



MASH as a network disease: therapeutic modulation of interorgan immunometabolic architecture

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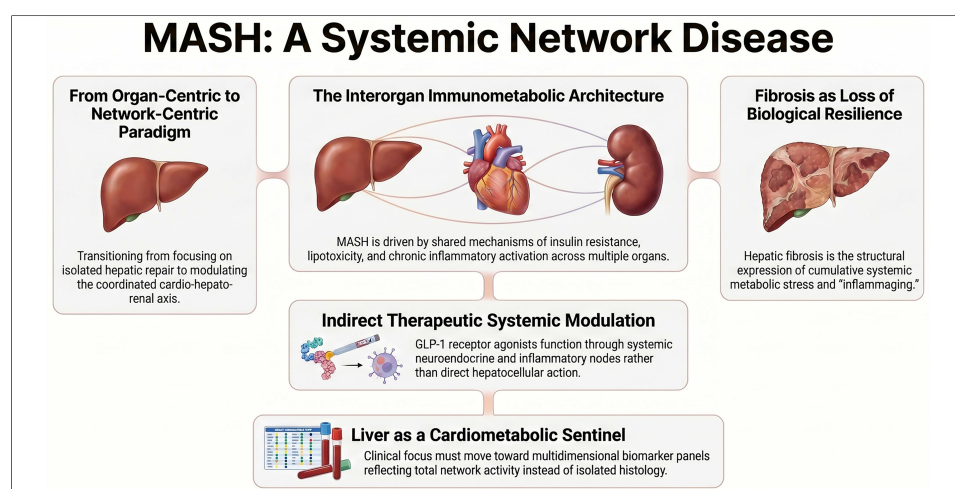
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MASH AS A NETWORK DISEASE

The study by Jara *et al.* represents a mechanistic contribution of particular significance to the field of metabolic dysfunction-associated steatohepatitis (MASH), integrating histological, proteomic and preclinical data to delineate the coordinated modulation of metabolic, inflammatory and fibrogenic pathways under semaglutide treatment^[1]. Beyond documenting histological resolution, the study provides consistent evidence of a coordinated reorganization of interconnected regulatory nodes, reinforcing the interpretation of MASH as a tissue-level manifestation of a systemic immunometabolic network.

MASH constitutes the hepatic expression of a systemic metabolic derangement whose population burden has reached global proportions^[2]. Its bidirectional association with type 2 diabetes is not merely epidemiological but pathophysiological, reflecting shared mechanisms of insulin resistance, lipotoxicity



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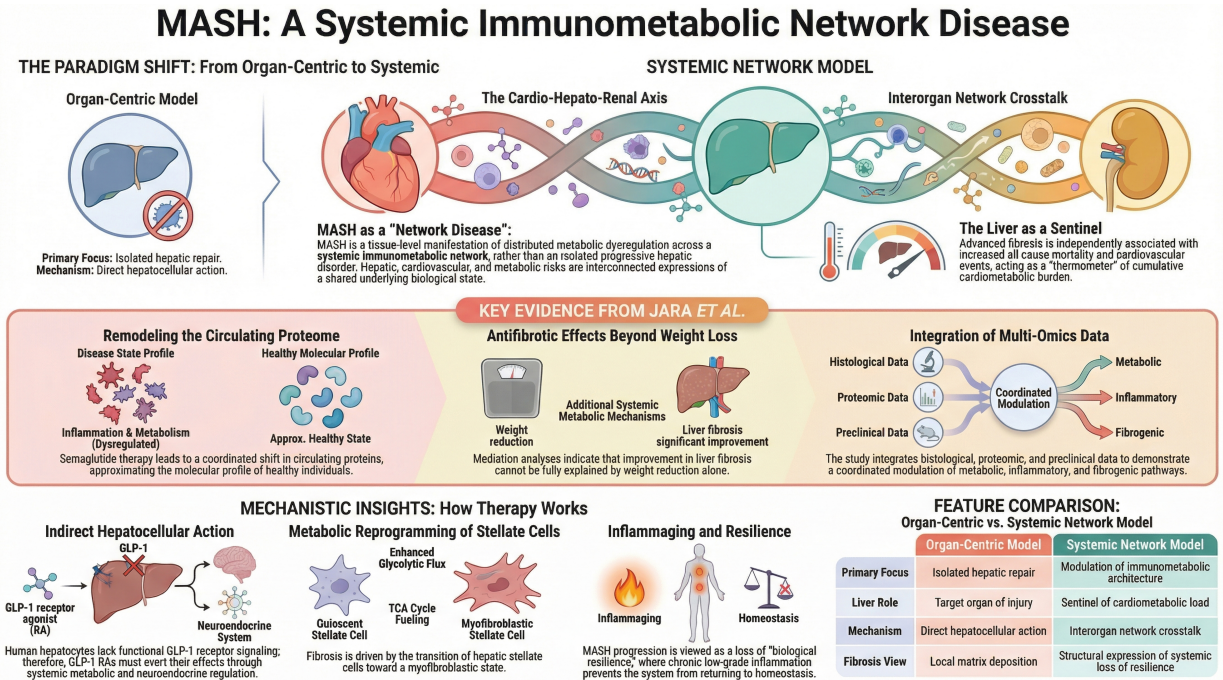


