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Pathophysiology of Hepatic Injury due to liver fibrosis: Diagnosis and management

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Abstract

Liver fibrosis and cirrhosis are result of chronic liver injury, which leads to an excessive accumulation of extracellular matrix proteins (ECM). If untreated, this stage can aggravated to severe complications like liver failure and hepatocellular carcinoma. In depth analysis of liver fibrosis diagnosis, treatment and emphasizing of various causes i.e. genetic disorders, viral infections, dietary influences and exposure of foreign substances. Innovations in diagnostic methods, particularly non-invasive imaging techniques that are Fibro Scan, Transient elastography and alongside biomarker assessments have increased early detection capabilities. Now modern therapies are including antifibrotic medications, antiviral therapies and modification of lifestyles. They have contributed better prognosis for patient. This chapter underscores the necessity of a multidisciplinary approach that combines recent diagnosis, therapeutic strategies and obstructive measures to inhibit disease progression. It aims to equip researchers and medical professionals with a thorough understanding of current liver fibrosis management.

Keywords: Liver; Collagen; Fibrosis; Cirrhosis; Therapy; Diagnosis

Introduction

Fibrosis derived from the Latin word fibra means thread or filament, refers to the excessive buildup of collagenous fiber and non-collagenous extracellular matrix (ECM) portion in tissue and organs, resulting from the more active and multiplication of fibroblast and myofibroblast. So, fibrosis poses a significant global health implication with considerable medical and impact on socioeconomic activity such as effecting workforce productivity due to the post-infectious fibrotic conditions, connective tissue disorders, atherosclerosis and it remains an understudied issue. These pathological processes come to light on various conditions like Viral or bacterial inflammations, Autoimmuno-disordes, foreign body particles, neoplastic growths and tissue injury (**Younossi et al., 2016).**

Liver fibrosis can change to cirrhosis, liver failure and hepatocellular carcinoma, contributing significantly to liver related illness and mortality. In the early conditions of fibrosis, different types of immune cells, including eosinophils (in parasitic infections), neutrophils (in bacterial infections), mast cells, macrophages/monocytes and lymphoid cells such as natural killer and natural killer T (NKT) cells, increases in the infected liver tissue. In inflammation, neutrophils play key roles; contain granules filled with enzymes that influence fibrosis in two major steps. In first steps, enzymes such as elastase, matrix metalloproteinases (MMPs) and cathepsins involved in tissue remodelling by degrade of collagenous and non – collagenous components of connective tissue. In second steps, neutrophils indirectly stimulated fibrogenesis through activating other immune cells. Particularly, TNF-α and IL-1 release by macrophase, which stimulate fibroblasts, leading to build-up extracellular matrix (ECM) protein concentration. NF-κB signaling activated by the TNF-α signaling pathway, which regulate the expression of fibrogenic cytokines, further driving fibrosis progression **(Wick, G., et al., 2013)**.

Liver –

The adult human liver, typically weighing around 1.5 kg, is the body's largest internal organ and is essential for various metabolic processes. It plays a crucial role in intermediary metabolism and is responsible for

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processing and eliminating xenobiotics. Additionally, the liver facilitates the excretion of bile pigments and produces bile acids, which are vital for regulating cholesterol levels and aiding in the absorption of dietary fats in the intestine. Moreover, the liver contributes significantly to cholesterol balance and lipoprotein metabolism. It serves as the primary site for synthesizing key serum proteins, including albumin, clotting factors, and complement proteins. Furthermore, it is responsible for amino acid breakdown and urea production. Under normal conditions, the liver maintains a size that allows for functional redundancy **(Wallace et al., 2008).**

The liver originates from the ventral foregut endoderm around embryonic day 8 (E8) in mice. By approximately E10, hematopoietic cells from the aorta-gonad-mesonephros (AGM) region migrate to the developing fetal liver. One of the liver's most remarkable attributes is its exceptional regenerative ability. In rodent models, even when 70% of the adult liver is surgically removed, it can restore its original mass and function within a week. Liver diseases, particularly metabolic dysfunction-associated steatotic liver disease (MASLD), have become a significant global health issue, affecting millions worldwide and contributing to higher rates of illness and death. MASLD includes a range of conditions, from simple fat accumulation in the liver to more advanced stages such as metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. The rising incidence of these liver disorders is closely linked to the increasing prevalence of obesity, lack of physical activity, and unhealthy dietary patterns.

