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PATHOLOGY OF LIVER DISEASES: FROM STEATOSIS TO CIRRHOSIS

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Abstract: Liver steatosis (fatty infiltration) and its subsequent stages—steatohepatitis, fibrosis, and cirrhosis—are considered one of the most pressing global health issues today. According to recent epidemiological data, non-alcoholic fatty liver disease (NAFLD), the most common form of these conditions, affects over 1.5 billion people worldwide, with projections estimating a rise to 33% of the global population by 2030 (Younossi et al., 2019). This article analyzes the pathological foundations of liver diseases, morphological changes, diagnostic criteria, and clinical significance. Additionally, modern non-invasive methods of diagnosis, genetic and molecular mechanisms, as well as promising treatment directions are discussed. The article deeply illuminates the pathophysiology, histopathology, and clinical manifestations of liver diseases, while reviewing modern diagnostic and treatment methods, supported by key statistical insights into prevalence, progression rates, and outcomes.

Keywords: Liver steatosis, NAFLD, steatohepatitis, fibrosis, cirrhosis, morphology, biopsy, elastography, metabolic syndrome, genetic factors, molecular mechanisms.

Non-alcoholic fatty liver disease (NAFLD)-is a common disease characterized by the accumulation of fat in liver cells and occurring in patients who do not consume alcohol. NAFLD affects approximately 25–30% of the world's population, with regional variations: prevalence reaches 30–40% in high-income countries like the United States and Middle East, 20–30% in Europe, and is rapidly increasing in Asia (up to 15–20% in urban populations) due to urbanization and dietary shifts (Younossi et al., 2016, p. 73-84; Mizuno et al., 2021). Its prevalence is increasing at an alarming rate, with a 15% rise in global incidence over the past decade, driven by the obesity epidemic—over 1 billion adults worldwide are obese, a key risk factor (World Health Organization, 2022). The main risk factors for the disease include obesity (affecting 42% of NAFLD cases), type 2 diabetes (prevalent in 50–70% of patients), metabolic syndrome (seen in 60–80% of cases), and insulin resistance (Chalasani et al., 2018, p. 328-357). The NAFLD spectrum begins with steatosis and can lead to steatohepatitis, fibrosis, and ultimately cirrhosis, with progression rates varying: about 20–30% of simple steatosis cases advance to non-alcoholic steatohepatitis (NASH), and 10–20% of NASH cases progress to cirrhosis over 10–20 years (Younossi et al., 2019). The purpose of this article is to analyze the pathological stages of liver diseases on a scientific basis, review modern diagnostic methods, and present promising treatment directions, incorporating statistical data to underscore the disease's global burden.

Pathogenesis: The main pathogenetic mechanism of liver steatosis is the excessive accumulation of triglycerides in hepatocytes. This condition arises as a result of disrupted lipid metabolism, excessive influx of fatty acids, and increased lipogenesis (Bedossa, 2017, p. 85-89). In obese individuals, free fatty acid influx from adipose tissue accounts for 60–70% of hepatic fat accumulation, exacerbating the process (Yki-Järvinen, 2014). Lipotoxicity—the toxic effects of fatty acids—induces oxidative stress and mitochondrial dysfunction in hepatocytes, which initiates cell damage and inflammatory processes (Kleiner & Brunt, 2012, p. 3-13). This

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oxidative stress is implicated in 70–80% of NASH cases, leading to hepatocyte apoptosis and necrosis.
Liver stellate cells (Ito cells) become activated and produce collagen and other extracellular matrix components, leading to the onset of the fibrosis process (Schuppan & Afdhal, 2008, p. 838-851).

