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MECHANISMS OF DEVELOPMENT OF VIRAL HEPATITIS AND LIVER FIBROSIS: A REVIEW OF SCIENTIFIC LITERATURE.

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ANNOTATSIYA:

This article analyzes the pathophysiological processes caused by viral hepatitis in liver tissues and the mechanisms underlying the development of fibrosis. Viral hepatitis, particularly hepatitis B and C infections, not only directly damage hepatocytes but also enhance chronic inflammatory processes through excessive activation of the immune system and the release of cytokines and profibrotic mediators. Moreover, the activation of hepatic stellate cells, excessive accumulation of extracellular matrix proteins, and the formation of irreversible morphological changes in tissues play a crucial role in the progression of fibrosis. Based on a review of scientific literature, the article highlights the molecular and cellular mechanisms involved in the pathogenesis of fibrosis, as well as the potential of modern biomarkers for its detection and early

diagnosis. The paper also summarizes ongoing research on novel diagnostic and therapeutic approaches and emphasizes their clinical significance. The findings may serve as an important scientific resource for young researchers aiming to deepen their understanding of viral hepatitis and liver fibrosis, as well as to improve treatment efficacy.

Introduction: Viral hepatitis remains a serious global public health problem today. According to the World Health Organization (WHO, 2023, p. 15), millions of people worldwide are infected annually with hepatitis B (HBV) and hepatitis C (HCV), a significant proportion of whom develop severe complications such as liver cirrhosis and hepatocellular carcinoma. Hepatitis C infection, in particular, is often referred to as the "silent killer" because it frequently progresses without clinical symptoms and is usually detected only at the stage of fibrosis or cirrhosis (Sheikh et al., 2021, p. 78). Moreover, chronic hepatitis B infection affects more than 240 million people globally, among whom the risk of developing liver failure is considerably high (Lok & McMahon, 2016, p. 112).

The development of liver fibrosis is one of the major pathophysiological outcomes of viral hepatitis. Fibrosis is a process characterized by the excessive accumulation of collagen and other extracellular matrix components in the liver parenchyma, which is directly associated with the activation of hepatic stellate cells (Bataller & Brenner, 2005, p. 173). Under conditions of prolonged inflammation, fibrosis becomes irreversible, leading to cirrhosis and hepatocellular carcinoma (Schuppan & Afdhal, 2008, p. 837). Therefore, studying the mechanisms of fibrosis, developing early diagnostic methods, and formulating effective treatment strategies remain among the most urgent priorities in modern medicine. According to the literature, the development of liver fibrosis is influenced not only by the direct cytopathic effects of the virus but also by immune-mediated inflammation, cytokine imbalance, oxidative stress, and genetic factors (Friedman, 2010, p. 1303). Furthermore, recent scientific studies emphasize the diagnostic value of biomarkers such as hyaluronic acid, laminin, and procollagen III peptide in assessing fibrosis progression (Zhou et al., 2020, p. 1422). In addition, non-invasive diagnostic techniques—such as FibroScan,

elastography, and specialized laboratory indices—are increasingly being integrated into clinical practice (EASL Guidelines, 2018, p. 124).

In conclusion, the mechanisms underlying the development of viral hepatitis and liver fibrosis are of great importance not only for fundamental scientific research but also for clinical practice. Ongoing studies in this field play a vital role in the early detection of liver diseases and in improving the effectiveness of therapeutic interventions.

Main part: The development of liver fibrosis in viral hepatitis is based on prolonged and complex pathogenetic mechanisms. The key pathological process involves the remodeling of hepatic tissue under chronic inflammation, in which the direct cytopathic effect of the virus, cytotoxic immune responses, cytokine and growth factor imbalance, oxidative stress, epigenetic alterations, and genetic predisposition interact in an interrelated manner (Friedman, 2010, p. 1303; Schuppan & Afdhal, 2008, p. 837).

In hepatitis B virus (HBV) infection, the integration of viral DNA into hepatocyte genomes plays a significant role in fibrosis progression. HBV DNA insertion affects cell proliferation and apoptotic mechanisms. The HBV X protein activates signaling pathways such as TGF-β, IL-6, NF-κB, and STAT3, thereby enhancing the production of inflammatory mediators (Lok & McMahon, 2016, p. 112). This process stimulates the transformation of hepatic stellate cells (HSCs) into myofibroblast-like cells and accelerates fibrosis. Additionally, the immune response against HBV, particularly cytolytic damage caused by CD8+ T lymphocytes, further aggravates fibrotic processes (Ganem & Prince, 2004, p. 1015).