Pathophysiology

Liver fibrosis develops as a response to prolonged liver damage, leading to hepatocyte death and inflammation. Injured liver cells release pro-inflammatory cytokines and growth factors, which stimulate hepatic stellate cells (HSCs)—the key drivers of fibrosis. Once activated, HSCs undergo trans-differentiation into myofibroblasts, which produce extracellular matrix (ECM) proteins, including collagen. This accumulation of ECM components contributes to increased liver stiffness over time **(Younossi et al., 2016).** Several key factors drive fibrosis, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and reactive oxygen species (ROS). These elements contribute to both inflammation and fibrotic progression while simultaneously preventing the breakdown of ECM components **(Friedman et al., 2008, and Younossi et al., 2016).**

Etiology

Liver fibrosis can arise from various underlying conditions. The most prevalent causes include genetic disorders, chronic viral and bacterial infections, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). Additional contributing factors include autoimmune liver diseases, metabolic disorders, and cholestatic liver conditions. Genetic disorders play a crucial role in fibrosis development, often resulting from mutations in genes responsible for liver metabolism, bile acid production, or metal transport, ultimately leading to progressive liver damage.

Viral infections are also major contributors to liver fibrosis, with pathogens such as hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV), hepatitis E (HEV), and COVID-19 being significant culprits. These infections trigger chronic liver injury, which can advance to fibrosis over time.

Alpha-1 Antitrypsin Deficiency (AATD)

Alpha-1 antitrypsin deficiency (AATD) causes from genetic mutation in the SERPINA1 gene, if abnormal folded in alpha-1 antitrypsin (AAT) protein to accumulate in liver cells. This accumulation leads to stress in the endoplasmic reticulum, initiating inflammatory responses and fibrosis **(Teckman, J. H., et al., 2023).** Current research highlights the significance of gene treatment and AAT augmentation as potential approaches for treating liver fibrosis in individuals with AATD **(Strand, P., et al., 2023).**

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Autosomal Dominant Polycystic Kidney Disease (ADPKD)

If mutation occurs in the PKD1 or PKD2 genes are responsible for autosomal dominant polycystic kidney disease (ADPKD), which is also connected to the polycystic liver disease (PLD). The progressive enhancement of liver cyst responsible to fibrosis and enhance portal hypertension **(Gevers, T. J. G., et al., 2023**). Current studies underline the importance of somatostatin analogs and mTOR inhibitors in the treatment of liver fibrosis linked with polycystic liver disease (PLD) **(Hogan, M. C., et al., 2023).**

Cystic Fibrosis (CF)

Liver disease impacts around 30 % of persons with cystic fibrosis, a condition resulting from abnormal in the CFTR gene. Known as CFLD is a CF- associated liver disease, this complication typically involves biliary cirrhosis and the development of filamentous tissue in localized of the liver **(Debray, D., et al., 2023).** Nowadays advances in CFTR modulator treatment, like lumacaftor and ivacaftor, have shown potential in decreasing liver complications (Wainwright, C. E., et al., 2023).

Glycogen Storage Diseases (GSD)

GSD type 1 is a glycogen storage disease, which also known as Von Gierke disease and type III known as Cori disease, which are causes in mutation of G6PC and AGL gene. These genes are involved in glycogen metabolism. If mutation occurs in these gene lead to enhance glycogen storage in the liver, resulting fibrosis and hepatomegaly **(Kishnani, P. S., et al., 2023**). Current studies highlight the benefits of dietary regulations and emerging gene treatment in decreasing liver abnormalities **(Derks, T. G. J., et al., 2023).**

Lysosomal Acid Lipase Deficiency (LAL-D)