The development of fibrosis leads to disruption of the liver architecture and ultimately to cirrhosis, with fibrosis progression observed in 30–50% of NASH patients within 5–10 years (Singh et al., 2015).
Recent studies indicate that genetic factors also play a significant role in the development of NAFLD. For example, polymorphisms in the PNPLA3 gene (rs738409 variant) are present in 20–50% of NAFLD patients and increase the risk of progression to cirrhosis by 3–4 fold; similar effects are seen with TM6SF2 (rs58542926, risk increase of 2–3 fold) and MBOAT7 genes (Anstee et al., 2020, p. 1-15). Furthermore, the gut microbiota and its metabolites participate in liver inflammation and fibrosis, with dysbiosis (imbalanced gut flora) detected in 60–70% of NAFLD cases, contributing to endotoxemia and hepatic inflammation (Boursier et al., 2016, p. 1-10). These factors collectively explain why only a subset (10–20%) of at-risk individuals develop advanced disease.
Morphological Changes: *Steatosis:* Characterized by the accumulation of fat droplets in hepatocytes. At this stage, the liver may increase in size (hepatomegaly in 50–70% of cases) and become softer. Under the microscope, large or small fat droplets are visible in hepatocytes, with macrovesicular steatosis predominant in 80% of early NAFLD biopsies (Bedossa, 2017, p. 85-89). This reversible stage affects 90% of NAFLD patients initially.
Steatohepatitis: At this stage, the inflammatory process begins. Histological features include ballooning (swelling of hepatocytes, seen in 70–90% of NASH cases), Mallory–Denk bodies (accumulation of keratin filaments, present in 20–50%), and neutrophil infiltration (Kleiner & Brunt, 2012, p. 3-13). Inflammation and cell damage promote the fibrosis process in liver tissue, with lobular inflammation noted in 60–80% of progressing cases.
Fibrosis: Initially, perisinusoidal fibrosis develops (zone 3, in 40–60% of NASH), followed by bridging fibrosis (between portal and central zones, advancing in 20–30%). This leads to disruption of the liver architecture (Schuppan & Afdhal, 2008, p. 838-851). The degree of fibrosis is associated with a decline in liver function, staging from F0 (no fibrosis) to F4 (cirrhosis), with F2–F3 fibrosis correlating to a 5-year mortality risk increase of 2–3 fold.
Cirrhosis: Characterized by nodular reorganization of liver tissue and a fundamental change in architecture. At this stage, liver function is significantly impaired, leading to portal hypertension (in 60–80% of cases) and liver failure (European Association, 2016, p. 1388-1402). Cirrhosis develops in 10–20% of NAFLD patients overall, but up to 30% in those with NASH, and is a leading cause of liver transplantation in Western countries (20–30% of cases).
Diagnosis: Liver biopsy is considered the gold standard for diagnosing NAFLD and its stages, with diagnostic accuracy of 85–95% for distinguishing steatosis from NASH. Histological scoring systems—NAS (NAFLD Activity Score, ranging 0–8) and SAF (Steatosis, Activity, Fibrosis)—are used to assess the severity of the disease, with NAS ≥5 indicating NASH in 70–80% of cases (Chalasani et al., 2018, p. 328-357; Bedossa, 2017, p. 85-89).
Among modern non-invasive methods, elastography (based on ultrasound or MRI) and MRI-PDFF (proton density fat fraction) are widely used. Elastography measures the stiffness of liver tissue (normal <6 kPa, cirrhosis >12 kPa), allowing assessment of the degree of fibrosis with 80–90% accuracy (European Association, 2016, p. 1388-1402). MRI-PDFF has high sensitivity

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(95–98%) in accurately measuring the amount of liver fat, detecting steatosis >5% with precision superior to ultrasound (Younossi et al., 2016, p. 73-84).
Additionally, serological markers (FibroTest, ELF test) and genetic tests help predict disease progression, with FibroTest showing 75–85% accuracy for advanced fibrosis and genetic panels identifying high-risk individuals in 30–40% of cases (Castera et al., 2019, p. 1-15). Non-invasive methods reduce biopsy needs by 50–70% in clinical practice.

