LIVER FIBROSIS: PATHOGENESIS, DIAGNOSIS AND TREATMENT — A CONCISE LITERATURE REVIEW

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Introduction

Liver fibrosis is a common pathological outcome of chronic liver injury and represents excessive deposition of extracellular matrix (ECM) proteins, especially collagens, which distort hepatic architecture and impair liver function (1,2). It is not a separate disease but a shared pathway of chronic viral hepatitis, alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune liver diseases, and drug-induced injury (1,2). The stage of fibrosis is the strongest predictor of cirrhosis, portal hypertension, hepatocellular carcinoma, and liver-related mortality (1). Therefore, early and accurate assessment of fibrosis is essential for clinical management (2).

Pathogenesis

Hepatic stellate cells (HSCs) are the main effector cells of liver fibrogenesis. In the healthy liver, they are quiescent and store vitamin A. After chronic injury, HSCs transdifferentiate into myofibroblast-like cells that produce large amounts of type I and type III collagen (3,4). This activation is driven by injured hepatocytes, Kupffer cells, sinusoidal endothelial cells, and immune cells (3,5).

The transforming growth factor-β (TGF-β)/Smad pathway is the master regulator of fibrogenesis. TGF-β1 binds to its receptor on HSCs, activates Smad2/3, and induces transcription of profibrogenic genes such as COL1A1, COL1A2, and TIMP1 (4,5). Other important pathways include platelet-derived growth factor (PDGF), Wnt/β-catenin, Hedgehog, and Notch (4). Oxidative stress, endoplasmic reticulum stress, autophagy, and mechanical signals also promote HSC activation (3,4).

An important concept is that liver fibrosis is potentially reversible. Removal of the causative injury can lead to inactivation, senescence, or apoptosis of activated HSCs and degradation of excess ECM by matrix metalloproteinases (4,5). This reversibility provides the rationale for antifibrotic therapy (4).

Diagnosis and Staging

Liver biopsy has traditionally been considered the gold standard for staging fibrosis. However, it is invasive, painful, associated with rare but serious complications, and limited by sampling and interobserver variability (6). Several histological scoring systems are used. The METAVIR system grades fibrosis from F0 to F4 and is widely applied in chronic viral hepatitis and MASLD (6). The Ishak system uses stages F0–F6 and is also commonly used (7).

Because of biopsy limitations, non-invasive tests (NITs) have become central in clinical practice (2,8). Serum-based tests are divided into indirect and direct markers. The Fibrosis-4 (FIB-4) index, calculated from age, AST, ALT, and platelet count, is the most widely used first-line test for fibrosis risk stratification (8). The Enhanced Liver Fibrosis (ELF) test combines hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of metalloproteinases-1 and shows good diagnostic accuracy (9).

Imaging-based elastography is now recommended by major guidelines (2,10). Vibration-controlled transient elastography (FibroScan) is the most validated method (10). Magnetic resonance elastography (MRE) and shear wave elastography (SWE) are reliable alternatives, although MRE is more expensive and less available (2). The WHO 2024 hepatitis B guidelines suggest that an APRI >0.5 or FibroScan >7.0 kPa identifies most adults with significant fibrosis (≥F2), while FibroScan >12.5 kPa identifies most with cirrhosis (F4) (11). The EASL-EASD-EASO 2024 MASLD guidelines recommend a stepwise approach using FIB-4 followed by elastography in people with cardiometabolic risk factors (2).

Treatment

Treatment of the underlying cause remains the cornerstone of fibrosis management (2,12). Effective antiviral therapy in chronic hepatitis B and C can halt progression and lead to fibrosis regression (11,12). In autoimmune hepatitis, corticosteroids and immunomodulators may regress fibrosis (12). In alcohol-related liver disease, abstinence is the single most effective intervention (12).

Direct antifibrotic pharmacotherapy has historically been limited. However, resmetirom, an oral liver-directed thyroid hormone receptor beta-selective agonist, was approved in 2024 for noncirrhotic non-alcoholic steatohepatitis (NASH) with liver fibrosis (13). In the Phase 3 MAESTRO-NASH trial, resmetirom was superior to placebo for NASH resolution and improvement in fibrosis by at least one stage (13). Emerging strategies target HSC activation, induce HSC apoptosis or senescence, or promote reversion to a quiescent state (14). Monoclonal antibodies, fibrates, organelle-specific agents, and nanomedicine platforms are under investigation (14).

Conclusion

Liver fibrosis is a dynamic and potentially reversible process with a major global health burden (1,4). HSC activation and TGF-β/Smad signaling are central to its pathogenesis (3,4). Non-invasive tests such as FIB-4, ELF, and elastography have largely replaced liver biopsy for routine staging, and recent guidelines provide clear thresholds for clinical decisions (2,10,11). The approval of resmetirom marks an important advance in antifibrotic therapy, and many new agents are in development (13,14). Future efforts should focus on combination therapies, validated surrogate endpoints, and equitable access to diagnostic and therapeutic advances (2,4,14).

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