

Visceral Adipose Tissue and its Crosstalk With the Liver Allograft: Implications for Transplant Outcomes

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Abstract. Liver transplantation (LT) is the definitive treatment for end-stage liver diseases such as hepatocellular carcinoma (HCC) or cirrhosis, in a clinical context increasingly influenced by the high prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease. Organ shortages have expanded the use of extended-criteria donor grafts, including steatotic livers from donors after brain death or cardiocirculatory death. However, graft steatosis remains a major risk factor for ischemia/reperfusion (I/R) injury, early allograft dysfunction, and posttransplant outcomes, and current protective strategies are insufficient to fully overcome these challenges. Visceral adipose tissue (VAT) is an active endocrine and immunometabolic organ that can shape systemic inflammation and immune tone. Clinical studies report an association between increased VAT and I/R injury, graft dysfunction, rejection, frailty, and HCC recurrence after LT, particularly in recipients with obesity and in recipients transplanted for cirrhosis and/or HCC. Under stress conditions, dysfunctional VAT shifts toward a proinflammatory phenotype characterized by altered secretion of cytokines, adipokines, chemokines, and lipid mediators. This review analyzes the role of the adipose tissue-liver axis in LT, with emphasis on how adipose-related mediators may modulate I/R injury and alloimmune responses in clinically relevant settings. We synthesize evidence from human cohorts and preclinical LT and warm I/R models, highlight major knowledge gaps related to tissue-source attribution and context-dependent mechanisms, and discuss emerging therapeutic strategies to modulate adipose tissue inflammation and immunometabolic signaling. Integrating adipose biology into LT research may help refine risk stratification and identify new avenues to improve graft utilization and long-term outcomes.

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INTRODUCTION

Liver transplantation (LT) is the definitive treatment for end-stage liver diseases such as cirrhosis and hepatocellular carcinoma (HCC), both highly prevalent conditions associated with significant comorbidities and mortality in

patients. Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly nonalcoholic fatty liver disease) is extremely common worldwide and has become one of the leading disease pathways ultimately resulting in cirrhosis or HCC, the main indications for LT.¹

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The persistent shortage of suitable hepatic grafts has prompted the use of extended-criteria donor (ECD) livers. In this context, steatosis is a key determinant of posttransplant performance in grafts from donors after brain death (DBDs) and donors after cardiocirculatory death (DCDs). Steatotic grafts are more vulnerable to ischemia/reperfusion (I/R) injury and are at higher risk of early allograft dysfunction and primary nonfunction.² As 30%–50% of deceased donor livers show some degree of steatosis, these organs are frequently declined, especially when steatosis is severe, further worsening organ availability.²

Importantly, transplant outcomes are shaped not only by graft quality but also by the recipient's metabolic and inflammatory environment. Many LT candidates with cirrhosis or HCC exhibit preexisting obesity, visceral adipose inflammation, or metabolic dysfunction. Moreover, post-transplant metabolic syndrome, obesity, and insulin resistance frequently develop or worsen, further aggravating adipose tissue dysfunction. As a result, even after replacing the diseased liver, recipients often retain or develop a pathological adipose phenotype characterized by chronic inflammation, altered adipokine secretion, lipotoxicity, and immune dysregulation. Dysfunctional visceral adipose tissue (VAT) is associated with I/R injury, immune activation, and graft rejection.² MASLD, cirrhosis, and HCC often coexist along a disease continuum, rather than representing isolated entities. In obesity-driven MASLD, VAT

dysfunction contributes to hepatic steatosis and inflammation and may accelerate progression to fibrosis, cirrhosis, and ultimately HCC.^{3,4} In this setting, VAT-derived metabolic and inflammatory signals are better viewed as disease amplifiers than as parallel bystanders. After transplantation, MASLD can (re)emerge in 30%–60% of recipients and negatively affect long-term health and quality of life.⁵ Notably, VAT expansion and inflammatory activity may be more pronounced in MASLD-related cirrhosis than in other cirrhosis etiologies.⁶

Beyond I/R injury and alloimmune activation, in recipients transplanted for HCC, removal of the diseased liver does not eliminate the recipient's systemic inflammatory and metabolic milieu. Although the underlying mechanisms remain to be clarified, increasing clinical evidence, mainly derived from HCC transplant recipients and patients transplanted for cirrhosis and HCC, indicates that recipient adipose tissue, particularly VAT, plays an important role in modulating HCC recurrence after LT.^{4,7}

Accordingly, this review analyzes how adipose tissue dysfunction within VAT may influence LT outcomes by modulating I/R injury and immune responses. We focus on clinically relevant settings, including ECD graft use and vulnerable recipient profiles (obesity, cirrhosis, and HCC), and discuss emerging therapeutic strategies targeting adipose tissue-derived pathways to improve graft function and long-term outcomes (Figure 1).