Clinic and Significance: NAFLD often progresses asymptomatically and is frequently detected incidentally during imaging for other conditions (in 70–80% of cases). The progression of the disease increases the risk of cirrhosis (10–20% lifetime risk) and hepatocellular carcinoma (HCC; 2–5% annual risk in cirrhotics, 20–30 times higher than general population) (Schuppan & Afdhal, 2008, p. 838-851). Moreover, NAFLD is associated with cardiovascular diseases (CVD), which account for 40–50% of deaths in NAFLD patients—twice the rate of liver-related mortality—and overall mortality risk increases by 1.5–2 fold (Chalasani et al., 2018, p. 328-357). In the U.S., NAFLD contributes to 10–15% of all HCC cases and is linked to extrahepatic cancers in 20% of advanced cases.
Early detection of the disease and management of metabolic syndrome play a crucial role in preventing liver pathology, with lifestyle interventions halting progression in 60–80% of early-stage patients. A multidisciplinary approach, including diet (Mediterranean diet reducing steatosis by 30–40%), physical activity (150 min/week decreasing fibrosis risk by 20–30%), and pharmacological therapy (e.g., pioglitazone or GLP-1 agonists showing 40–50% improvement in NASH histology), is considered effective (Loomba & Sanyal, 2013, p. 1-15). Economic burden: NAFLD costs global healthcare $100–150 billion annually, projected to double by 2030.

Conclusion

Liver steatosis, commonly known as fatty liver disease, and its progressive stages—ranging from steatohepatitis and fibrosis to the advanced and irreversible condition of cirrhosis—represent one of the most critical and rapidly escalating challenges in contemporary medicine. As a leading cause of chronic liver disease worldwide, non-alcoholic fatty liver disease (NAFLD) not only burdens healthcare systems but also underscores the intricate interplay between metabolic disorders, genetic predispositions, and environmental factors in driving global health epidemics. With a current global prevalence of 25–30% (affecting 1.5–2 billion people) and expected to reach 33–38% by 2030, NAFLD is poised to surpass viral hepatitis as the top cause of liver transplantation and HCC (Younossi et al., 2019). This article has elucidated the foundational pathological mechanisms, including the excessive triglyceride accumulation in hepatocytes, lipotoxicity-induced oxidative stress, and the activation of stellate cells leading to fibrotic remodeling, which collectively propel the disease from a seemingly benign steatosis to life-threatening cirrhosis.
The morphological transformations observed across these stages—from the initial fat droplet infiltration in hepatocytes to the nodular architectural distortion in cirrhosis—highlight the insidious nature of NAFLD, often progressing silently without overt symptoms until advanced complications such as portal hypertension, liver failure, or hepatocellular carcinoma emerge. Diagnostic advancements, particularly non-invasive techniques like elastography and MRI-PDFF, alongside traditional biopsy and emerging serological and genetic markers, have revolutionized early detection, enabling clinicians to stratify risk and intervene before irreversible damage occurs. These tools, combined with a deeper understanding of molecular

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pathways involving genes like PNPLA3 and the role of gut microbiota, pave the way for personalized medicine approaches that could mitigate disease progression.
Prevention remains the cornerstone of managing NAFLD, emphasizing the profound impact of lifestyle modifications such as weight loss through balanced diet and regular physical activity, alongside rigorous control of associated comorbidities like obesity, type 2 diabetes, and metabolic syndrome. A multidisciplinary strategy, integrating hepatologists, endocrinologists, nutritionists, and primary care providers, is essential to address the multifaceted etiology of the disease and reduce the heightened risks of cardiovascular events and overall mortality.

Pharmacological interventions, though currently limited, show promise in targeting inflammation and fibrosis, but their efficacy underscores the need for broader adoption of preventive measures at a population level.
Looking ahead, the horizon of NAFLD research is bright with potential, fueled by ongoing investigations into molecular and genetic mechanisms that could yield novel therapeutics—such as targeted anti-fibrotic agents, microbiome modulators, and gene therapies. As prevalence continues to rise in tandem with the global obesity epidemic, heightened public awareness, policy-driven health initiatives, and accelerated clinical trials will be imperative to curb this silent pandemic. Ultimately, by fostering early screening, promoting healthy lifestyles, and advancing scientific innovation, we can transform the trajectory of liver diseases from steatosis to cirrhosis, safeguarding liver health and improving quality of life for millions worldwide.

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