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Mini Review

Increased Susceptibility to Hepatic Ischemia–reperfusion Injury in MASLD: A Mini Review

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly prevalent worldwide and is frequently encountered in patients undergoing liver transplantation and hepatic surgery. Although hepatic steatosis was once considered a relatively benign condition, accumulating evidence indicates that MASLD is associated with reduced tolerance to ischemic stress and increased susceptibility to ischemia–reperfusion injury, which may contribute to graft dysfunction and postoperative liver injury. In this mini review, we used the concept of hepatic resilience, referring to the ability of the liver to maintain homeostasis during stress and recover after injury. We discussed how MASLD may reduce hepatic resilience through mechanisms involving lipotoxicity, mitochondrial dysfunction, oxidative stress, inflammatory activation, regulated cell death, and impaired regeneration. MASLD represents a heterogeneous disease spectrum, and susceptibility to ischemia–reperfusion injury may differ according to disease stage and phenotype, particularly in the presence of progressive inflammation and fibrosis. We further summarized strategies aimed at improving hepatic resilience, including metabolic optimization, mitochondrial protection, modulation of reperfusion-associated inflammation, and enhancement of tissue repair. However, current evidence remains limited by the paucity of human studies and validated approaches for assessing hepatic resilience. Further investigation of these mechanisms may help develop individualized strategies to protect the liver in patients with MASLD during hepatic surgery and transplantation.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease, has emerged as the most prevalent chronic liver disorder worldwide, affecting approximately 30% of the global population.[1,2] Driven by the increasing prevalence of obesity, insulin resistance, and metabolic syndrome, MASLD has become a major contributor to liver-related morbidity and mortality.[3,4] Beyond lipid accumulation, MASLD is associated with disturbed lipid metabolism, mitochondrial dysfunction, chronic low-grade inflammation, and impaired cellular adaptation to stress. These changes may reduce the liver's ability to maintain metabolic and functional stability when exposed to acute injury.

Evidence suggests that MASLD-affected livers may be more susceptible to hepatic ischemia–reperfusion injury (HIRI), particularly in liver transplantation and hepatic surgery.[5-7] Compared with nonsteatotic livers, MASLD-affected livers may exhibit more pronounced inflammatory responses, impaired mitochondrial adaptation, increased oxidative stress, and delayed recovery after acute challenges.[8,9] Thus, MASLD should be viewed not simply as excessive lipid accumulation but as a condition associated with reduced hepatic stress tolerance and impaired resilience.[10] Unlike hepatic reserve, which mainly reflects baseline functional capacity, hepatic resilience refers to the dynamic ability of the liver to adapt to acute stress and recover after injury.

The mechanisms underlying this increased susceptibility involve interconnected alterations in metabolism, immunity, and tissue repair. Lipid overload promotes the accumulation of toxic lipid species, disrupts energy homeostasis, and impairs mitochon-

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drial function, thereby limiting hepatocyte adaptation to stress.[11] Meanwhile, chronic metabolic inflammation, particularly in progressive MASLD phenotypes, may prime immune pathways that amplify inflammatory responses after acute insults.[12] These processes are closely interconnected, as mitochondrial dysfunction and oxidative stress further promote inflammatory activation, while persistent inflammation impairs tissue repair. Defective regenerative responses further compromise recovery and may prolong hepatic injury.[13]

Understanding why livers affected by MASLD respond differently to acute injury has important clinical implications. With the increasing prevalence of MASLD, more patients with steatosis are undergoing liver transplantation or hepatic surgery, where HIRI represents an important determinant of postoperative outcomes.[14] However, effective strategies to prevent or attenuate HIRI remain limited.[15]

In this mini review, we aim to summarize current knowledge regarding the mechanisms responsible for increased susceptibility to HIRI in MASLD. We discussed how metabolic dysfunction alters hepatic stress adaptation, amplifies injury responses, and impairs recovery. We further highlighted emerging strategies aimed at restoring hepatic resilience in the settings of liver transplantation and hepatic surgery.