Lysosomal acid lipase deficiency (LAL - D) caused through genetic mutation in the LIPA gene, resulting cholesteryl esters and triglycerides to accumulate in liver cells. This storage stimulate inflammatory responses, fibrotic changes and eventual cirrhosis **(Burton, B. K., et al., 2023).** Emerging research highlight the enzyme replacement therapy, specifically Sebelipase-alfa, can effectively slow or again liver fibrosis in affected individuals **(Valayannopoulos, V., et al., 2023).**

Wilson's-Disease

Wilson's disease is an inherited condition resulting from defects in the ATP7B gene, which disrupts copper elimination and causes its buildup in the liver. Excessive copper damages liver cells, triggering inflammation and scar tissue formation (Roberts, E. A., et al., 2023). Advances in genetic screening now allow for earlier detection, and therapeutic approaches like copper-chelating drugs (e.g., D-penicillamine) and zinc therapy have proven effective in reducing hepatic fibrosis progression (Schilsky, M. L., et al., 2023).

Hepatitis A Virus (HAV)

Hepatitis A is a viral infection that causes acute inflammation of the liver, typically spread through ingestion of contaminated food or water due to poor hygiene (Feng, Z., et al., 2023). Recent outbreaks have been associated with unsanitary conditions where food and water supplies are compromised. While the illness usually resolves on its own, it can progress to fulminant liver failure in high-risk groups, such as elderly individuals or those with chronic liver conditions. Immunization has proven to be the best strategy for prevention, with current research confirming its durable protective effects (Jeong, S. H., et al., 2023).

Hepatitis B Virus (HBV)

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Hepatitis B remains a critical public health issue, affecting more than 250 million individuals globally with chronic infections. The virus spreads via exposure to infected blood, sexual contact, and mother-to-child transmission. Persistent HBV infection can progress to severe liver complications, including cirrhosis and hepatocellular carcinoma (HCC), contributing to nearly half of all liver cancer cases worldwide. Advances in antiviral treatments, particularly tenofovir and entecavir, have enhanced patient outcomes by effectively controlling viral activity and minimizing liver damage (**Revill, P. A., et al., 2023**). Furthermore, emerging therapies aimed at targeting the hepatitis B surface antigen (HBsAg) offer potential breakthroughs in achieving sustained remission **(Lok, A. S., et al., 2023 and Yuen, M. F., et al., 2023).**

Hepatitis C Virus (HCV)

Chronic hepatitis C virus (HCV) infection affects approximately 58 million people worldwide and is a major contributor to liver fibrosis (Blach, S., et al., 2023). The progression of fibrosis depends on the virus's ability to persist and the extent of immune-related liver damage. Transmission primarily occurs through exposure to infected blood, commonly linked to intravenous drug use or inadequate medical hygiene. **The introduction of direct-acting antivirals (DAAs) has revolutionized HCV treatment, enabling high cure rates (sustained virologic response, SVR) and slowing fibrosis development.** Despite these advances, delayed or absent treatment can result in permanent liver damage, including cirrhosis (Afdhal, N. H., et al., 2014 and Dore, G. J., et al., 2023).

Hepatitis D Virus (HDV)

Hepatitis D virus (HDV), also known as delta hepatitis, is an incomplete virus that depends on hepatitis B virus (HBV) for its replication. Coinfection with HDV leads to more aggressive liver damage and accelerates the development of cirrhosis when compared to HBV infection alone (Stockdale, A. J., et al., 2023). **Current research suggests that around 5% of people with HBV also carry HDV, with particularly high rates observed in areas like Central Asia and sub-Saharan Africa** (Revill, P. A., et al., 2023). Emerging treatments, such as bulevirtide, have demonstrated potential in lowering viral levels and enhancing liver health in affected individuals (Rizzetto, M. 2023).

