, autoimmune hepatitis, alcohol-associated liver disease, and primary biliary cholangitis) remain unproven.

These findings are further supported by a large real-world analysis of newer antihyperglycemic agents, which demonstrated that GLP-1RAs were associated with a significantly lower risk of progression to cirrhosis, hepatic decompensation, and mortality compared with other glucose-lowering therapies, including DPP-4 inhibitors and SGLT2 inhibitors, in those with T2DM, particularly in patients without established cirrhosis.[56]

Evidence in Compensated Cirrhosis

Cirrhosis significantly alters glucose homeostasis, with insulin resistance present in nearly all patients with cirrhosis—primarily owing to decreased peripheral muscle glucose uptake and impaired glycogen synthesis—predisposing patients to both fasting hypoglycemia and postprandial hyperglycemia. These risks are compounded by potential sarcopenia, renal dysfunction, cognitive impairment with diminished hypoglycemia awareness, and concomitant beta blocker use that can mask adrenergic warning signs.[4,57,58] In this context, GLP-1RAs may be considered in carefully selected patients with compensated cirrhosis given their low intrinsic risk of hypoglycemia, favorable weight loss profile, and potential hepatic benefits; however, rigorous long-term studies in this population remain limited. Available data in cirrhotic populations are limited to short-term studies and observational cohorts; there are no adequately powered RCTs.

Prospective data in compensated cirrhosis remain limited but generally reassuring. Short-term studies (≤48 weeks) in patients with compensated MASLD/MASH cirrhosis suggest that GLP-1RAs can achieve weight loss and meaningful hemoglobin A1c (HbA1c) reductions without clear signals of increased hepatic decompensation. Notably, in a phase 2b randomized, placebo-controlled trial of 71 patients with MASH-related compensated cirrhosis, semaglutide 2.4 mg once weekly for 48 weeks reduced liver fat content but did not significantly improve fibrosis (11% vs 29% with placebo; OR, 0.28; *P*=.087) or achieve MASH resolution, with no decompensating

Table 2. Clinical Pearls for GLP-1RA Use in Liver Transplant Candidates

Greatest potential benefit of GLP-1RAs: patients with compensated cirrhosis (Child-Pugh A), obesity, and T2DM, particularly earlier in disease progression.
Avoid or use caution until further studies are available in patients with decompensated cirrhosis (ascites, hepatic encephalopathy, variceal bleeding): where no clear outcome benefit has been demonstrated and malnutrition risk is high.
Timing matters: observational data suggest benefit in preventing progression to cirrhosis but limited impact once cirrhosis is established.
Multidisciplinary management is essential: coordination among transplant hepatology, endocrinology, primary care, nutrition, and physical therapy teams optimizes safety and candidacy.

GLP-1RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus.

events or deaths in either group.[59] LIVERAGE, the ongoing phase 3 clinical trial program of survodutide for the treatment of MASH with moderate-to-advanced fibrosis (stage F2-F3) and for the treatment of MASH-associated compensated cirrhosis (stage F4), will assess the effects of survodutide on a more advanced MASH population.[60,61] Importantly, across available cohort studies, GLP-1RA use in compensated populations has not been associated with consistent increases in ascites, variceal bleeding, or hepatic encephalopathy.[12,51] In fact, in a population-based cohort of patients with cirrhosis and T2DM, GLP-1RA therapy was associated with relative risk reductions of hepatic decompensation events compared with other antidiabetic therapies of approximately 20% to 30%.[12,51]

Patients with MASH have higher waitlist and postdelisting mortality yet derive substantial survival benefit from LT.[62] In this context, GLP-1RAs may help optimize candidacy and bridge patients to transplant, although long-term prospective data are needed.

Evidence in Decompensated Cirrhosis

In contrast, available data do not demonstrate a clear benefit of GLP-1RA initiation in patients with established decompensated cirrhosis. Accordingly, insulin remains the guideline-recommended therapy for T2DM management in decompensated cirrhosis owing to its predictable titratability and extensive clinical experience, despite its hypoglycemia risk.[63-65] No major society currently recommends routine GLP-1RA use in decompensated cirrhosis pending further prospective data, underscoring the need for careful patient selection. The November 2025 American Association for the Study of Liver Diseases Practice Guidance update notes that semaglutide has approval for MASH with F2-F3 fibrosis. However, it clarifies that semaglutide is not approved for MASH-related cirrhosis and advises careful monitoring for use in patients with compensated cirrhosis who are taking semaglutide for another FDA-approved indication, such as T2DM.[63]