Mechanisms underlying increased susceptibility to HIRI in MASLD

MASLD is not merely a consequence of excessive lipid storage but represents a metabolically reprogrammed state in which hepatocytes undergo metabolic adaptations to chronic lipid overload.[16] Under physiological conditions, hepatocytes maintain lipid homeostasis through coordinated regulation of fatty acid uptake, synthesis, oxidation, and export. However, persistent nutrient excess and metabolic dysfunction disrupt this balance, leading to excessive lipid deposition, altered lipid flux, mitochondrial stress, and impaired cellular adaptability.[17] Rather than serving as a passive reservoir of excess fat, MASLD creates a vulnerable metabolic environment characterized by reduced stress tolerance and impaired hepatic resilience.[18] These alterations may predispose the liver to exaggerated responses when exposed to acute stressors.

Lipotoxicity and mitochondrial dysfunction impair hepatic stress adaptation

Excessive lipid accumulation is a defining feature of MASLD and represents a major contributor to increased susceptibility to acute injury.[19] Although triglyceride storage within lipid droplets is relatively inert, persistent lipid overload promotes the accumulation of lipotoxic species, including saturated fatty acids, ceramides, and other bioactive lipid metabolites.[20] These toxic lipid intermediates disrupt cellular membranes, impair insulin signaling, and activate stress-responsive pathways, thereby reducing hepatocyte tolerance to ischemic stress.[21] Importantly, lipotoxicity-induced metabolic stress directly impairs mitochondrial function, a central determinant of hepatic stress adaptation.[22,23]

Mitochondria are essential regulators of hepatic energy metabolism and cellular resilience. In MASLD, excessive fatty acid influx increases the burden on mitochondrial β-oxidation and electron transport chain activity.[24] Although mitochondrial adaptations may initially compensate for increased metabolic demand, persistent lipid stress ultimately leads to mitochondrial dysfunction, characterized by impaired oxidative phosphorylation, excessive reactive oxygen species (ROS) generation, and defective mitochondrial quality control.[25] Consequently, steatotic hepatocytes exhibit reduced metabolic flexibility and a reduced capacity to respond to sudden increases in energy requirements.[26]

This mitochondrial vulnerability is particularly evident during HIRI. Ischemia–reperfusion imposes a rapid transition from oxygen deprivation to oxidative stress, requiring efficient mitochondrial recovery and antioxidant defense mechanisms. In MASLD, reduced mitochondrial reserve compromises adenosine triphosphate production and antioxidant capacity, which may accelerate hepatocellular injury during reperfusion.[27] Thus, metabolic dysfunction may convert adaptive mitochondrial responses into impaired stress tolerance, contributing to reduced hepatic resilience.

Inflammatory priming amplifies HIRI

Inflammatory activation represents an important contributor to hepatic vulnerability, although its magnitude varies across the MASLD spectrum.[28] In particular, persistent inflammatory signaling and immune activation are more prominent in metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrotic MASLD than in simple steatosis. In progressive MASLD phenotypes, lipid accumulation, metabolic disturbances, and altered interorgan communication continuously activate inflammatory pathways, creating a preexisting immune-activated state before ischemic stress occurs.[29] This inflammatory priming increases hepatic responsiveness and lowers the threshold for excessive inflammatory activation during reperfusion.

Hepatic macrophages, particularly Kupffer cells, are central regulators of this inflammatory environment. Metabolic stress, hepatocyte injury, and altered gut-derived signals promote macrophage activation and the release of proinflammatory mediators, including tumor necrosis factor-α, interleukin-1β, and other cytokines.[30] Persistent activation of inflammasome-related pathways further sustains a chronic inflammatory state, increasing susceptibility to exaggerated inflammatory responses after reperfusion.[31]