Figure 1. MASH as a systemic immunometabolic network disease. Schematic representation of the paradigm shift from an organ-centric model - focused on isolated hepatic repair and direct hepatocellular mechanisms - to a systemic network framework integrating the cardio-hepato-renal axis. Key evidence from Jara *et al.* demonstrates coordinated remodeling of the circulating proteome toward a non-disease molecular profile and antifibrotic effects not fully explained by weight reduction alone^[1]. Mechanistically, GLP-1 receptor agonism acts indirectly through systemic metabolic and neuroendocrine pathways, modulates stellate cell metabolic reprogramming, and attenuates fibrogenic activation. Advanced fibrosis is conceptualized as a structural expression of systemic immunometabolic dysregulation and loss of biological resilience, positioning the liver as a sentinel of cumulative cardiometabolic burden rather than an isolated target organ. MASH: Metabolic dysfunction-associated steatohepatitis; GLP-1: glucagon-like peptide-1; GLP-1 RA: glucagon-like peptide-1 receptor agonist; TCA: tricarboxylic acid.

and chronic inflammatory activation^[3]. Convergentlly, its integration within the cardio-hepato-renal axis does not represent additive comorbidity but rather parallel manifestations of a common disrupted metabolic architecture^[4,5], as shown in Figure 1. The joint European Association for the Study of the Liver (EASL)-European Association for the Study of Diabetes (EASD)-European Association for the Study of Obesity (EASO) guidelines have formalized this conceptual shift by embedding hepatic, cardiovascular and metabolic risk stratification within a unified clinical framework^[6].

International recognition of metabolic dysfunction-associated steatotic liver disease (MASLD)/MASH as a systemic entity further consolidates this paradigm^[7]. Within this framework, the liver may be interpreted as a sensor of cumulative cardiometabolic burden, given that advanced fibrosis is independently associated with increased all-cause mortality and cardiovascular events^[4,8]. This association suggests that hepatic stage reflects the temporal integration of systemic metabolic exposures rather than purely local injury.