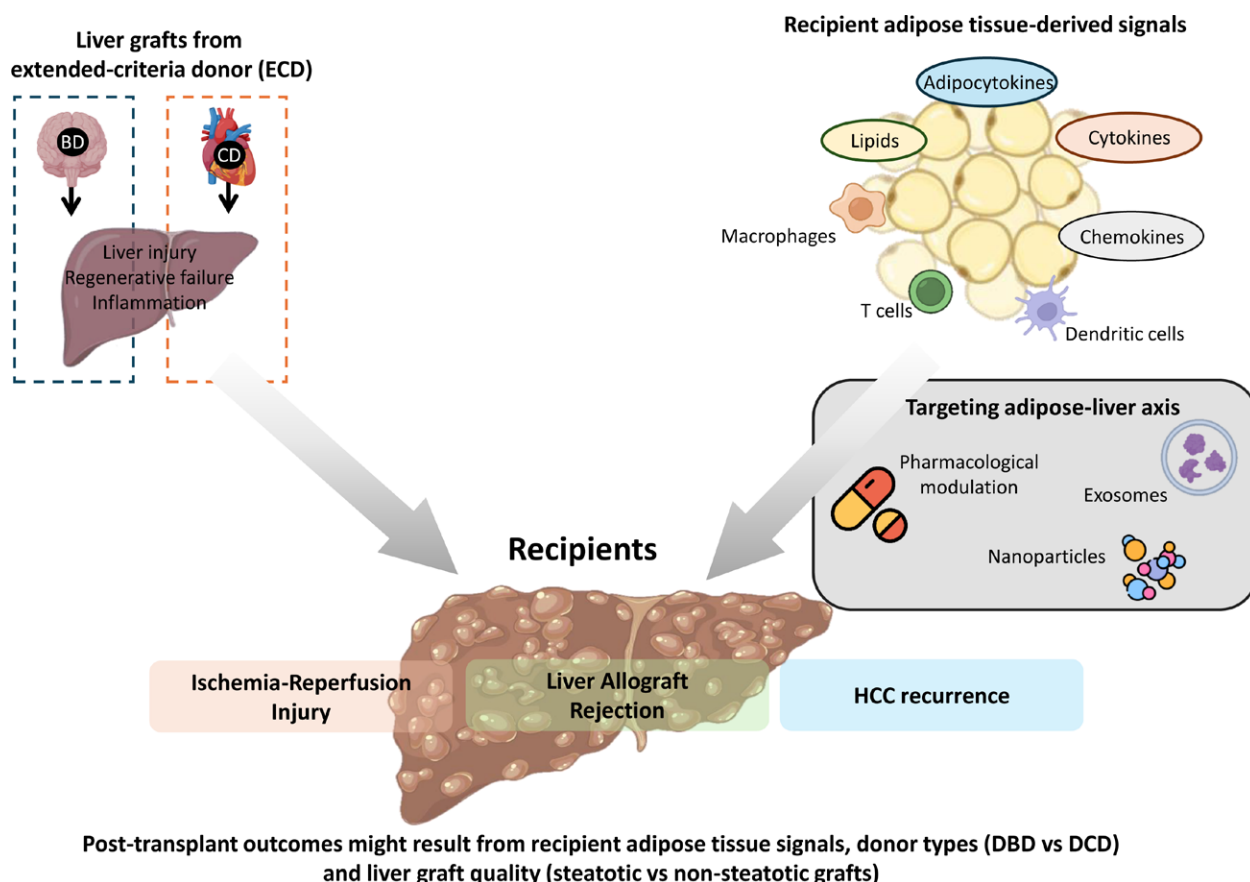


FIGURE 1. The adipose-liver axis as a determinant of clinical outcomes in liver transplantation. Schematic representation of the interplay between donor-derived graft quality (DBD and DCD) and recipient-derived immunometabolic signals. These factors converge to shape posttransplant pathophysiology, including ischemia/reperfusion injury, allograft rejection, and HCC recurrence while offering distinct targets for therapeutic intervention. DBD, brain-dead donor; DCD, donors after circulatory death; HCC, hepatocellular carcinoma.

ROLE OF ADIPOSE TISSUE-RELATED MEDIATORS IN I/R INJURY AND LIVER ALLOGRAFT REJECTION

VAT is increasingly recognized as an active endocrine and immunometabolic organ with the capacity to shape systemic inflammation and immune tone, thereby influencing I/R injury and alloimmune responses after LT. However, direct “source-level” causal evidence linking adipose-derived mediators to graft injury or rejection in LT remains limited, heterogeneous, and highly context-dependent.

The strongest experimental support comes from a small number of studies showing that the adipose-liver axis can modulate adipocytokine availability and downstream signaling in a manner that depends on donor type and graft quality. In steatotic grafts from donors after DCD (but not in nonsteatotic DCD or in DBD LT), adipose tissue sequestration of adiponectin and resistin during reperfusion has been associated with reduced hepatic AMP-activated protein kinase and phosphoinositide 3-Kinase/protein Kinase B (PI3K/Akt) and worsened graft injury, whereas restoring these adipocytokines improves outcomes.² Complementary evidence from warm hepatic I/R models relevant to LT further supports a functional role for adipose-derived cues in steatotic livers (but not in nonsteatotic ones), where resistin-visfatin interactions influence injury severity and tissue regeneration,⁸ and where lipectomy in obese animals abolishes the benefit of nutritional interventions on I/R injury and regeneration, consistent with an endocrine signaling role beyond energy supply.⁹ In addition, recent work has identified T-cell Immunoglobulin and Mucin-domain containing protein 4 (TIM-4) signaling in recipient adipose immune cells as a regulator of adipose-liver cross-talk that reduces endoplasmic reticulum stress, metabolic dysfunction, and hepatocyte apoptosis after LT, providing a mechanistic bridge between adipose immune activation, I/R injury, and rejection-related pathways.¹⁰

I/R injury in LT is shaped by a diverse set of soluble mediators and metabolic cues that influence graft inflammation, cell death, and regenerative capacity. Beyond graft-intrinsic mechanisms, adipose tissue can produce cytokines, chemokines, and adipokines that have been associated with increased vulnerability of ECD grafts. To date, these mediators have been predominantly quantified in plasma or liver tissue, and the specific contribution of adipose tissue as a source has rarely been addressed in LT. This review not only integrates functional evidence on adipose tissue-derived mediators implicated in I/R and liver rejection but also mediators involved in these processes even when their adipose origin has not been demonstrated, to identify biologically relevant pathways and to determine which mediators/pathways should be prioritized for future studies aimed at defining adipose tissue derivation, causality, and therapeutic potential in LT. The complexity and context dependency of mediators implicated in I/R injury are summarized in Table 1. Importantly, several of these mediators also influence alloimmune activation and tolerance, suggesting overlapping pathways contributing to both I/R injury and liver allograft rejection. Where available, we highlight evidence from human LT cohorts alongside findings from preclinical LT and warm I/R models, emphasizing context-dependent differences related to donor type (DBD versus DCD) and graft quality (steatotic versus nonsteatotic).

Cytokines, Chemokines, and Adipokines in I/R Injury and Liver Allograft Rejection

Cytokines in I/R

Cytokines play a central role in I/R injury after LT, sharpening inflammatory activation, hepatocellular survival, and regenerative responses. In recipients with metabolic dysfunction, VAT may amplify cytokine signaling, although most LT studies do not discriminate between hepatic and extrahepatic sources.