Practical Considerations in Liver Transplant Candidates

When considering GLP-1RA–based therapies in transplant candidates, several factors warrant careful attention, including Child-Pugh class, baseline nutritional status, sarcopenia, frailty indices, renal function, and volume status (Table 2). Gradual dose titration, close nutritional monitoring, and early assessment of gastrointestinal tolerability are essential, as nausea and reduced intake may precipitate muscle loss in patients living with cirrhosis. Excessive or rapid weight loss (>1%-1.5% body weight per week) may exacerbate frailty and potentially delay listing if nutritional parameters decline. Maintenance of adequate protein intake (≥1.2-1.5 g/kg/day in cirrhosis per guideline recommendations) and resistance exercise is essential to mitigate sarcopenia risk.[66] The Figure outlines a stage-based approach to considering GLP-1RA therapies in patients with MASLD and related metabolic comorbidities before and after LT.

After Liver Transplant Use

Metabolic complications following LT are common and clinically consequential. Posttransplant diabetes mellitus (PTDM), weight gain, recurrent or de novo MASLD, and cardiovascular disease contribute substantially to long-term morbidity and mortality in LT recipients. Immunosuppressive regimens—particularly corticosteroids and calcineurin inhibitors—worsen insulin resistance, dyslipidemia, and weight gain, creating a metabolic milieu in which traditional lifestyle interventions are often insufficient.[67]

GLP-1RA–based therapies offer a mechanistically appealing approach to addressing these posttransplant metabolic challenges. Accordingly, GLP-1RAs are increasingly being used for three principal posttransplant indications: management of PTDM, treatment of overweight, obesity or weight gain or regain, and mitigation of recurrent or de novo MASLD in the graft.

Management of Posttransplant Diabetes Mellitus and Weight Gain

PTDM is defined as diabetes diagnosed after LT, regardless of whether pretransplant hyperglycemia was unrecognized. The condition develops in up to one-third of recipients and is associated with increased cardiovascular