During acute injury, this preexisting inflammatory activation amplifies hepatic damage. Ischemia–reperfusion injury, for example, induces the release of damage-associated molecular patterns, triggering innate immune activation and inflammatory cell recruitment.[32] Mitochondrial dysfunction and hepatocellular stress in MASLD further promote the release of these molecules, providing an additional link between metabolic injury and inflammatory activation. In MASLD, enhanced macrophage activation, impaired inflammatory resolution, and increased oxidative stress may contribute to prolonged inflammation and greater hepatocellular injury after ischemia–reperfusion.[33]

Thus, inflammatory priming represents a key link between chronic metabolic dysfunction and increased susceptibility to HIRI. Therapeutic strategies aimed at restoring immune balance rather than broadly suppressing inflammation may help attenuate reperfusion-associated injury while preserving essential repair responses in MASLD.

Impaired regenerative responses delay recovery after HIRI

The severity of HIRI is determined not only by the extent of initial cellular damage but also by the capacity of the liver to initiate effective repair. Although the liver possesses remarkable regenerative potential, metabolic dysfunction associated with steatosis compromises this adaptive response and delays recovery after acute insults.[34] Thus, impaired repair represents an important component of reduced hepatic resilience in MASLD.

In nonsteatotic livers, acute injury initiates coordinated processes involving hepatocyte proliferation, inflammatory resolution, extracellular matrix remodeling, and restoration of tissue homeostasis.[35] In contrast, MASLD-affected livers exhibit defective repair responses due to persistent metabolic stress and altered cellular signaling. Persistent metabolic stress in MASLD may impair hepatocyte proliferation and regenerative signaling, thereby delaying hepatic recovery after injury.[36]

Chronic inflammatory activation further contributes to defective repair. Although inflammation is required for initiating regeneration, timely resolution of inflammatory signaling is essential for successful recovery. In MASLD, persistent inflammatory mediators, oxidative stress, and cellular stress signals impair this resolution phase, promoting prolonged injury and maladaptive repair responses that may contribute to fibrotic remodeling.[37,38]

The clinical relevance of impaired repair capacity is particularly evident when acute stress occurs on a background of chronic steatosis. Steatotic grafts used in liver transplantation and steatotic livers subjected to ischemia–reperfusion stress have been reported to exhibit greater hepatocellular injury than nonsteatotic counterparts.[39,40] These observations indicate that hepatic vulnerability reflects not only increased initial injury but also a reduced ability to restore normal liver function.

Collectively, metabolic stress, inflammatory priming, and defective repair responses form an interconnected network underlying reduced hepatic resilience in MASLD, explaining why ischemic stress tolerated by nonsteatotic livers may result in disproportionate injury and delayed recovery (Fig. 1).

Regulated cell death pathways contribute to HIRI

Regulated cell death pathways have emerged as important mechanisms contributing to hepatocellular injury during HIRI. These processes are tightly linked to metabolic stress, oxidative damage, and inflammatory signaling. In MASLD, preexisting metabolic disturbances may increase hepatocyte susceptibility to activation of these pathways during ischemia and reperfusion, resulting in more severe tissue injury. Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation and impaired antioxidant defense, has gained attention in the context of liver injury.[39,40] Hepatic steatosis may increase susceptibility to ferroptosis through lipid accumulation, mitochondrial dysfunction, and altered redox balance. During ischemia–reperfusion, excessive ROS production and impaired antioxidant responses can promote lipid peroxidation and membrane damage, contributing to hepatocellular injury in MASLD.[41] Experimental studies suggest that inhibition of ferroptosis may reduce ischemia–reperfusion-associated injury, although its clinical relevance remains to be established.[42] Other regulated cell death pathways, including pyroptosis, may also contribute to HIRI by linking cellular stress with inflammatory responses.[43] Activation of inflammasome-related signaling promotes the release of inflammatory mediators and enhances innate immune activation. In MASLD, chronic metabolic stress and inflammatory priming may facilitate excessive activation of these pathways after reperfusion, further worsening tissue injury. However, the relative contribution of individual cell death pathways in MASLD-associated HIRI remains unclear, and these mechanisms likely interact with mitochondrial dysfunction and inflammation rather than functioning independently. Overall, regulated cell death pathways represent important mediators linking lipotoxicity, oxidative stress, and inflammation during HIRI. These mechanisms provide another explanation for reduced hepatic resilience and impaired recovery after ischemic injury in MASLD.