The mechanisms of fibrosis in hepatitis C virus (HCV) infection differ slightly. HCV proteins induce oxidative stress, disrupt mitochondrial function, and increase lipid peroxidation. As a result, reactive oxygen species (ROS) are generated, triggering HSC activation (Paradis et al., 2001, p. 68). Furthermore, HCV infection enhances the production of cytokines such as IL-1β, TNF-α, and IL-17 through the NF-κB and JAK-STAT signaling pathways (Sheikh et al., 2021, p. 78). These mediators not only sustain inflammation but also promote fibrogenesis. During HCV infection, hepatic microatrophy, angiogenesis, and endothelial dysfunction are additional factors that accelerate fibrosis. The central event in hepatic fibrosis is the activation of hepatic stellate cells (HSCs). Under normal conditions, these cells remain quiescent and store vitamin A; however, in pathological states, they acquire a myofibroblast-like phenotype. Activated HSCs produce extracellular matrix components such as type I and III collagen, fibronectin, and laminin,

thereby disrupting the hepatic architecture (Bataller & Brenner, 2005, p. 173). Early stages of fibrosis may be reversible, but persistent inflammation leads to cirrhosis and hepatocellular carcinoma.

In recent years, molecular mechanisms of fibrogenesis have been extensively studied. Transforming growth factor-beta (TGF-β) serves as the principal stimulator of fibrosis by enhancing HSC differentiation and collagen synthesis. Moreover, platelet-derived growth factor (PDGF) accelerates HSC proliferation, vascular endothelial growth factor (VEGF) promotes angiogenesis, and interleukins IL-17 and IL-22 amplify fibrogenesis under inflammatory conditions (Zhou et al., 2020, p. 1422). A better understanding of these mechanisms has opened new avenues for antifibrotic therapeutic targets.

Significant progress has also been made in diagnostics. Although liver biopsy remains the "gold standard" for fibrosis assessment, non-invasive techniques are increasingly applied in clinical practice. Elastography using FibroScan evaluates liver stiffness to estimate fibrosis severity, while magnetic resonance elastography provides more precise results. Blood biomarkers—such as hyaluronic acid, procollagen III N-terminal peptide, laminin, and tissue inhibitors of metalloproteinases—offer supplementary information about fibrosis stage (Castera et al., 2019, p. 48). These methods are essential for monitoring treatment efficacy.

Antiviral therapy plays a central role in treatment strategies. In HBV infection, nucleos(t)ide analogues—such as tenofovir and entecavir—effectively suppress viral replication and contribute to fibrosis regression. In HCV infection, direct-acting antivirals (DAAs) achieve viral eradication in more than 95% of patients, enabling partial reversal of fibrosis (Poynard et al., 2002, p. 1546). Moreover, research on antifibrotic agents—such as TGF-β receptor inhibitors, HSC activation blockers, antioxidants, and epigenetic modulators—represents promising future directions (EASL Guidelines, 2018, p. 124).

In conclusion, the mechanisms of fibrosis in viral hepatitis are multifactorial, with immune-mediated inflammation, oxidative stress, and dysregulated signaling pathways playing leading roles. Advances in diagnostic technologies and antiviral therapy now make it possible to detect and slow the progression of fibrosis at earlier stages. These developments have crucial clinical implications, improving both the life expectancy and quality of life of patients.

Conclusion: Viral hepatitis, particularly hepatitis B and C, remains one of the most significant global public health challenges today. Their long-term consequences can lead to

liver fibrosis, which may progress to cirrhosis and hepatocellular carcinoma. Therefore, an in-depth understanding of the pathogenesis of these diseases and the development of effective control strategies are of paramount importance.

The mechanisms underlying liver fibrosis are complex and involve immune cell activation, inflammatory mediators, oxidative stress, hepatocyte apoptosis, and the collagen synthesis process mediated by hepatic stellate cells. Consequently, integrating immunological, molecular, and clinical research is essential for developing early diagnostic tools and effective therapeutic approaches. According to medical literature, one of the main factors accelerating fibrosis in viral hepatitis is chronic inflammation and the repeated injury of hepatocytes. Additionally, genetic predisposition, viral load, alcohol consumption, metabolic syndrome, and other comorbidities influence the rate of fibrosis progression. Recent scientific studies indicate that the process of fibrosis can be reversible, which provides both theoretical and practical evidence for the development of new drugs and therapeutic approaches. Clinical research conducted in Uzbekistan and internationally, as well as discussions presented in local scientific literature, demonstrate the growing scope of investigations in this field.

A comprehensive understanding of the mechanisms of viral hepatitis and liver fibrosis not only enables the development of effective treatment plans for individual patients but also contributes to improving national strategies aimed at protecting public health. Thus, evidence-based approaches to prevention, diagnosis, and treatment can significantly help mitigate the global burden of these diseases.

Recommendations:

1. Expand screening programs for early detection of viral hepatitis and actively implement them at the primary healthcare level.
2. Introduce non-invasive diagnostic methods (such as elastography and biochemical markers) more widely in the assessment of liver fibrosis.
3. Continue scientific research aimed at improving the effectiveness of antiviral therapy and introducing new drugs into clinical practice.
4. Develop large-scale health promotion programs targeting lifestyle modifications (reducing alcohol consumption, improving nutrition, and preventing obesity) in patients with viral hepatitis.
5. Support scientific research on viral hepatitis and liver fibrosis at local medical universities and research centers, and train young specialists in this field.

6. Strengthen public awareness campaigns promoting the prevention of viral hepatitis, vaccination, and the reduction of risk factors through healthy lifestyle education.

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