Metabolism Open 25 (2025) 100335

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

The role of lipoprotein sulfatides in MASLD fibrosis transition: A new frontier in hepatic immunomodulation

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver pathological condition marked by excessive triglyceride accumulation in hepatocytes [1]. If left untreated, MASLD can progress to steatohepatitis, fibrosis, and, eventually cirrhosis or hepatocellular carcinoma [2]. MASLD is closely linked to metabolic disorders such as obesity, type 2 diabetes, and dyslipidemia, which contribute to persistent metabolic stress in the liver and accelerate disease progression [3]. A critical turning point in MASLD occurs when fibrotic tissue disrupts the liver's architecture and function, significantly increasing the risk of cirrhosis and liver cancer. Early detection of fibrosis is vital for improving patient outcomes, but current diagnostic methods—primarily based on invasive liver biopsies—are limited [4,5]. While imaging and biomarker tools are available, they are predominantly designed to detect advanced fibrosis, thus restricting their application in early-stage diagnosis [6,7]. There is, therefore, an urgent need for non-invasive diagnostic method that can detect early-stage fibrosis, when interventions are most likely to be effective (see Fig. 1).

Recent advances in lipidomics [8], the study of lipid profiles in biological systems, offer promise for identifying biomarkers linked to various disease states, including liver pathological conditions [9,10]. The liver plays a central role in lipid metabolism [11], and emerging research is increasingly focusing on how circulating lipoproteins and their lipid compositions contribute to liver inflammation and fibrosis. These developments open new avenues for both diagnostics and therapeutic strategies in MASLD [12].

A recent study by Lam et al. [13] aimed to develop a blood-based diagnostic panel for detecting mild to moderate fibrosis in MASLD. The authors employed lipidomic, proteomic, and sterolomic analyses of serum samples from 519 individuals. Using a machine learning-based Lasso regression model, they identified lipid and clinical variables that could distinguish mild fibrosis (Kleiner score F1–F2) from non-fibrotic (F0) conditions. They developed a lipid-based diagnostic panel capable of detecting mild fibrosis with an area under the receiver operating characteristic curve (AUROC) of 0.775—substantially outperforming the fibrosis-4 (FIB-4) score, which has limited sensitivity for early-stage fibrosis. This lipid-based diagnostic tool, when combined with clinical variables, offers the potential for earlier detection and timely intervention to prevent further disease progression. Although non-invasive lipid panels are not yet widely available in clinical practice, this study highlights the need to refine these diagnostic tools, which could significantly improve early-stage MASLD management.

A key focus of this paper is the role of lipoprotein sulfatides (SLs) [14,15]—a class of sulfolipids—associated with MASLD and their modulation of hepatic immunology during fibrosis. Traditionally, lipids have been viewed primarily as energy sources or structural components of cell membranes [19]. However, emerging research suggests that specific lipid molecules, including sulfatides, play critical roles in regulating immune responses within the liver, especially during the transition from simple steatosis to more complex fibrotic stages [16]. In MASLD patients, sulfatides that are typically carried by high-density lipoproteins (HDLs) in healthy individuals shift to low-density lipoproteins (LDLs). This redistribution suggests that sulfatides could serve as novel biomarkers for early-stage fibrosis, reflecting changes in lipid transport and metabolism that occur alongside liver fibrosis.

The study also found that LDL-bound sulfatides influence the liver's immune microenvironment by activating natural killer T (NKT) cells [17,18], which are key drivers of fibrosis. LDL-associated sulfatides from MASLD patients triggered a more modest activation of type II NKT cells than those from healthy controls, suggesting that this change is part of an adaptive immune response as fibrosis develops. The emerging link between sulfatides, lipoproteins, and immune activation presents exciting opportunities for therapeutic exploration. Specifically, targeting the sulfatide content of lipoproteins could offer new ways to monitor liver inflammation and potentially intervene in the early stages of fibrosis.

The findings of this research emphasize the role of lipid changes in early fibrosis and highlight potential therapeutic targets for intervention. The redistribution of sulfatides from HDL to LDL particles points to a mechanism by which lipid metabolism influences immune modulation in MASLD. The involvement of LDL-associated sulfatides in activating NKT cells provides a deeper understanding of the complex interactions between lipid profiles and immune responses in the liver. This new perspective on MASLD pathology may lead to novel treatment approaches focused on modulating lipid metabolism, distinct from traditional anti-inflammatory or antifibrotic therapies.

Additionally, lipidomic profiling could enable a more personalized approach to MASLD management, tailoring treatments based on disease stage and individual lipidomic profiles. A lipid-based diagnostic panel that identifies early fibrosis markers could revolutionize MASLD management by facilitating early detection and intervention. Moreover, manipulating sulfatide levels or their distribution may offer a new strategy for controlling liver inflammation and slowing fibrosis progression.

In conclusion, this study provides a novel framework for non-invasive fibrosis diagnosis in MASLD by leveraging the unique properties of circulating lipids, particularly sulfatides. This lipid-based diagnostic panel could transform MASLD care, offering early detection and insights into lipid-immune interactions that drive fibrosis. Further

https://doi.org/10.1016/j.metop.2024.100335
Received 26 November 2024; Accepted 27 November 2024
Available online 28 November 2024

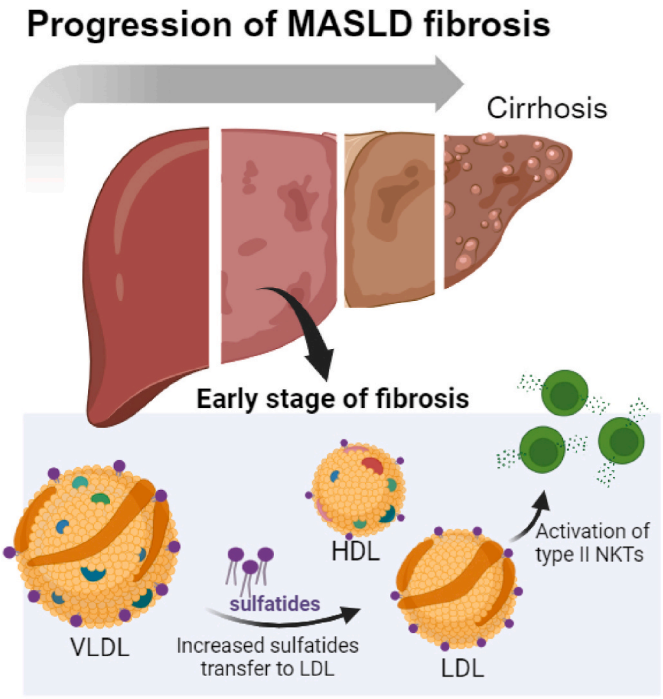

Fig. 1. Hepatic crosstalk with systemic immunity mediated by lipoprotein metabolism underlies fibrosis initiation in early-stage MASLD (Created in https://BioRender.com).

research is needed to refine and validate this lipid panel across diverse patient populations and to explore its clinical applications. Understanding the role of sulfatides and NKT cells in liver fibrosis will be essential for developing new therapeutic strategies. Ultimately, this study lays a strong foundation for integrating lipidomics into MASLD care, enhancing diagnostic precision and identifying novel treatment options for this increasingly prevalent liver disease.

CRediT authorship contribution statement

Yifan Zhou: Writing – original draft. **Junli Liu:** Writing – review & editing.

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