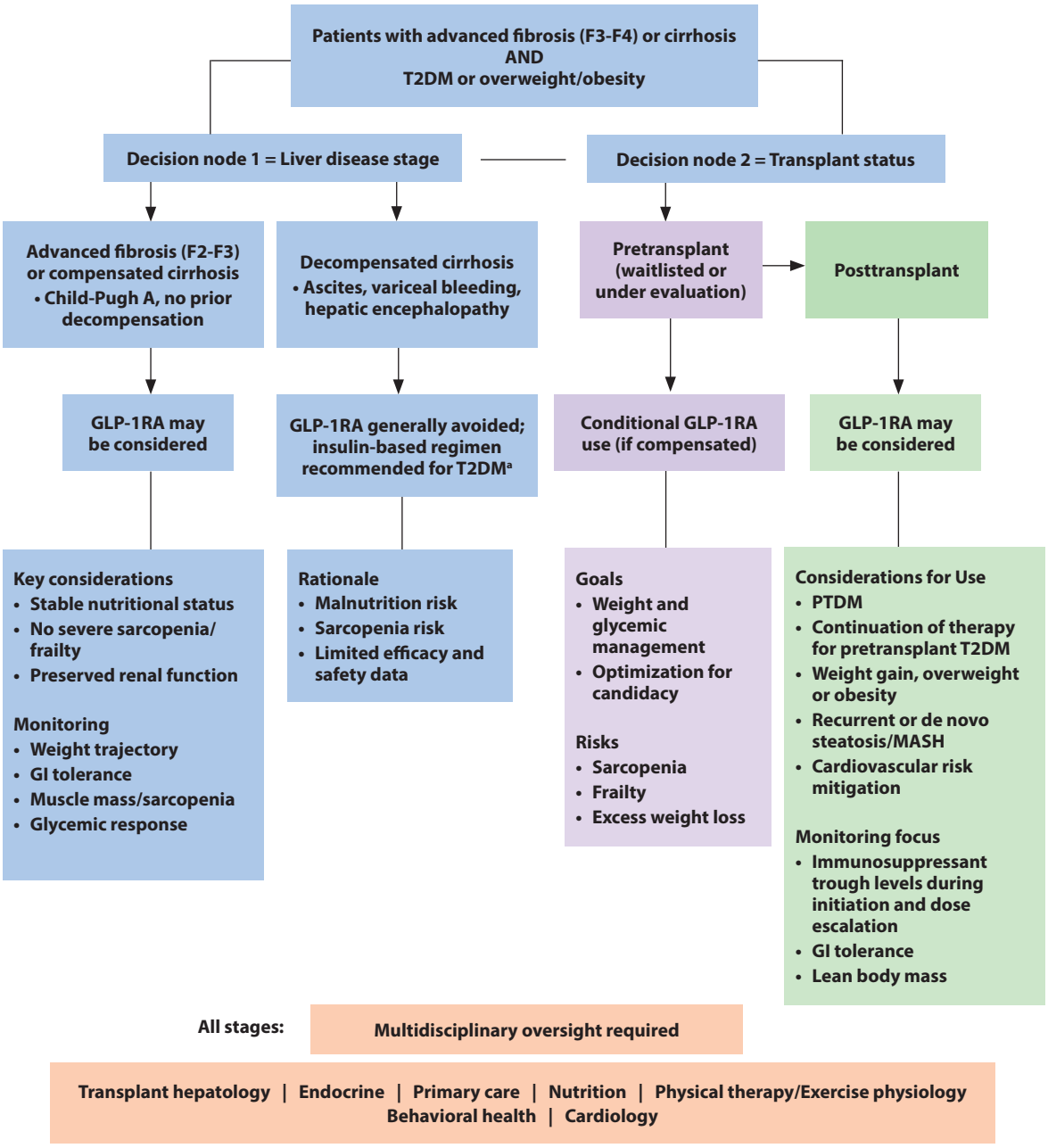

Figure. Proposed stage-based clinical algorithm for GLP-1RA use across the liver transplant continuum. GLP-1RAs may be considered for metabolic optimization in patients without cirrhosis or with compensated cirrhosis, with careful attention to nutritional status, frailty, GI tolerability, and sarcopenia risk. In decompensated cirrhosis, GLP-1RA use is generally avoided owing to limited efficacy and safety data, with insulin remaining the preferred therapy. In transplant candidates/recipients, multidisciplinary oversight and monitoring of nutritional status, lean muscle mass, and immunosuppressant exposure are essential. This algorithm is intended to guide clinical consideration and reflects the current evidence base, which remains largely observational. [a]Until further data are available.

GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; PTDM, posttransplant diabetes mellitus; T2DM, type 2 diabetes mellitus.

events, infections, kidney disease, and reduced graft and patient survival.[67,68] Although RCTs are lacking, observational studies and small prospective cohorts consistently demonstrate that GLP-1RAs improve glycemic control and promote weight loss in LT recipients, with additional favorable effects on waist circumference and cardiometabolic markers.[69-76] Importantly, these benefits have not been associated with consistent signals of graft rejection, pancreatitis, or clinically meaningful instability in immunosuppressant levels in limited studies.[69,70]

In a prospective study of 68 LT recipients with PTDM, GLP-1RA therapy reduced HbA1c by approximately 0.4% to 0.5% and produced progressive weight loss up to 3.0 kg at 18 months, along with reductions in waist circumference, low-density lipoprotein (LDL) cholesterol, and liver stiffness. Tacrolimus levels remained stable, and adverse events were primarily mild gastrointestinal symptoms, with discontinuation in a minority of patients.[72] Retrospective studies corroborate these findings, demonstrating HbA1c reductions (~0.75% to 1.1%), mean weight loss (~4 to 5 kg), and body mass index (BMI) reduction (~1.6). GLP-1RA–based regimens achieve greater weight and BMI reduction than other glucose-lowering therapies, while combination GLP-1RA/SGLT2 inhibitor therapy may yield the largest HbA1c improvements.[69-71] In a matched cohort of 70 solid organ transplant recipients with PTDM (including LT recipients), GLP-1RA use reduced insulin dependence at 12 months (69% vs 94% with insulin-only therapy). Gastrointestinal adverse effects were more frequent, and a higher rate of rejection was observed (29% vs 6%), although no causal relationship was established.[71]

Interim results from a 24-month study in LT recipients with diabetes demonstrated sustained improvements in glycemic control and weight with GLP-1RA therapy, with an acceptable safety profile, although full peer-reviewed outcomes remain pending. These findings further support feasibility but highlight the need for longer-term, adequately powered studies.[77]

Beyond glycemic control, GLP-1RAs appear to mitigate posttransplant weight gain. In a retrospective study of 38 LT recipients, GLP-1RA therapy resulted in approximately 8% weight loss, compared with approximately 10% weight gain in insulin-treated patients, and was associated with a lower incidence of graft steatosis.[73] Smaller cohorts report similar findings, including greater 1-year weight loss vs controls (7.9% vs 4.2%) and sustained weight reduction with semaglutide over approximately 17 months, with generally mild gastrointestinal adverse effects.[74]

A matched cohort study of 318 solid organ transplant recipients, including LT recipients, found that GLP-1RA users had a 54% lower risk of MACE (hazard ratio [HR], 0.46; 95% CI, 0.27-0.78) and a 61% lower risk of all-cause mortality (HR, 0.39; 95% CI, 0.18-0.84) compared with nonusers over a median 3.1-year follow-up.[76] Additional metabolic benefits included reductions in total and LDL cholesterol, decreased liver stiffness, and improvements in alanine aminotransferase levels.