Clinical implications of increased susceptibility to HIRI

The increased vulnerability of MASLD-affected livers has important clinical implications, particularly in settings involving hepatic ischemia–reperfusion stress. With the rising prevalence of MASLD, more patients with steatosis are undergoing liver transplantation and hepatic surgery, where ischemic stress may result in disproportionate injury and delayed recovery. These clinical scenarios highlight how metabolic dysfunction modifies hepatic responses to ischemia–reperfusion and emphasize the need for strategies to identify high-risk patients and improve perioperative outcomes (Table 1).[44]

Ischemia–reperfusion injury in MASLD

HIRI represents one of the most clinically relevant manifestations of the vulnerable steatotic liver. This process is particularly important in liver transplantation and major hepatic surgery, where transient interruption and restoration of blood supply impose substantial metabolic stress on hepatocytes. Compared with nonsteatotic livers, MASLD-affected livers may exhibit exaggerated responses to HIRI, potentially resulting in greater hepatocellular damage, impaired graft function, and delayed recovery.[45]

Multiple mechanisms contribute to the enhanced sensitivity of MASLD-affected livers to HIRI. Reduced mitochondrial function compromises the ability of hepatocytes to maintain energy homeostasis during ischemia and recover after oxygen restoration. During reperfusion, preexisting lipid accumulation and mitochondrial dysfunction further promote oxidative stress, leading to increased ROS generation, mitochondrial injury, and activation of cell death pathways.[46] In parallel, preexisting inflammatory priming in MASLD facilitates excessive immune cell recruitment and amplifies inflammatory cascades after reperfusion, thereby aggravating tissue damage.[47]

The clinical impact of this phenomenon is particularly evident in liver transplantation. Steatotic grafts are more susceptible to preservation-related injury and are associated with an increased risk of early graft dysfunction compared with nonsteatotic grafts.[48] These observations highlight the importance of improving metabolic fitness and reducing hepatic vulnerability before transplantation or surgical intervention. More broadly, HIRI provides a clinically relevant model demonstrating how metabolic dysfunction impairs hepatic stress tolerance and converts otherwise manageable ischemic stress into more severe tissue injury and delayed recovery.