Among proinflammatory cytokines, tumor necrosis factor alpha (TNF- α) and interleukin (IL)-6 exhibit marked context dependency in I/R injury. TNF- α is associated with inflammatory activation and increased susceptibility to I/R injury, yet it may also support adaptive responses related to cell survival and metabolic regulation.^{11,12} Similarly, IL-6 displays pleiotropic actions: chronic elevation, frequently associated with metabolic dysfunction, contributes to systemic inflammation, insulin resistance, and damage in clinical LT.¹¹ However, experimental LT studies indicate that reduced IL-6 associates with increased inflammation and injury in nonsteatotic grafts, and IL-6 protects under warm I/R, regulating steatosis and mitochondrial dysfunctions.¹³ IL-10 can be protective in LT, whereas IL-1 β shows a more consistently deleterious profile: increased IL-1 β is observed in warm I/R and in both steatotic and nonsteatotic grafts (notably in DBD settings) and associates with enhanced inflammation.¹³

Cytokines and Liver Allograft Rejection

Sustained TNF- α signaling has been linked to impaired immune tolerance and rejection, in part by promoting Th17 cell differentiation and suppression of regulatory T-cell (Treg) expansion, thereby disrupting the Treg/Th17 balance required for graft acceptance.²³ IL-6 has also been implicated in acute and chronic rejection through effects on innate and adaptive immunity. Although transient IL-6 signaling may be protective during I/R,¹³ persistent elevation (often associated with metabolic dysfunction) may favor prorejection immune pathways and sustained inflammation, depending on LT context.^{25,26} Clinically, elevated TNF and IL-6 have been reported in association with rejection.²⁴ Elevated IL-10 has also been associated with acute rejection in clinical LT cohorts²⁹ and in allogeneic LT models using nondeceased donors and healthy recipients, by dysregulation in Th17/Treg cells.²⁸ Elevated posttransplant IL-1 β has been correlated with rejection, supporting the concept that injury-associated cytokines can promote downstream alloimmune dysregulation.²⁷

In summary, IL-1 β is consistently deleterious in I/R across models; TNF- α and IL-6 exert context-dependent effects in I/R; IL-10 is generally protective in experimental I/R settings. Sustained TNF- α /IL-6 signaling, IL-10 and IL-1 β associate with prorejection immune programs.

Chemokines in I/R Injury

Chemokines contribute to I/R injury primarily by promoting the recruitment of inflammatory cells to the liver graft. C-C motif ligand 2 (CCL2) and CCL8 are key drivers of monocyte and macrophage infiltration and neutrophil recruitment and have been implicated in hepatic inflammation in liver diseases and LT,¹⁴ whereas the role of C-X-C motif chemokine ligand 10 (CXCL10) in I/R associated with LT remains less well defined.

TABLE 1.
Role of cytokines, chemokines, adipokines, lipids, and related metabolites on I/R injury and liver rejection

Mediator	Effect	Surgical conditions	Main effects on liver graft (I/R)
TNF α	↑	LT from deceased and donors, warm I/R	Context-dependent effects on damage ^{11,12}
IL-6	↓	Nonsteatotic DBD LT, LT from deceased donors, warm I/R	Context-dependent effects on inflammation and damage ^{11,13}
IL-10	↓	Steatotic DBD LT	↑Inflammation and injury ¹³
IL-1 β	↑	Steatotic and nonsteatotic DBD LT	↑Inflammation and injury ¹³
CCL2 and CXCL8	↑	LT from nondeceased donors	↑Macrophage and neutrophil recruitment, inflammation and damage ¹⁴
Leptin	↑	Steatotic LT from nondeceased donors	↓Inflammation and damage ¹⁵
Adiponectin	Altered	LT from nondeceased donors; DBD LT; steatotic DCD LT	Context-dependent effects on damage ¹⁶⁻¹⁸
Resistin	↓	DBD LT; steatotic DCD LT	↑Inflammation and injury ^{2,8,18}
Visfatin	↑	LT from nondeceased donors, PH+I/R	Context-dependent effects on damage ^{8,18}
FFAs	↑	Warm I/R	↑Lipotoxicity, mitochondrial dysfunction and related with insulin resistance ¹⁹
ALOX12, 12-HETE, and 4-HNE	↑	Warm I/R	↑ Ferroptosis and damage ^{20,21}
Phosphocholine	↑	LT from deceased donors	↓ Hepatic damage and LT outcomes ²²
Mediator	Effect	Surgical conditions	Main effects on liver graft (rejection)
TNF- α	↑	LT from deceased and nondeceased donors	↑Prorjection signaling ^{23,24}
IL-6	↑	LT from deceased and nondeceased donors	Differential effects in liver rejection ^{13,24-26}
IL-1 β	↑	LT from deceased donors	↑ Liver rejection ²⁷
IL-10	↑	LT from deceased and nondeceased donors	↑Liver rejection ²⁸
CXCL10	↑	LT from deceased donors	↑Chronic rejection ^{14,29}
Adiponectin	↑	LT from nondeceased donors	Association with immunological tolerance ³⁰
Resistin	↑	LT from nondeceased donors	↑Monocyte-mediated rejection ³¹
Ceramides	↓	LT from deceased donors	↑ Liver rejection influencing dendritic cells and T-cell responses ³²
HNE and related	↑	LT from deceased donors	↑ Acute liver rejection ³³

ALOX12, arachidonate 12-lipoxygenase; CCL2, C-C motif chemokine ligand 2; CXCL8, C-X-C motif chemokine ligand 8; CXCL10, C-X-C motif chemokine ligand 10; CXCL12, C-X-C motif chemokine ligand 12; DBD, brain-dead donors; DCD, donors after circulatory death; FFA, free fatty acid; 12-HETE, 12-hydroxyeicosatetraenoic acid; HNE, hydroxynonenal; IL, interleukin; I/R, ischemia/reperfusion; LT, liver transplantation; TNF- α , tumor necrosis factor alpha.

Chemokines in Liver Allograft Rejection

Certain chemokines have been linked to immune-mediated graft damage and rejection. In particular, CXCL10 has been associated with chronic rejection and graft failure in LT recipients, an association consistently reported in clinical studies.^{14,29} Although adipose tissue dysfunction is known to influence chemokine production, the specific contribution of VAT-derived chemokines to graft rejection or tolerance in LT remains poorly defined.

Summarizing, CCL2 and CXCL8 predominantly amplify I/R injury via inflammatory recruitment, whereas CXCL10 is most consistently associated with chronic rejection.

Adipokines in I/R Injury

Adipokines represent a major link between metabolic dysfunction and immune regulation after LT. Through their endocrine and paracrine actions, adipokines modulate inflammatory signaling, immune cell activation, and hepatocellular responses, thereby influencing both I/R injury and liver allograft rejection.