Collectively, these data support clinically meaningful improvements in glycemic control and weight with GLP-1RAs in LT recipients, with a safety profile broadly comparable to the nontransplant population. However, these findings are derived primarily from retrospective cohorts and small prospective studies, which are underpowered to detect less common but clinically significant outcomes such as rejection, graft dysfunction, and pharmacokinetic interactions. Notably, the impact of GLP-1RAs on body composition remains poorly characterized. Existing studies rely on bioimpedance-derived measures, and data on skeletal muscle mass, strength, and sarcopenia are lacking. Thus, it remains unclear whether posttransplant weight loss preferentially reduces adiposity, preserves lean mass, or contributes to sarcopenia risk.

Recurrent or De Novo Metabolic Dysfunction-Associated Steatotic Liver Disease in the Graft

Recurrent and de novo MASLD following LT is increasingly recognized and may progress to steatohepatitis and fibrosis, particularly in the setting of obesity, PTDM, and metabolic syndrome. Although histologic outcome data remain limited, emerging observational studies suggest that GLP-1RA therapy may reduce hepatic steatosis and improve noninvasive fibrosis markers in LT recipients.[5,11,63,76] Among available glucose-lowering medications, tirzepatide and semaglutide demonstrate the highest efficacy for both glucose lowering and weight loss, followed by dulaglutide (Trulicity, Lilly) and liraglutide.[64] These findings are biologically plausible given the established effects of GLP-1RAs on visceral adiposity, insulin resistance, and inflammatory signaling pathways. Notably, although improvements in weight, glycemic control, and noninvasive markers have been observed, there are currently no data demonstrating histologic fibrosis regression or improvement in hard clinical outcomes such as graft survival, decompensation, and mortality in LT recipients.

Safety, Drug Interactions, and Special Populations

Drug-Drug Interactions and Immunosuppression Considerations

Concerns regarding potential drug-drug interactions between GLP-1RAs and immunosuppressive agents, particularly calcineurin inhibitors, are biologically plausible

but incompletely characterized. GLP-1RAs delay gastric emptying, which may alter the absorption kinetics of orally administered agents such as tacrolimus and cyclosporine. Although existing studies have not shown consistent clinically meaningful changes in immunosuppressant levels, they are limited by small sample sizes, short follow-up, and heterogeneity, and are likely underpowered to detect modest but relevant pharmacokinetic effects.[69-78] Thus, absence of a signal should not be interpreted as absence of interaction, particularly given the clinical importance of tacrolimus variability for rejection and toxicity. Current guidelines suggest minimal interaction risk based on available data. Accordingly, close monitoring of immunosuppressant trough levels is recommended during GLP-1RA initiation and dose escalation, especially early posttransplant or in patients with variable gastrointestinal tolerance. GLP-1RAs may be used in selected LT recipients with multidisciplinary oversight and routine monitoring of metabolic and clinical parameters.

Safety Profile

The safety profile of GLP-1RAs in LT recipients is generally consistent with that observed in nontransplant populations. Gastrointestinal adverse effects, including nausea, vomiting, and early satiety, are the most reported and typically occur during dose titration. Rates of therapy discontinuation owing to adverse effects are low, and severe events such as pancreatitis and gallbladder disease have not been consistently observed at higher rates than expected background risk.[69-78] Importantly, no clear signal of increased infection risk or immunologic complications has been identified in available studies.

Volume depletion and acute kidney injury remain theoretical concerns, particularly in patients with concomitant diuretic use or chronic kidney disease (CKD), warranting careful monitoring of renal function. CKD is common both before and after LT and may influence the selection of antihyperglycemic agents in T2DM and PTDM. Most GLP-1RAs can be used in mild-to-moderate CKD without dose adjustment.[79,80] In LT recipients, observational data suggest no increased risk of acute kidney injury attributable to GLP-1RA therapy when patients are euvolemic and monitored appropriately. Nevertheless, caution is warranted in individuals with advanced CKD or concomitant diuretic use, and renal function should be monitored regularly following initiation.