INTERORGAN IMMUNOMETABOLIC ARCHITECTURE

The data generated by Jara *et al.* demonstrate that histological resolution is accompanied by coordinated modulation of circulating proteins implicated in inflammation, metabolism and fibrogenesis, approximating the molecular profile observed in individuals without disease^[1]. Such a pattern is consistent with an intervention acting on interorgan regulatory networks rather than on an isolated anatomical compartment. The functional absence of glucagon-like peptide-1 (GLP-1) receptor expression in human hepatocytes^[9-11] further excludes a dominant direct hepatocellular mechanism, although more complex intrahepatic effects cannot be fully excluded. Emerging evidence suggests potential contributions from paracrine signaling,

modulation of non-parenchymal cells, and hepatic microenvironment remodeling. MASH progression depends on sustained activation of the hepatic microenvironment, wherein lipotoxic hepatocytes trigger pro-inflammatory signaling and activation of hepatic stellate cells^[12,13]. Metabolic reprogramming of these cells constitutes a critical axis of fibrogenesis. Loss of phosphoenolpyruvate carboxykinase 1 (PCK1) in hepatic stellate cells drives enhanced glycolytic flux and tricarboxylic acid cycle fueling, promoting fibrogenic activation^[14]. This myofibroblastic transition entails mitochondrial remodeling and redox alterations, reflecting integrated metabolic adaptation rather than an exclusively local phenomenon.

Recent single-cell transcriptomic analyses further demonstrate that hepatic stellate cell activation in MASLD is characterized by coordinated shifts in metabolic gene expression programs, including enhanced glycolysis, altered oxidative phosphorylation, and pro-fibrogenic cytokine signaling, reinforcing that fibrogenesis represents a metabolically rewired cellular state rather than a passive scarring process^[15]. Parallel experimental evidence indicates that adipose tissue inflammation and dysregulated adipokine secretion amplify hepatic stellate cell activation and extracellular matrix deposition, thereby functionally linking visceral adiposity to hepatic fibrosis progression^[16].

The therapeutic rationale for intervention “beyond the liver” therefore gains mechanistic coherence^[17]. Incretin biology modulates energy intake, energy expenditure, systemic inflammation and central neuroendocrine regulation^[18,19]. Cardiovascular benefits demonstrated in clinical trials^[20], together with the efficacy of dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonism in MASH^[19], confirm that therapeutic effects operate at shared regulatory nodes. Mediation analyses reported by Jara *et al.* further indicate that improvement in fibrosis cannot be explained solely by weight reduction, implying the contribution of additional metabolic mechanisms^[1]. Large cardiovascular outcome trials with GLP-1 receptor agonists have consistently shown reductions in major adverse cardiovascular events independent of baseline body mass index, supporting the concept that incretin-based therapies act on systemic inflammatory and metabolic pathways beyond weight loss alone^[21]. In addition, the AMPK (adenosine monophosphate-activated protein kinase)-centric hypothesis further supports this systemic view, as AMPK acts as a central metabolic regulator linking energy homeostasis, inflammation and fibrogenesis, reinforcing the notion that therapeutic efficacy in MASH extends beyond the liver^[22].

In summary, these findings support the view that fibrogenesis in MASH reflects coordinated immunometabolic dysregulation across interconnected organ systems rather than an isolated hepatic process.

TEMPORAL BIOLOGY, INFLAMMAGING AND FIBROSIS TRAJECTORIES

Histological reversal following substantial weight loss is well established^[23,24]. However, equivalent weight reductions may be associated with divergent metabolic signatures^[25], and inflammatory changes may precede maximal weight loss under incretin agonism^[26]. These findings suggest that systemic inflammatory modulation may exert an independent influence on reversal trajectories.

From a temporal perspective, MASH progression can be interpreted as the tissue crystallization of a deviated biological trajectory shaped by chronic low-grade inflammation and persistent metabolic dysregulation. This framework converges with the concept of inflammaging, which defines sustained immunometabolic activation as a transversal substrate of biological aging and multiple chronic diseases^[27,28]. The updated hallmarks of aging further integrate metabolic dysfunction and loss of adaptive resilience as core components of the aging process^[29].

Chronic low-grade inflammation has been mechanistically linked to progressive organ fibrosis through sustained activation of innate immune pathways, redox imbalance, and epigenetic remodeling, thereby connecting metabolic stress to durable structural tissue change^[27].