Adiponectin is generally hepatoprotective and anti-inflammatory. In LT models, adiponectin signaling attenuates inflammation, suppresses TNF- α and nuclear

factor kappa B pathways, reduces apoptosis, and limits I/R injury, particularly in steatotic grafts.¹⁶ Reduced adiponectin levels, commonly observed in obesity and metabolic disease, are associated with impaired liver regeneration, increased fibrosis, and greater susceptibility to graft injury.¹⁷

The adiponectin-resistin axis appears strongly dependent on donor type and graft characteristics: In LT from DBD, higher adiponectin and lower resistin have been associated with inflammation and graft injury, and modulation of these adipokines can confer protection.¹⁸ In DCD, reduced levels of both adipokines (particularly in steatotic grafts) are linked to impaired AMP-activated protein kinase-PI3K/Akt signaling and worsened outcomes.² In warm I/R models relevant to LT, exogenous resistin can mitigate injury and regenerative failure by limiting hepatic uptake of visfatin from adipose tissue.⁸

Leptin shows hepatoprotective effects in selected experimental settings: in steatotic LT from nondeceased donors, adding leptin to preservation solutions increases signal transducer and activator of transcription 3 activation and reduces injury.¹⁹ Nevertheless, translational relevance remains uncertain given frequent leptin resistance in obesity and MASLD.

Other adipokines (visfatin, apelin, chemerin, and omentin) are less well characterized in LT. Visfatin contributes to damage and regenerative failure in steatotic warm I/R models⁸ whereas it appears to play a minor role in some LT setting.^{2,18}

Adipokines in Liver Allograft Rejection

Adiponectin may be necessary for overcoming liver rejection, promoting tolerance induction in experimental LT from nondeceased donors,³⁰ although direct evidence linking adiponectin to rejection modulation in experimental and clinical LT remains limited. However, resistin mediates graft rejection in experimental LT from nondeceased donors via intermediate monocytes.³¹ There is currently no clear evidence to support an association between posttransplant leptin level increases and rejection.

In summary, adiponectin may be protective or harmful in I/R and liver rejection depending on donor type and graft condition. Resistin tends to protect in I/R conditions, whereas promote rejection. The role of visfatin in I/R is context-dependent and unknown in liver rejection. The limited available evidence suggests a protective role for leptin in I/R, whereas its role in liver allograft rejection remains to be elucidated.

Lipids, Phospholipids, and Related Metabolites

Lipids, Phospholipids, and Related Metabolites in I/R Injury

Free fatty acids (FFAs) and lipid-derived metabolites contribute to I/R-induced metabolic stress. In warm I/R models, hepatic FFAs accumulation might increase oxygen consumption, reduce ATP availability, promoting mitochondrial dysfunction and injury.¹⁹ Clinically, metabolic syndrome after LT is associated with elevated FFAs and insulin resistance, reinforcing the link between systemic metabolic dysregulation and graft vulnerability.

Activation of the 12-lipoxygenase-12-hydroxyeicosatetraenoic acid axis promotes hepatic damage in warm I/R²⁰ and lipid peroxidation products such as 4-hydroxynonenal have been linked to ferroptosis and aggravated injury in steatotic livers subjected to ischemic stress.²¹ The lipid-related metabolite phosphocholine has been proposed to mitigate I/R injury in clinical steatotic LT through a fatty acid desaturase 6-dependent pathway.²²

Lipids, Phospholipids, and Related Metabolites in Liver Rejection

In LT patients with acute rejection, decreased serum ceramide levels have been associated with altered immune cell function by influencing dendritic cell and T-cell responses.³² Reactive aldehydes (including hydroxynonenal) in the transplanted liver have been implicated in acute cellular rejection pathways.³³ Nonetheless, many lipids and lipid-related species, phospholipids (lysophospholipids such as lysophosphatidylcholines), sphingolipids, diacylglycerols, and acylcarnitines have been investigated mainly as biomarkers rather than as established causal mediators of I/R injury or rejection.

In summary, lipid dysregulation contributes to I/R injury through mitochondrial stress and oxidized lipid pathways, whereas selected lipid signatures associate with immune dysfunction in rejection; however, much of the LT lipid-omic evidence remains associative.

Together, these data support substantial overlap between mediators implicated in I/R injury and those shaping alloimmune activation after LT, mainly focused in healthy recipients (Table 1; Figure 2), but their net effects are strongly context-dependent, influenced by donor type, graft quality, and perioperative conditions. A key limitation is that most studies quantify mediators in plasma or liver without resolving their tissue source, leaving the specific contribution of recipient VAT largely inferential. Thus, we next analyze how common recipient phenotypes (obesity, cirrhosis, and HCC) modulate this balance and interact with graft vulnerability.

EVALUATING THE ROLE OF ADIPOSE TISSUE IN RECIPIENTS WITH UNDERLYING PATHOLOGIES

Association of Adipose Tissue With Liver Rejection in Recipients

Clinical evidence in LT is largely associative, and the extent to which adipose tissue is a causal driver of rejection remains unclear. Obesity is an increasing problem that affects organ transplantation by raising the number of obese transplant recipients and steatotic donor livers.

In solid organ transplantation, including LT, obese recipients experience increased postoperative complications and poorer graft outcomes, including higher rates of acute rejection.³⁴ In LT, higher recipient body mass index, as a surrogate for increased adipose tissue, is associated with a higher risk of early acute cellular rejection.³⁵

Mechanistic links are plausible but not definitively established in LT. Obese adipose tissue exhibits hypertrophy, hypoxia, oxidative stress, dysregulated mediator release, increased lipolysis, and chronic inflammation. In this setting, adipose tissue-derived mediators such as leptin, TNF, IL-6, and monocyte chemoattractant protein-1 (MCP-1) might support innate and adaptive immune activation, promoting immune cell recruitment, particularly M1 macrophages, Th1 cells, and CD8⁺ T cells into metabolic tissues, exacerbating inflammation, neutrophil chemotaxis, and reactive oxygen species generation, and natural killer cell differentiation, proliferation, and cytotoxicity.³⁴ Limited experimental evidence in LT suggests that, especially in obesity, TIM-4 signaling in recipient adipose immune cells, regulating adipose-liver crosstalk, reduces endoplasmic reticulum stress, lipotoxicity, and hepatocyte apoptosis, thereby improving hepatic I/R injury and innate immune activation¹⁰ (Figure 2).