Hepatitis E Virus (HEV)

Hepatitis E virus (HEV) has emerged as a significant public health threat, especially in resource-limited regions where waterborne transmission predominates (Kamar, N., et al., 2023). In industrialized nations, HEV is now identified as a foodborne illness, primarily associated with eating insufficiently cooked pork products or wild animal meat (Rein, D. B., et al., 2023). **Although the majority of HEV cases resolve spontaneously, the infection can become life-threatening in specific high-risk groups such as expectant mothers and patients with weakened immune systems, potentially progressing to acute liver failure** (Shrestha, M. P., et al., 2023). Scientific efforts have recently concentrated on creating reliable vaccines, with phase III clinical studies showing encouraging outcomes.

NAFLD (Non-Alcoholic Fatty Liver Disease) Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disorder worldwide, primarily associated with obesity, insulin resistance, and metabolic syndrome. This condition includes a range of liver abnormalities, from simple fat accumulation in the liver (hepatic steatosis) to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation and liver cell injury **(Angulo, P., et al., 2007).** Among NAFLD patients, NASH is the leading driver of fibrosis progression and can eventually lead to cirrhosis and hepatocellular carcinoma (HCC). Several factors influence fibrosis progression in NAFLD, including obesity, diabetes, and hypertension. Additionally, genetic

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predisposition plays a crucial role, with specific gene polymorphisms, such as PNPLA3 and TM6SF2, being linked to increased liver fat deposition and a heightened risk of fibrosis **(Buzzetti, E., et al., 2016).**

Alcoholic Liver Disease (ALD)

Prolonged alcohol consumption is a major contributor to liver fibrosis. The development of alcohol-related liver fibrosis is driven by multiple factors, including oxidative stress, inflammation, and hepatocyte apoptosis. Alcohol-induced liver damage activates hepatic stellate cells (HSCs), leading to collagen buildup and fibrosis **(Addolorato, G., et al., 2010).** Alcoholic liver disease (ALD) advances through various stages, beginning with fatty liver (steatosis), progressing to alcoholic hepatitis, and ultimately resulting in cirrhosis **(Rehm, J., et al., 2009).** Additionally, coexisting conditions like viral hepatitis can significantly hasten the progression of fibrosis in ALD.

Foreign Particles

Foreign substances have the potential to induce liver fibrosis. A range of foreign particles, such as environmental contaminants, industrial toxins, and medical implants, may contribute to the development of liver fibrosis by causing direct tissue injury, persistent inflammation, or immune system activation.

Metal Particles: Metallic particles, including iron, copper, and aluminum, have the ability to accumulate in the liver, leading to fibrosis. Notably, excessive iron levels are widely recognized as a key factor in liver fibrosis, primarily due to oxidative stress and prolonged inflammation. Recent research indicates that copper nanoparticles can trigger hepatocyte apoptosis and contribute to fibrosis development **(Roberts, E. A., et al., 2023).**

Nanoparticles: Carbon nanoparticles, widely utilized in industrial applications, have been found to contribute to liver fibrosis by inducing oxidative stress and inflammation. Recent studies indicate that these nanoparticles can infiltrate hepatocytes, causing mitochondrial dysfunction and fibrosis **(Brown, S. D., et al., 2023).** Additionally, research has emphasized the role of autophagy in alleviating liver damage caused by nanoparticles. Similarly, pharmaceutical nanoparticles used in drug delivery systems may lead to liver fibrosis through immune-related mechanisms. Studies suggest that specific nanoparticles can activate Kupffer cells, triggering persistent inflammation and fibrosis **(Anderson, J. M., et al., 2023).** Furthermore, modifying nanoparticle surfaces has been identified as a crucial strategy to minimize liver toxicity **(White, R. L., et al., 2023).**

Silica Particles: Occupational exposure to crystalline silica dust, prevalent in industries like mining and construction, may contribute to liver fibrosis development through inflammatory pathways and oxidative damage mechanisms. Emerging research demonstrates that silica particles trigger the transformation of hepatic stellate cells, initiating the critical fibrotic cascade (Chen, Y., et al., 2023). Long-term inhalation of silica nanoparticles has been associated with increased serum markers of liver injury and histo- pathological evidence of fibrosis in experimental studies.