Epigenetic alterations induced by metabolic overload - including DNA methylation changes and histone modifications - have been described in MASLD and may contribute to persistent fibrogenic programming even after partial metabolic improvement^[30].

Interaction with the intestinal microbiome introduces an eco-biological dimension to metabolic susceptibility^[31]. Within this context, fibrosis may be understood as the cumulative structural expression of impaired biological resilience, defined as the capacity of the system to absorb metabolic and inflammatory perturbations and return to homeostasis^[32]. Gut-derived microbial metabolites, including short-chain fatty acids and endotoxin-related signals, modulate hepatic inflammation and stellate cell activation, providing a mechanistic bridge between intestinal ecology and hepatic fibrogenesis^[33]. A neuroimmunometabolic dimension further broadens this interpretation. Obesity-induced inflammation alters hypothalamic circuits and peripheral-central communication^[31], and GLP-1 receptor agonists are being explored as modulators in neurodegenerative disease^[34]. Digestive chronobiology introduces an additional regulatory layer linking circadian rhythms, metabolism and inflammation^[35].

Circadian misalignment has been shown to exacerbate insulin resistance and hepatic steatosis through disruption of clock-controlled metabolic genes, indicating that temporal regulation constitutes an additional layer of vulnerability in MASLD progression^[36].

CLINICAL TRANSLATION: FROM ORGAN-CENTRIC TREATMENT TO NETWORK MODULATION

Taken together, the work of Jara *et al.* compels a definitive departure from an organ-centric reading of MASH^[1]. Their findings not only support a systemic interpretation of the disease but suggest that incretin-based interventions act upon shared regulatory nodes within an interorgan immunometabolic network. The conceptual implication is unambiguous: MASH can no longer be regarded as an isolated progressive hepatic disorder, but rather as the tissue-level manifestation of distributed metabolic dysregulation. In this light, the liver ceases to be merely a target organ and emerges as a sentinel of cumulative cardiometabolic load^[8]. Fibrosis is not simply extracellular matrix deposition but the structural expression of progressive loss of biological resilience within a context of chronic low-grade inflammation and immunometabolic aging. Under this framework, GLP-1 receptor agonists do not act exclusively upon hepatic parenchyma; they modulate neuroendocrine, inflammatory and metabolic axes that organize systemic homeostasis. The shift is neither rhetorical nor terminological - it redefines the clinical objective. Treating MASH entails intervening upon the integrated metabolic architecture of the system, not upon an isolated anatomical compartment. Liver, heart and kidney are not independent entities, but coordinated expressions of a shared underlying biological state. The identification of dynamic biomarker panels reflecting immunometabolic network activity - rather than single-organ injury - represents a critical step toward validating the network disease model and translating it into clinical practice. Importantly, the immunometabolic network underlying MASH is unlikely to be uniform across all patient populations. Variability related to phenotypes such as lean MASH, sex differences, and pediatric disease may reflect distinct configurations of interorgan signaling and metabolic regulation, highlighting the need for more personalized approaches within this framework^[25,27,37].

This systemic reframing has implications for endpoint selection in clinical trials, favoring composite cardio-hepato-metabolic outcomes and multidimensional biomarker panels over isolated histological improvement as sole markers of therapeutic success^[38]. Regulatory science is progressively incorporating such multidimensional risk constructs, recognizing that MASLD/MASH therapies may confer benefits across cardiovascular, renal and metabolic domains beyond hepatic histology alone^[19].

DECLARATIONS

Authors' contributions

Responsible for the ideation, supervision and review: Crespo J, Iruzubieta P
Performed the literature search, original draft preparation and editing: Jiménez-González C
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tools Claude Opu (Claude 4.8, released 2026-05-28) and ChatGPT Instant (ChatGPT 5.5, released 2026-04-26) were used solely for language editing without unsupervised automatic generation. In addition, the AI tool NotebookLM (NotebookLM IA Google Pro, released 2025-02-10) was used solely to generate the Figure 1 and the Graphical Abstract. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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