Obesity has been associated with altered alloimmune responses and poorer post-LT outcomes, but LT-specific evidence remains limited and confounded by comorbidities (eg, diabetes, hypertension, dyslipidemia) and infections. In severely obese recipients, the higher infectious risk often leads to individualized, closely monitored immunosuppression strategies (eg, steroid minimization and weight-adjusted tacrolimus), and the observed rejection risk does not necessarily imply a need for more

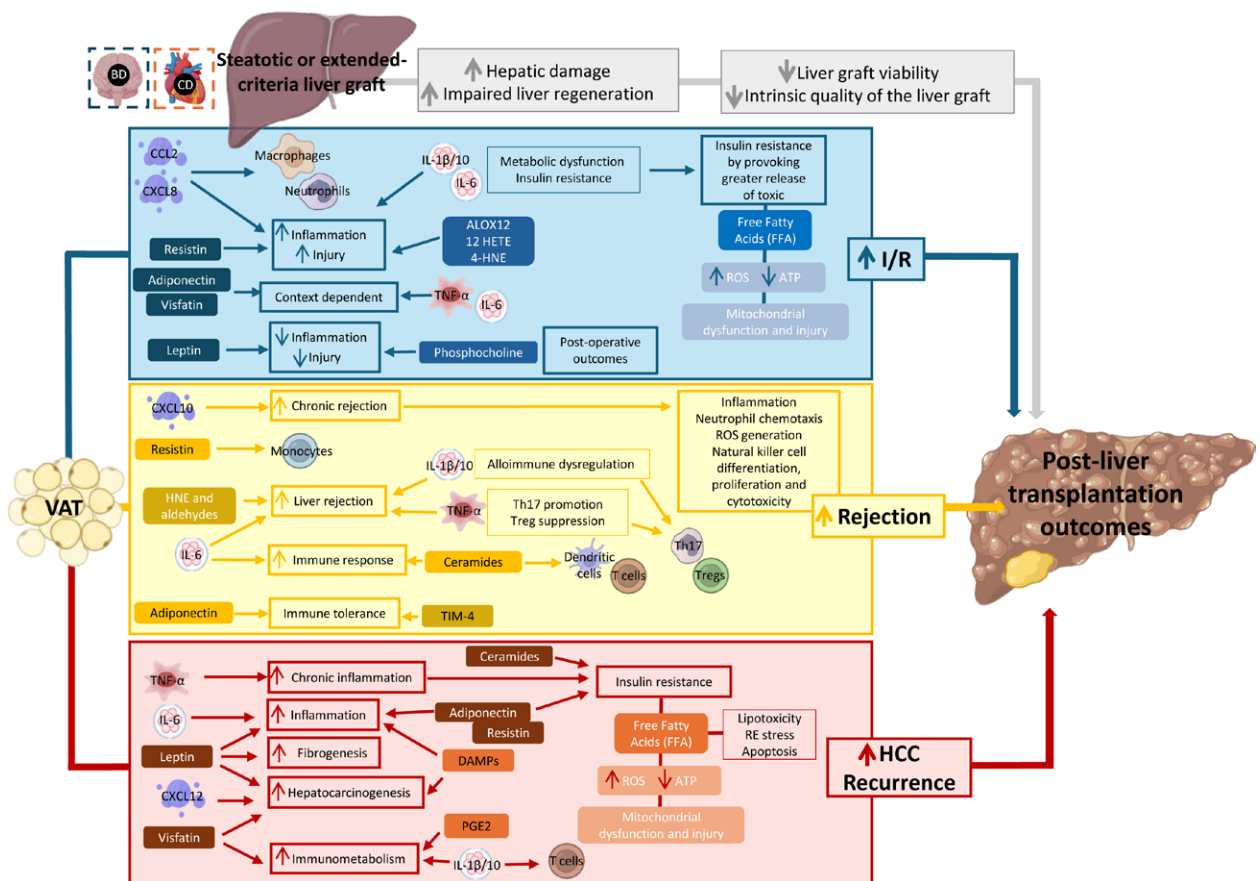


FIGURE 2. Putative mechanistic pathways of the adipose tissue-liver allograft crosstalk. Schematic integration of unresolved hypotheses on how VAT-derived mediators, including adipokines, cytokines, and lipid metabolites, modulate posttransplant complications: I/R injury, allograft rejection, and HCC recurrence in pathological recipients undergoing LT. The diagram highlights the convergence of recipient-driven immunometabolic signals and donor graft variables (eg, steatosis, ECD status) in shaping clinical trajectories. ALOX12, arachidonate 12-lipoxygenase; BD, brain-dead; CD, circulatory death; CXCL10, C-X-C motif chemokine ligand 10; CXCL12, C-X-C motif chemokine ligand 12; DAMP, danger-associated molecular pattern; HCC, hepatocellular carcinoma; IL, interleukin; I/R, ischemia/reperfusion; LT, liver transplantation; 12-HETE, 12-hydroxyeicosatetraenoic acid; PGE₂, prostaglandin E₂; RE, endoplasmic reticulum; ROS, reactive oxygen species; TNF- α , tumor necrosis factor alpha; VAT, visceral adipose tissue.

intensive immunosuppression.³⁶ Further studies are needed to define optimal immunosuppressive management in this population.

Obesity, often characterized by increased VAT accumulation, has been associated with frailty and sarcopenia in patients with cirrhosis.³⁷ The possibility that VAT expansion contributes to frailty in LT candidates should not be dismissed. This remains a hypothesis, but it is biologically plausible: excess VAT is linked with insulin resistance, mitochondrial dysfunction, and persistent low-grade systemic inflammation, which accelerate muscle catabolism, metabolic derangements, and loss of physiologic reserve components of the frailty phenotype in cirrhosis.³⁷ Supporting an interaction between adiposity and obesity, studies in cirrhotic recipient candidates have reported that frailty and obesity (often assessed using body mass index as a surrogate of adiposity) interact and associate with increased mortality risk.³⁸ In the same direction, higher VAT has been associated with worse performance across multiple frailty assessments in LT candidates in preliminary data sets, including preliminary (conference-reported) data sets (Cremen S, et al, 2022, written communication). Nevertheless, prospective studies integrating body composition, standardized frailty metrics, and clinical outcomes

are needed to clarify whether VAT is merely a marker of risk or a causal contributor to frailty in this population.