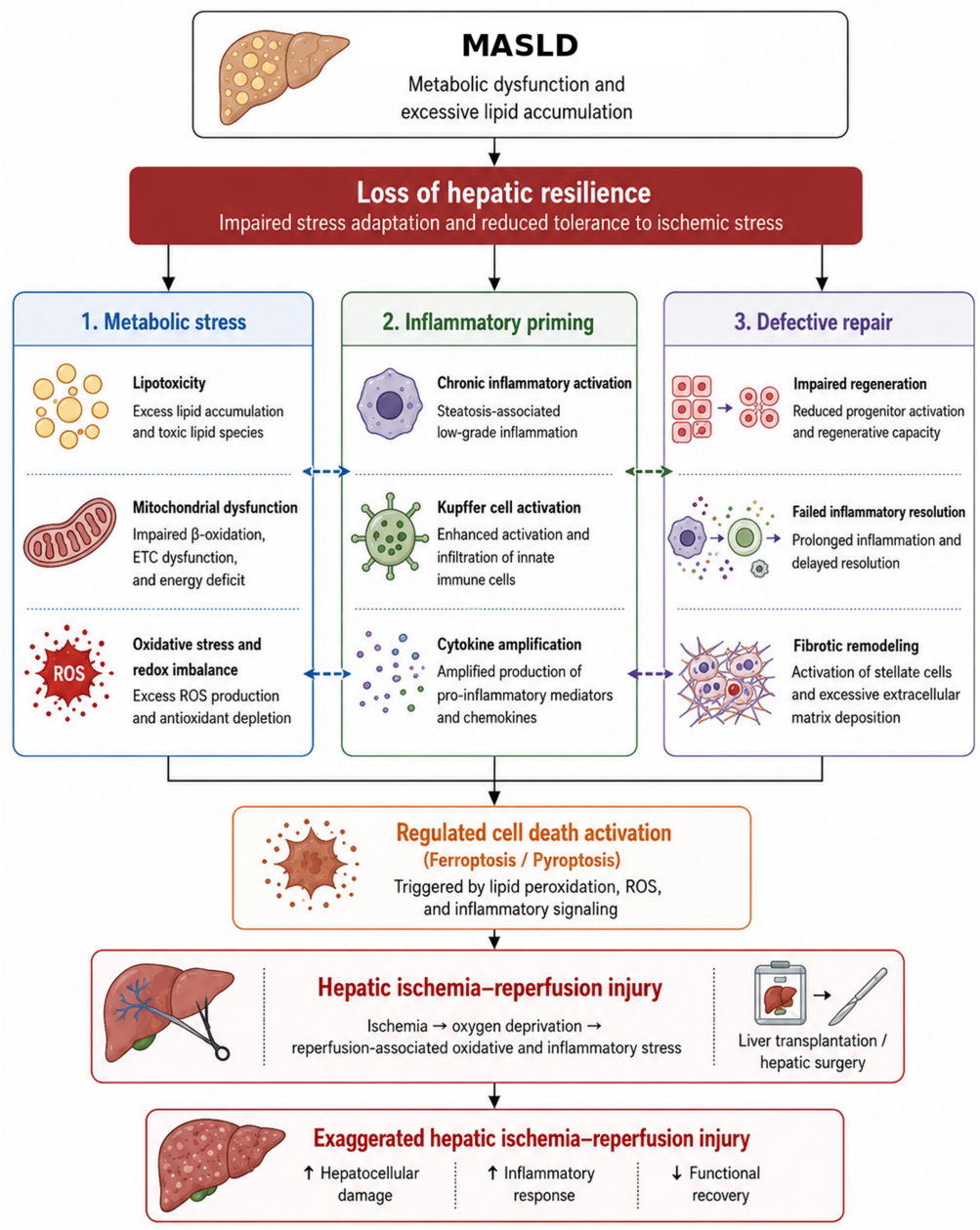

Fig. 1. Mechanisms underlying increased susceptibility to HIRI in MASLD. MASLD may impair hepatic resilience through metabolic stress, inflammatory priming, defective repair, and activation of regulated cell death, thereby increasing hepatocellular injury and delaying recovery after ischemia–reperfusion. Upward and downward arrows indicate increases and decreases, respectively. Bidirectional dashed arrows indicate interactions between the corresponding pathways, with different colors used to distinguish the pathways. ETC, electron transport chain; HIRI, hepatic ischemia–reperfusion injury; MASLD, metabolic dysfunction-associated steatotic liver disease; ROS, reactive oxygen species.

HIRI in liver transplantation and hepatic surgery

Hepatic surgery is another common clinical setting in which MASLD-affected livers are subjected to ischemia–reperfusion stress. Temporary interruption of hepatic blood flow during procedures such as vascular inflow control results in ischemic injury followed by reperfusion-associated metabolic and inflammatory responses. The ability of the liver to withstand this stress depends on baseline metabolic status and the capacity of hepatocytes to adapt to injury. In MASLD, mitochondrial dysfunction, impaired antioxidant defenses, and chronic inflammatory activation may reduce tolerance to ischemic stress.[45] Excess lipid accumulation increases mitochondrial vulnerability and impairs maintenance of energy homeostasis during ischemia and recovery after reperfusion. In addition, persistent inflammatory activation may enhance reperfusion-induced immune responses and prolong

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Table 1. Clinical contexts associated with increased susceptibility to HIRI in MASLD