Polycyclic Aromatic Hydrocarbons (PAHs): *Polycyclic aromatic hydrocarbons (PAHs), toxic compounds released during the incomplete burning of organic matter, contribute to liver fibrosis by triggering oxidative stress and inflammatory responses. Emerging evidence indicates that PAH exposure activates hepatic stellate cells, promoting fibrosis in experimental animal studies. Additionally, research underscores the involvement of the Aryl hydrocarbon receptor (AHR) pathway in mediating PAH-related liver injury* (Miller, B., et al., 2023).

Environmental Dust Particles: *Inhalable dust particles, including those from desert winds, contribute to liver fibrosis by inducing systemic inflammatory responses and oxidative damage. Experimental studies have*

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demonstrated that prolonged exposure to these particles results in increased liver enzyme levels and fibrotic changes in animal models **(Lee, S., et al., 2023**). *Furthermore, investigations emphasize the significant impact of fine particulate matter (PM2.5) in driving liver fibrosis* **(Kim, H., et al., 2023).**

Diagnosis

The fibrogenic response, marked by excessive extracellular matrix (ECM) production and deposition, plays a critical role in scar formation, ultimately leading to significant alterations in liver structure. Hepatic stellate cells (HSCs) possess distinct features, including the storage of retinyl esters within intracellular lipid droplets and structural similarities to vascular pericytes, which help regulate sinusoidal blood flow. The process of HSC activation and their transition into myofibroblasts, along with their role in fibrosis progression, has been well studied and forms a key foundation for understanding liver disease. When hepatocytes die, they release cellular components like DNA, damage-associated molecular patterns (DAMPs), and reactive oxygen species, which activate Kupffer cells (liver-resident macrophages). These cells then produce pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, as well as pro-fibrogenic mediators like TGF-β. Other inflammatory drivers include chemokines such as CCL2 and gut-derived pathogen-associated molecular patterns (PAMPs). For example, activation of toll-like receptor 4 (TLR4) suppresses the activin membrane-bound inhibitor BAMBI, further amplifying TGF-β-driven HSC activation **(Trautwein, C., et al., 2015).**

Consequently, non-invasive approaches for evaluating liver fibrosis have been developed to improve diagnostic efficiency, including serum biomarkers and elastography-based imaging. Various biomarkers have proven useful in predicting fibrotic progression in chronic liver disease patients. These encompass indicators of hepatic damage (e.g., alanine aminotransferase, ALT) as well as fibrosis-specific scores like the aspartate aminotransferase-to-platelet ratio index (APRI) and the Fibrosis-4 (FIB-4) index **(Sterling, R. K., et al., 2006). Additionally, imaging-based elastography techniques—such as transient elastography (FibroScan), magnetic resonance elastography (MRE), and shear wave elastography (SWE)—quantify liver stiffness, providing a reliable estimate of fibrosis severity (Castéra, L., et al., 2010).** Given their diagnostic accuracy, reproducibility, and practicality, these non-invasive tools are gaining widespread adoption in clinical settings.

Conclusion: Liver fibrosis continues to be a major global health challenge, with causes ranging from genetic conditions and viral infections to environmental factors and dietary influences. Early and precise diagnosis is crucial to preventing disease progression, and recent advancements in non-invasive diagnostic techniques and biomarkers have significantly improved the early detection of fibrosis. The approach to managing liver fibrosis has also advanced, incorporating targeted therapies such as antiviral treatments, antifibrotic medications, and lifestyle modifications, all of which play a key role in enhancing patient outcomes. Despite these developments, significant obstacles remain, particularly in providing access to advanced diagnostic and therapeutic options in resource-limited regions.

Future research should prioritize the discovery of novel antifibrotic treatments, the enhancement of early detection strategies, and a deeper understanding of the molecular pathways driving fibrosis progression. A multidisciplinary strategy—integrating early diagnosis, personalized treatment plans, and preventive measures—is essential to reducing the global impact of liver fibrosis and improving patients' quality of life. This review highlights the ongoing need for innovation and collaboration in hepatology to effectively address the complexities of liver fibrosis.

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