Association of Adipose Tissue With HCC Recurrence in Recipients

Most data linking adiposity to post-LT HCC recurrence are observational, and proposed mechanisms remain largely inferential in the LT setting. HCC accounts for up to 40% of LT worldwide, making tumor recurrence after LT a major clinical challenge.⁴ Growing clinical evidence, largely derived from studies in cirrhotic patients and predominantly in recipients transplanted for HCC, suggests that recipient adipose tissue, particularly VAT, play modulate HCC recurrence after LT.^{4,7} High visceral adiposity, including a VATI (VAT index) $\geq 65 \text{ cm}^2/\text{m}^2$ and an elevated visceral-to-subcutaneous fat ratio, is associated with increased recurrence and mortality after LT.^{4,39}

Mechanistically, VAT may contribute to a pro-tumor milieu, given its proinflammatory immunometabolic secretory profile and portal delivery of adipokines and metabolites to the liver, which may promote chronic inflammation and insulin resistance-processes implicated in hepatocarcinogenesis.⁴

It has been suggested that HCC-associated adipose tissue, reprogrammed by the tumor microenvironment, accumulates tumor-associated macrophages, myeloid-derived suppressor cells, and proinflammatory lymphocytes, secreting mediators (IL-10, FFAs, TNF- α , IL-6, leptin, FFAs or ceramides, and CXCL12) generating a mixed state of chronic inflammation and focal immunosuppression that impairs antigen presentation, T-cell activity, and macrophage function, thereby increasing graft immunogenicity (Figure 2). In HCC, dysfunctional adipose tissue also enhances the release of danger-associated molecular patterns, APC activation, and antigen availability, disrupting regulatory immunity and metabolic homeostasis, and promoting T cell-mediated rejection.⁴⁰ However, whether recipient adipose tissue directly increases graft immunogenicity or promotes rejection in HCC recipients remains speculative, and should be framed as a hypothesis rather than a demonstrated pathway in LT.

I/R Injury as a Driver of Rejection and HCC Recurrence

I/R injury after LT is a major determinant of early allograft dysfunction and a key modulator of posttransplant immune responses. Mechanistically, I/R injury induces endothelial activation, damage-associated molecular patterns release, adhesion molecule upregulations, cytokine cascades, and enhanced antigen presentation, thereby initiating innate immune activation.⁴¹ This inflammatory milieu can facilitate alloimmune activation and increase rejection risk, particularly in grafts exposed to more severe ischemic stress, such as ECD, and might contribute to chronic immune-mediated injury.⁴¹ Beyond its immunologic effects, I/R injury may also reshape the graft microenvironment in ways that correlate with oncologic outcomes: greater reperfusion injury has been correlated with increased HCC recurrence after LT, whereas ischemia-free LT using continuous normothermic machine perfusion reduces I/R injury and improves recurrence-free survival compared with conventional transplantation.⁴² Thus, although I/R injury is not the primary trigger of rejection or tumor recurrence, it may act as an amplifier linking perioperative injury to longer-term immune and oncologic outcomes.

Graft-related Variables Influencing I/R Injury, Liver Rejection, and HCC Recurrence

The severity and consequences of I/R injury are strongly influenced by graft-related and donor type. Steatotic grafts are more vulnerable to I/R-associated damage and have been linked (without establishing direct causality) to increased HCC recurrence, potentially through injury-induced alterations in the posttransplant immune microenvironment.⁴⁰ Donor type further conditions graft biology before implantation. Donation after DBD is characterized by catecholamine storm, hormonal imbalance, and systemic inflammatory activation, whereas donation after DCD adds warm ischemia, hemodynamic collapse, acidosis, and metabolic disturbances before procurement.² Whether these distinct preprocurement environments differentially prime intracellular stress and inflammatory pathways within the graft, and thereby modulate susceptibility to I/R injury and its downstream immune-mediated and oncologic consequences, remains to be defined.

THERAPEUTIC STRATEGIES TARGETING ADIPOSE TISSUE WITH POTENTIAL RELEVANCE TO LT

Increasing attention has been directed toward therapeutic strategies targeting adipose tissue. These approaches differ in complexity, specificity, and translational readiness and can be broadly classified into interventions focused on functional reprogramming of adipose tissue, pharmacological modulation of adipose-driven inflammation, and cell- or vesicle-based therapies targeting adipose-liver crosstalk.

Functional Reprogramming of Adipose Tissue: Lifestyle and Metabolic Interventions

Lipectomy is neither feasible nor desirable in LT, as adipose tissue can exert both pro- and anti-inflammatory effects depending on its metabolic and immune context. In obesity, cirrhosis, and HCC, dysfunctional adipose tissue promotes systemic inflammation that may aggravate I/R injury, rejection, and tumor recurrence. Therefore, therapies should aim to modulate adipose tissue function rather than eliminate it, reshaping its inflammatory and metabolic outputs toward a more protective phenotype.

Lifestyle interventions such as caloric restriction, dietary modulation, intermittent fasting, and exercise reduce adipose inflammation, improve adipokine and exosomal microRNA (miRNA) profiles and insulin sensitivity, and promote anti-inflammatory macrophage polarization, thereby creating a less proinflammatory systemic environment.⁴³⁻⁴⁵ In the LT setting, pretransplant lifestyle optimization may reduce the proinflammatory adipose secretome in recipients with cirrhosis or HCC, whereas posttransplant continuation could limit adipose-driven inflammation, I/R injury, and rejection. Although frailty and disease severity restrict applicability in advanced liver disease, early clinical studies suggest that exercise-based prehabilitation is feasible in selected cirrhotic patients. However, robust translational and clinical data in LT are still lacking.

Pharmacological and Metabolic Targeting of Adipose Inflammation

Pharmacological strategies targeting adipose tissue inflammation and immune-metabolic signaling represent a promising, yet largely unexplored, adjunct to reduce I/R injury and liver allograft rejection. Importantly, the evidence supporting these approaches does not derive from LT models, but rather from experimental settings of metabolic disease, obesity, systemic inflammation, or non-hepatic transplantation. These data nonetheless provide a strong conceptual framework for future adaptation to LT.

Rather than acting exclusively on the liver graft, these approaches aim to reprogram dysfunctional adipose tissue toward a less inflammatory, more tolerogenic state, thereby attenuating systemic signals that exacerbate post-transplant injury.

Experimental studies based on mice lacking liver X receptors demonstrate that modulation of macrophage metabolism in adipose tissue can significantly influence immune responses. Activation of liver X receptor- α using synthetic agonists such as TO901317 reduces acute rejection by inhibiting proinflammatory macrophage polarization through ABCA1-dependent mechanisms and downstream MAPK and (PI3K/AKT/mechanistic target of rapamycin [mTOR]) signaling.⁴⁶ Anti-inflammatory lipid mediators such as

Lipoxin A₄ promote resolution of inflammation by limiting neutrophil recruitment and restoring macrophage homeostasis. Metabolic therapies also modulate adipose immune function. In obese patients, glucagon-like peptide-1 receptor agonists such as liraglutide resulted in the alteration of macrophage phenotype toward alternative activation and improved macrophage cytokine profiles⁴⁷ (Figure 3).

However, most small-molecule therapies act systemically and do not selectively target adipose tissue.