Acute insult	Clinical context	Key mechanisms in MASLD	Potential consequences
Ischemia–reperfusion injury	Liver transplantation; hepatic surgery with temporary vascular occlusion	Mitochondrial dysfunction; impaired energy metabolism; excessive ROS production; inflammatory activation; impaired stress adaptation	Exaggerated hepatocellular injury; increased risk of early graft dysfunction; delayed functional recovery

HIRI, hepatic ischemia–reperfusion injury; MASLD, metabolic dysfunction-associated steatotic liver disease; ROS, reactive oxygen species.

tissue injury.[46,47] Hepatic steatosis alone may not fully determine surgical outcomes but may influence how the liver responds to ischemic stress. The extent of HIRI is likely affected by several factors, including the degree of steatosis, the presence of inflammation or fibrosis, and the patient's overall metabolic status. The MASLD phenotypes encountered may differ between liver transplantation and hepatic resection. Steatotic donor grafts selected for transplantation may represent less advanced disease, whereas patients undergoing hepatic resection can have a broader range of MASLD severity. This difference should be considered when interpreting HIRI susceptibility across surgical settings. Assessment of hepatic resilience may therefore provide additional information beyond conventional liver function tests before major hepatic surgery. Unlike transplantation, hepatic surgery often involves predictable ischemic events, creating opportunities for preoperative optimization. Improving metabolic status, maintaining mitochondrial function, and controlling excessive inflammation may help enhance postoperative recovery, although their clinical benefits require further evaluation.

Therapeutic perspectives: restoring hepatic resilience

Given the increasing prevalence of MASLD and the clinical consequences of HIRI in patients with MASLD, strategies aimed at reducing hepatic vulnerability have become increasingly important. However, therapeutic approaches should extend beyond simply reducing hepatic lipid accumulation. Instead, restoring hepatic resilience by improving metabolic flexibility, enhancing stress adaptation, modulating inflammatory responses, and promoting effective repair may provide a more comprehensive strategy to reduce susceptibility to HIRI.[48] Targeting the mechanisms underlying this increased susceptibility may provide opportunities to improve hepatic tolerance to and recovery from acute stress in MASLD.

Improving metabolic fitness in MASLD

Improving metabolic fitness represents a fundamental strategy for reducing hepatic vulnerability. Lifestyle interventions, including weight reduction, dietary modification, and increased physical activity, remain the cornerstone of therapy for MASLD and can improve hepatic steatosis, insulin sensitivity, and metabolic inflammation.[49] Beyond reducing hepatic lipid burden, these approaches may restore metabolic flexibility and enhance hepatocyte adaptation to acute stress.

Recent advances in metabolic therapies have expanded the range of potential strategies for improving baseline hepatic resilience before predictable ischemic events. Pharmacological approaches targeting metabolic pathways, including glucagon-like peptide-1 receptor agonists and other emerging metabolic regulators, have demonstrated beneficial effects on hepatic steatosis, inflammation, and systemic metabolic homeostasis.[50] Although their direct protective effects against HIRI require further investigation, improving baseline metabolic fitness before elective procedures may help enhance stress tolerance and reduce subsequent injury severity.

Protecting mitochondrial function and reducing oxidative stress

Because mitochondrial dysfunction is a central feature of reduced hepatic resilience in MASLD, preserving mitochondrial function represents an attractive therapeutic strategy. Approaches aimed at preserving mitochondrial integrity, improving energy metabolism, and enhancing mitochondrial quality control may help maintain hepatocyte function during ischemia–reperfusion stress. Potential strategies include promoting mitochondrial biogenesis, enhancing mitophagy, and regulating oxidative stress pathways.

Beyond conventional antioxidant approaches, targeting regulated cell death pathways may provide additional opportunities to protect metabolically compromised livers. Ferroptosis and other oxidative stress-associated cell death mechanisms have been implicated in HIRI and other forms of metabolic stress-associated liver damage.[51,52] Modulating these pathways may limit excessive hepatocellular damage while preserving adaptive stress responses. However, further studies are required to determine whether these approaches can be effectively translated into clinical strategies for reducing ischemia–reperfusion-associated injury in patients with MASLD.