Frailty and Sarcopenia

Frailty and sarcopenia are prevalent among LT recipients and are independently associated with adverse posttransplant outcomes. Although GLP-1RAs promote weight loss, concerns exist regarding potential exacerbation of lean muscle loss in frail or sarcopenic patients. Available data in LT recipients are limited; however, observational studies suggest that weight loss with GLP-1RA therapy is predominantly driven by reductions in fat mass rather than lean mass when therapy is appropriately titrated and accompanied by nutritional support. Careful patient selection, gradual dose escalation, and concurrent resistance-based physical activity and protein optimization alongside dietitian and nutrition colleagues are recommended, particularly in older or frail recipients.[66,81-84]

Malnutrition Risk

Posttransplant patients remain vulnerable to malnutrition owing to persistent gastrointestinal symptoms, medication side effects, and fluctuating metabolic demands. GLP-1RA–associated nausea, early satiety, and reduced caloric intake may exacerbate this risk, while appetite suppression and effects on gastric emptying and bile acid secretion may further impair micronutrient intake and absorption. Although there are no published data specifically evaluating malnutrition, sarcopenia progression, or body composition changes with GLP-1RA therapy in LT recipients, baseline risk is high in this population. Sarcopenia affects 30% to 70% of patients with end-stage liver disease and persists or newly develops in a substantial proportion after transplant, with prevalence estimates around 40% to 45% and associations with worse clinical outcomes.[83]

For this reason, GLP-1RAs should be initiated cautiously in patients with low BMI, unintentional weight loss, or marginal nutritional reserves. Excessive weight loss warranting dose reduction or temporary cessation includes BMI less than 18.5, anorexia (consuming <800 calories/day), and very low protein intake. Close collaboration with transplant nutrition specialists and routine monitoring of weight trends, dietary intake, and micronutrient status are essential. Initial registered dietitian evaluation with follow-up every 2 to 3 months during dose escalation is recommended, emphasizing adequate protein intake and nutrient quality to minimize muscle loss.[84]

Use Alongside Sodium-Glucose Cotransporter 2 Inhibitors and/or Insulin

Combination therapy with GLP-1RAs and SGLT2 inhibitors is increasingly employed in PTDM management owing to complementary mechanisms of action and additive cardiometabolic benefits.[69,76] Narrative reviews across solid-organ transplant report no significant increase in adverse events or immunosuppressant interactions with this combination when used judiciously. Similarly, GLP-1RAs may be used in conjunction with insulin to improve glycemic control while allowing for insulin dose reduction and minimizing hypoglycemia risk. Careful titration

and close glucose monitoring are recommended during combination therapy initiation.

Conclusion

GLP-1RA–based therapies represent a promising strategy for addressing the growing burden of metabolic disease across the LT continuum. Emerging data support their safety and efficacy for improving glycemic control, weight management, and cardiometabolic risk in carefully selected pre-LT and post-LT populations, with no consistent signal of adverse graft outcomes or clinically meaningful immunosuppressant interactions. However, the current evidence base remains largely observational, retrospective, and heterogeneous, limiting causal inference and the ability to detect clinically meaningful safety signals.

Looking ahead, prospective, transplant-specific studies are needed to define the long-term effects of GLP-1RAs on graft and patient outcomes. In addition to traditional endpoints such as cardiovascular events, progression of CKD after LT, and the prevention or treatment of recurrent or de novo MASLD in the graft—particularly among recipients transplanted for MASH cirrhosis—future work must also clarify important safety and mechanistic considerations. These include the effects of GLP-1RAs on medication adherence and immunosuppressant pharmacokinetics in the setting of delayed gastric emptying, gastrointestinal intolerance, and variable oral absorption, as well as the impact of treatment-associated weight loss on sarcopenia, frailty, and nutritional status, particularly in patients with advanced liver disease and in the early posttransplant period, where preservation of lean muscle mass is critical. As newer incretin-based therapies with greater metabolic potency emerge, well-designed trials incorporating body composition, drug exposure, and functional outcomes will be essential to determine their role in transplant hepatology.

Future trials should incorporate clinically meaningful endpoints beyond glycemic control and weight loss, including histologic outcomes (steatohepatitis resolution and fibrosis regression), validated fibrosis biomarkers, graft-related outcomes (recurrent MASLD, graft dysfunction), and patient-centered endpoints such as cardiovascular events, hospitalization, and survival.

Translating these advances into meaningful patient outcomes and ensuring safe integration of these therapies into clinical practice will require coordinated, multidisciplinary care. Given that metabolic dysfunction is inherently multidisciplinary in its pathophysiology, its management should be equally integrated. Effective care requires coordination among primary care, hepatology, endocrinology, cardiology, and behavioral health specialists, among others.[85]

Disclosures

Dr Manolas and Dr Brown have consulted for Madrigal Pharmaceuticals.

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