To overcome this limitation, adipose-targeted drug delivery systems, including nanoparticles, liposomes, and ligand-conjugated carriers, have been developed to preferentially modulate adipose tissue macrophages. Nanoparticle encapsulation of anti-inflammatory agents enhances uptake by adipose macrophages, allowing more precise control of adipose inflammation while minimizing systemic immunosuppression.⁴⁸ Overall, selective pharmacological modulation of adipose tissue represents a promising strategy to mitigate both I/R injury and rejection, particularly in metabolically inflamed LT recipients (Figure 3).

Cell-based and Vesicle-based Therapies Targeting Adipose-liver Crosstalk

Extracellular vesicles (EVs), including exosomes, are key mediators of intercellular communication, transporting

miRNAs, lipids, and proteins between adipose tissue, immune cells, and the liver. Adipose tissue represents a major source of circulating miRNAs, largely packaged within EVs, which can modulate hepatic immunity, metabolic homeostasis, and susceptibility to I/R injury. Current evidence for these effects derives mainly from experimental models of obesity, metabolic dysfunction, and warm hepatic I/R, rather than from LT itself.

miRNAs regulate adipokine and cytokine production in dysfunctional adipose tissue, thereby affecting reperfusion injury and liver rejection. miR-378 overexpression reduces adiponectin, whereas miR-221/218 modulates its signaling, and miR-155 suppresses leptin and resistin. In inflammation, miR-132 increases IL-8 and MCP-1, miR-126 inhibits MCP-1, miR-145 upregulates TNF α , and miR-26a downregulates it.⁴⁵ Anti-inflammatory miRNAs include miR-30a, which inhibits interferon signaling, the miR-30 family promoting M2 macrophage polarization, and miR-17 suppressing proinflammatory responses via the signal transducer and activator of transcription 3- apoptosis signal-regulating kinase 1 pathway. Conversely, miR-27a and miR-130b target peroxisome proliferator-activated receptor, inducing M1 polarization, inflammation, and insulin resistance, whereas miR-27a knockout reduces cytokines, including IL-10. In liver disease and metabolic stress, adipocyte-derived EVs exhibit an altered miRNA cargo that

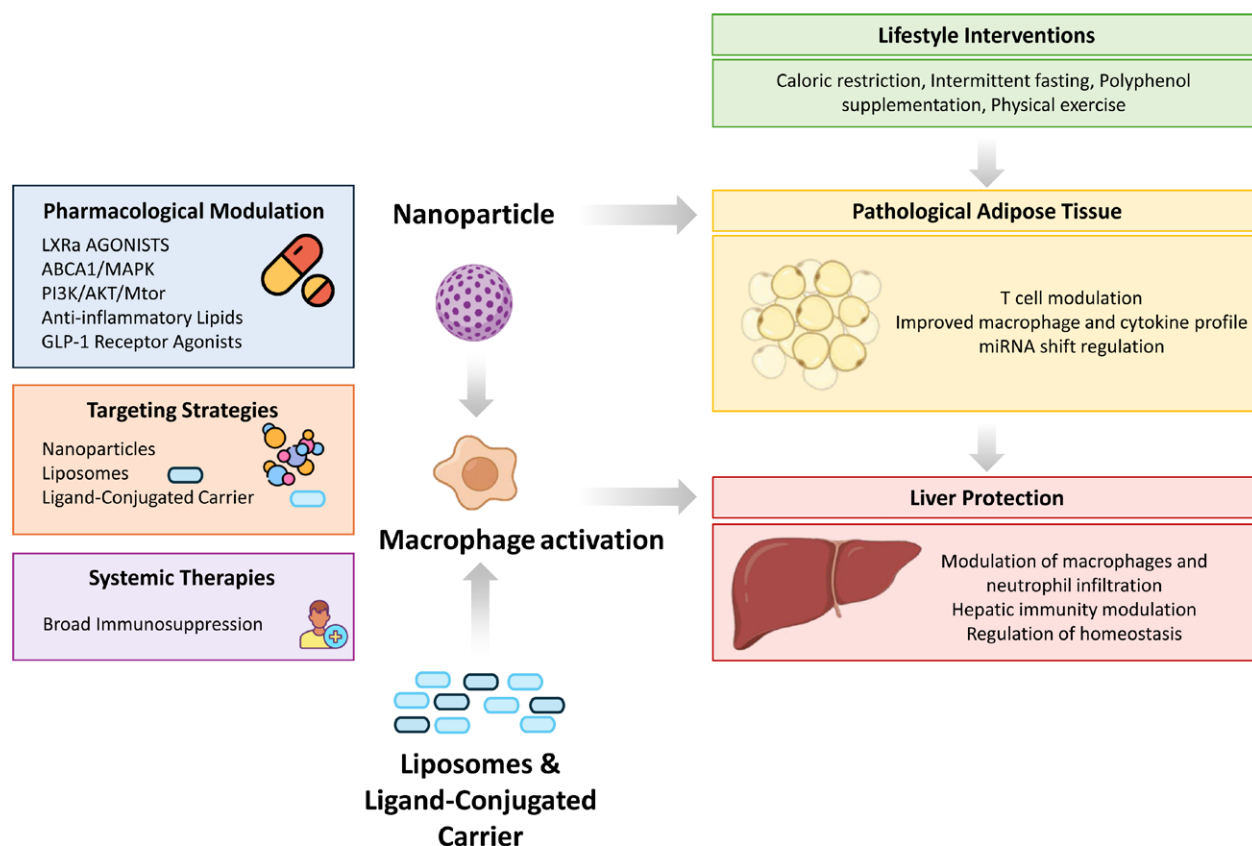


FIGURE 3. Therapeutic landscape for targeting adipose tissue dysfunction to optimize liver transplant outcomes. Schematic overview of multimodal strategies designed to mitigate the proinflammatory and metabolic disturbances inherent to pathological adipose tissue in the pretransplant setting. Lifestyle interventions, alongside pharmacological modulators, promote beneficial adipose tissue remodeling by regulating T-cell dynamics, miRNA expression, and macrophage profiles. The integration of advanced delivery systems, such as nanoparticles and ligand-conjugated liposomes, enables precise targeting and macrophage activation. These synergistic approaches foster a protective hepatic environment characterized by attenuated neutrophil/macrophage infiltration and restored homeostatic regulation, ultimately enhancing graft survival and recipient clinical trajectories. ABCA1, ATP-binding cassette transporter A1; AKT, protein kinase B; GLP-1R, glucagon-like peptide-1 receptor; LXR α , liver X receptor- α ; PI3K, phosphoinositide 3-Kinase.

impairs liver function,⁴⁵ highlighting their dual role in regulating inflammation, metabolism, and immune responses.