Modulating inflammation and promoting hepatic repair

Because inflammatory priming and defective resolution contribute significantly to HIRI progression, restoring immune balance represents another important strategy for improving hepatic resilience in MASLD. Rather than completely suppressing inflammation, future approaches should aim to prevent excessive inflammatory activation while preserving the coordinated immune responses required for tissue repair and regeneration.[53]

Strategies targeting macrophage function, inflammatory signaling pathways, and endogenous resolution mechanisms may help limit excessive tissue damage and facilitate recovery after ischemic injury. In addition, enhancing hepatocyte regeneration and improving repair responses may further promote restoration of hepatic function. Ultimately, effective therapies for MASLD-associated hepatic vulnerability will likely require integrated approaches that simultaneously address metabolic dysfunction, inflammatory dysregulation, and impaired regenerative capacity (Fig. 2).

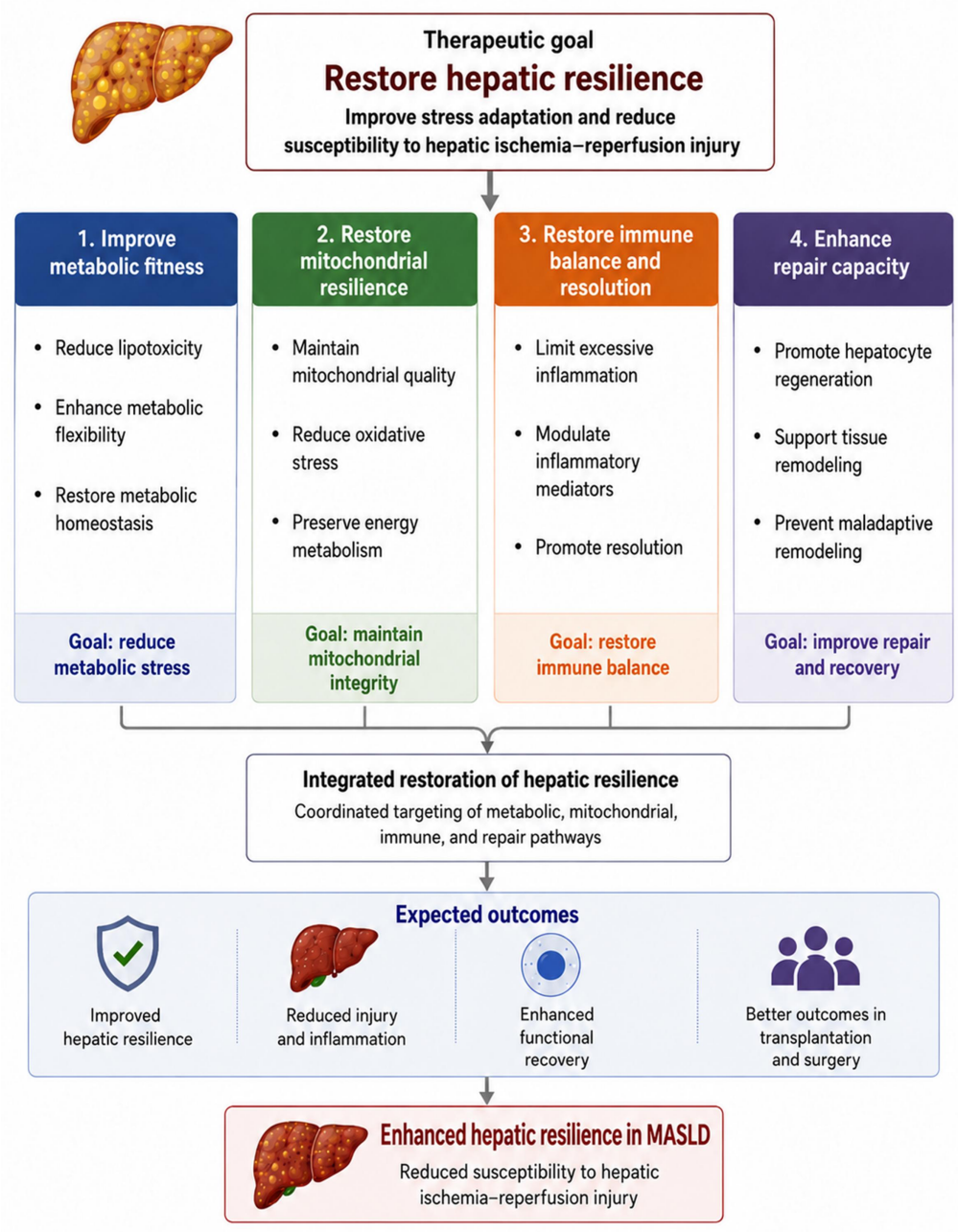

Fig. 2. Therapeutic strategies to restore hepatic resilience in MASLD. Metabolic optimization, mitochondrial protection, immune modulation, and enhancement of repair capacity may collectively improve stress adaptation and reduce ischemia–reperfusion-associated liver injury. MASLD, metabolic dysfunction-associated steatotic liver disease.

Current limitations and future perspectives

Despite advances in understanding hepatic vulnerability in MASLD, several aspects remain unclear. Much of the current mechanistic evidence is derived from experimental models, including animal and cellular studies. These models have improved our understanding of lipotoxicity, mitochondrial dysfunction, inflammatory activation, and regulated cell death, but their relevance to human MASLD-associated HIRI requires further validation. Clinical data connecting MASLD characteristics with outcomes after HIRI remain limited. Most available evidence comes from liver transplantation and surgical cohorts, in which steatosis is often assessed primarily by fat content rather than by the broader metabolic and pathological features of MASLD. Future studies should consider factors such as steatosis severity, inflammatory activity, fibrosis stage, and metabolic

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phenotype to improve patient risk stratification. Differences between lean and obesity-associated MASLD may also be relevant, although direct evidence regarding their susceptibility to HIRI remains limited. The heterogeneity of MASLD represents another important challenge. Patients with simple steatosis, MASH, and fibrotic MASLD may have different degrees of mitochondrial impairment, inflammation, and regenerative capacity, which could affect their responses to ischemic stress. However, studies addressing hepatic resilience across different disease stages and phenotypes remain limited. In addition, hepatic resilience currently lacks clinically validated biomarkers. Identifying indicators that reflect mitochondrial function, oxidative stress, inflammation, and regenerative potential may help identify high-risk patients and support individualized protective strategies in liver transplantation and hepatic surgery.

Conclusions

MASLD is not simply a condition of excessive lipid accumulation; it is associated with impaired hepatic adaptation to stress. Metabolic disturbances, mitochondrial dysfunction, immune activation, and defective regeneration contribute to increased hepatic vulnerability, particularly when the liver is exposed to ischemic stress. HIRI represents an important clinical example of this vulnerability in liver transplantation and hepatic surgery. The susceptibility of MASLD-affected livers to HIRI is driven by multiple processes, including lipotoxicity, mitochondrial injury, oxidative stress, inflammatory priming, regulated cell death, and impaired tissue repair, which collectively contribute to reduced hepatic resilience. Improving outcomes in patients with MASLD will require approaches that extend beyond lipid reduction and aim to enhance the liver's ability to respond to and recover from ischemic stress. Strategies targeting metabolic status, mitochondrial function, inflammation, and regeneration may offer opportunities for perioperative protection. Further clinical studies are needed to identify reliable markers of hepatic resilience and determine which patients are most likely to benefit from targeted interventions.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Study concept and design (QwY, GW), literature search and drafting of the manuscript (QwY), revision of the manuscript (QwY, QY, GW), and critical revision for important intellectual content (GW). All authors contributed to the interpretation of the literature and approved the final manuscript.

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