Cell-based therapies using adipose-derived mesenchymal stem/stromal cells (ADSCs) further expand therapeutic options. ADSCs secrete anti-inflammatory cytokines, growth factors, and EVs that suppress T-cell activation, inhibit dendritic cell maturation, promote regulatory T cells and M2 macrophages, and support hepatocyte survival and regeneration. Preclinical studies in models of liver fibrosis and warm I/R injury demonstrate that ADSCs and their secretome attenuate inflammation, reduce apoptosis, and enhance regenerative signaling.⁴⁹

However, the clinical translation of ADSC-based therapies faces important limitations.

Autologous ADSCs obtained from patients with cirrhosis, HCC, obesity, or metabolic syndrome may exhibit impaired proliferative capacity, altered secretome composition, increased senescence, and reduced immunomodulatory function due to chronic inflammation, oxidative stress, or tumor-associated reprogramming. Conversely, allogeneic ADSCs from healthy donors offer more consistent regenerative and immunoregulatory properties but raise concerns regarding immune recognition, persistence under immunosuppression, and potential interactions with posttransplant immunosuppressive regimens. In addition, the risk of unintended differentiation or tumor-promoting effects (particularly relevant in HCC recipients) remains incompletely understood.

To address these challenges, increasing interest has shifted toward cell-free approaches using ADSC-derived exosomes or conditioned media, which retain many immunomodulatory and regenerative properties while reducing the risks associated with whole-cell therapies. These vesicles modulate lipid metabolism, oxidative stress, and inflammation through miRNA-dependent pathways, improving outcomes in liver injury models.⁵⁰ Although early-phase clinical trials in cirrhosis indicate safety and functional improvement, application in LT remains investigational. Further studies are required to define optimal timing, tissue specificity, and efficacy in the transplant setting.

QUESTIONS TO BE RESOLVED AND FURTHER DIRECTIONS

Direct “source-level” evidence that recipient VAT-derived mediators causally drive I/R injury, liver allograft rejection, or HCC recurrence after LT remains limited and heterogeneous. Although adipokines, cytokines, and lipid-related mediators measured in blood or graft tissue correlate with dysfunction and immune activation, most LT studies do not resolve whether these signals originate from VAT, the graft, or both, constraining mechanistic interpretation and rational therapeutic targeting of the adipose tissue-liver axis. A second major gap is methodological; I/R and rejection have traditionally been investigated separately using isogenic versus allogeneic models, despite their frequent coexistence in clinical LT. Accordingly, a key unresolved question is which mediators exert convergent versus divergent effects across I/R injury and rejection, and under which donor-recipient scenarios. The roles of leptin, resistin, and visfatin in I/R and especially in liver rejection remain insufficiently defined. For lipids

and lipid-related species, LT evidence remains associative (biomarker-focused), with limited mechanistic support in either I/R injury or rejection. Importantly, most experimental LT studies use healthy recipients and fail to reproduce common clinical scenarios, including cirrhosis or HCC, obesity-related metabolic dysfunction with pathological VAT, and the use of extended-criteria grafts (including steatotic livers) from DBD and DCD donors. It remains unknown whether VAT-derived mediators are causal in these settings, how donor type and graft quality influence shared pathways, or whether the same signals drive early injury and long-term immune and oncologic outcomes. Addressing these gaps will require experimental and translational strategies aligned with clinical LT, integrating isogenic and allogeneic models, incorporating pathological VAT (obesity, cirrhosis, or HCC) together with extended-criteria grafts. Establishing causality will likely require adipose-focused approaches (eg, lipectomy and VAT-specific labeling/tracing) to determine whether mediators released from donor and recipient VAT reach the portal circulation and directly modulate graft injury and alloimmune activation. In parallel, source-informed sampling (paired donor/recipient VAT, portal and systemic blood, and graft biopsies before graft retrieval from donors, around reperfusion, and longitudinally) would improve inference on origin, timing, and hepatic delivery. Profiling circulating and adipose-derived EVs (including miRNA cargo) could further define temporal dynamics of adipose-driven inflammation after LT. Within this framework, machine perfusion provides a complementary platform to isolate graft-intrinsic vulnerability from recipient-derived influences and to test candidate mediators derived from adipose tissue through controlled addition or blockade. Clinically, standardized assessment of recipient visceral adiposity, together with donor/recipient metabolic-inflammatory characterization, should be linked to adjudicated outcomes (I/R injury, rejection, HCC recurrence). Once VAT-derived mechanisms are validated, translational priorities include interventions that reduce adipose inflammation or modulate adipose immune-metabolic pathways (including targeted delivery and cell-free EV-based strategies), with careful evaluation of timing, interactions with immunosuppression, and long-term safety.

CONCLUSIONS

Direct causal evidence linking adipose-derived mediators to I/R injury and graft rejection after LT remains limited and appears to depend on donor type and graft quality. Available data support specific adipose-liver crosstalk mechanisms mediated by a restricted set of adipocytokines and immune regulators, particularly adiponectin and resistin in I/R injury, and selected immune-regulatory pathways, such as TIM-4 signaling linking recipient adipose immune activation to graft stress responses. However, the narrow range of mediators analyzed, the lack of independent models, and insufficient validation across donor types, graft characteristics, and recipient pathological states constrain the generalizability of current findings and preclude definitive conclusions. Moreover, many LT studies assess inflammatory or immune mediators without resolving their tissue source. Without “source-level” attribution, it remains unclear

which pathways should be inhibited or enhanced to mitigate I/R injury and rejection across clinically relevant scenarios.

In clinical LT, recipient VAT is consistently associated with, but not causally linked to, I/R injury, graft dysfunction, rejection, frailty, and HCC recurrence. Although increased VAT correlates with poorer early and long-term outcomes, the mechanisms remain unclear. A plausible hypothesis is that dysfunctional VAT, enriched in inflammatory and immune cells, contributes to a proinflammatory and immunometabolic milieu by releasing cytokines, adipokines, chemokines, and lipid mediators that may reach the liver via the portal circulation. Interpretation of these associations is further complicated by interactions between recipient factors and graft-related determinants, including donor type and graft quality. Overall, current evidence supports a correlation rather than causation with major mechanistic gaps. Although adipose-targeted therapies are increasingly proposed, most supporting data derive from metabolic disease or nontransplant liver injury models rather than LT-specific studies. Establishing causality in clinically relevant donor-recipient contexts is therefore essential before prioritizing adipose-targeted interventions for LT.

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