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MORPHOLOGICAL CHANGES AT THE HEPATOCYTE LEVEL IN PATIENTS WITH CHRONIC HEPATITIS B AND C

Raxmonov Komiljon Shuhratovich
2nd-year student, Asia international university, Bukhara, Uzbekistan.
komiljonraxmonov.uz@gmail.com
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Abstract. *Chronic hepatitis B and C infections remain among the most pressing global public health challenges due to their widespread prevalence, silent progression, and potential to cause irreversible liver damage. The hepatotropic nature of HBV and HCV leads to persistent inflammation, immune-mediated injury, and significant morphological alterations at the hepatocyte level, ultimately resulting in fibrosis, cirrhosis, and hepatocellular carcinoma. This study aims to comprehensively evaluate and characterize the cellular and subcellular morphological changes in hepatocytes in patients with chronic viral hepatitis B and C. Emphasis is placed on cytoplasmic vacuolization, nuclear polymorphism, ballooning degeneration, apoptotic and necrotic changes, Mallory-Denk bodies, and mitochondrial dysfunction. By integrating histopathological findings with current virological and immunological data, the study highlights the mechanisms by which chronic infection alters liver architecture and function. The analysis also underscores the role of liver biopsy and advanced imaging techniques in detecting these morphological patterns and supports the development of targeted therapeutic strategies. These insights are critical for improving early diagnosis, patient stratification, and long-term clinical outcomes in individuals affected by chronic viral hepatitis.*

Keywords*: Chronic hepatitis B, chronic hepatitis C, hepatocyte injury, morphological changes, histopathology, liver biopsy, viral hepatitis, ballooning degeneration, Mallory-Denk bodies, hepatic fibrosis, hepatocellular carcinoma.*

Chronic viral hepatitis, particularly infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), represents a major public health concern globally due to its high prevalence, long-term asymptomatic progression, and significant risk of severe complications such as liver cirrhosis and hepatocellular carcinoma (HCC). As reported by the World Health Organization (WHO), an estimated 296 million individuals were living with chronic HBV and approximately 58 million with chronic HCV worldwide as of 2022, with over 1.1 million deaths annually attributed to related liver diseases. Despite advances in vaccination programs for HBV and the availability of direct-acting antiviral agents (DAAs) for HCV, the global burden remains significant, especially in regions with limited access to diagnostic tools and treatment. The liver, being a vital metabolic and detoxifying organ, is particularly susceptible to viral aggression, with hepatocytes as the primary targets of infection and immune-mediated injury. Chronic infection with HBV or HCV initiates a cascade of pathogenic processes including persistent inflammation, oxidative stress, mitochondrial dysfunction, and immunological disturbances, all of which culminate in structural and functional alterations of hepatocytes. These morphological changes—ranging from cellular ballooning and hydropic degeneration to the formation of Mallory-Denk bodies, apoptotic bodies, and nuclear polymorphism—are crucial histopathological hallmarks of ongoing liver injury.

They provide essential insights into disease severity, stage, and progression and serve as a basis for therapeutic decision-making. A comprehensive evaluation of these cellular alterations, combined with virological and immunohistochemical profiling, offers a deeper understanding of the mechanisms underlying chronic viral hepatitis and informs clinical strategies aimed at early detection, risk stratification, and personalized treatment. The objective of this study is to systematically examine the morphological manifestations of hepatocyte injury in chronic HBV and HCV infections and to elucidate their clinical and prognostic significance within the broader context of liver pathology.

Pathophysiology of hepatocyte injury in chronic HBV and HCV infections

The pathophysiological mechanisms underlying hepatocyte injury in chronic hepatitis B and C infections are complex and multifactorial, involving direct viral effects, host immune responses, and chronic inflammation-driven cellular stress. Hepatitis B virus (HBV), a partially double-stranded DNA virus, and hepatitis C virus (HCV), a single-stranded RNA virus, differ in their replication strategies and interaction with the host immune system; however, both ultimately lead to chronic liver damage through sustained immune-mediated cytotoxicity and hepatocellular degeneration. Upon infection, HBV does not exert direct cytopathic effects in most cases; instead, liver damage is largely a consequence of cytotoxic T lymphocyte (CTL)-mediated lysis of infected hepatocytes as part of the host's antiviral immune defense. HCV, on the other hand, has more direct cytopathic properties and can also provoke endoplasmic reticulum (ER) stress, oxidative stress, and mitochondrial dysfunction within hepatocytes, all of which contribute to cellular injury and death. The chronic inflammatory environment sustained by both viruses results in increased production of pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ, as well as reactive oxygen species (ROS), which impair the hepatocyte’s antioxidant defense systems and damage macromolecules including lipids, proteins, and DNA. These molecular events cause morphological changes at the cellular level such as ballooning degeneration, cytoplasmic rarefaction, nuclear pleomorphism, steatosis, and apoptotic body formation. In particular, HCV infection is strongly associated with hepatic steatosis due to its interference with lipid metabolism pathways. Continuous injury and regeneration cycles lead to aberrant hepatocyte proliferation, fibrogenesis, and ultimately architectural distortion of the liver parenchyma. Histopathologically, chronic hepatitis is graded based on the degree of necroinflammatory activity and staged according to the extent of fibrosis using scoring systems like METAVIR or Ishak. Furthermore, chronic injury induces activation of hepatic stellate cells (HSCs), which contribute to extracellular matrix deposition and scar tissue formation. Over time, these mechanisms not only compromise liver function but also set the stage for cirrhosis and the potential development of hepatocellular carcinoma. Understanding the intricate cellular and molecular processes driving hepatocyte injury in chronic HBV and HCV infections is critical for developing effective diagnostic markers and therapeutic interventions aimed at halting or reversing liver damage.

Morphological changes of hepatocytes in chronic hepatitis B and C

The morphological alterations of hepatocytes in chronic hepatitis B and C infections reflect the underlying pathological processes driven by persistent viral replication, immune-mediated cytotoxicity, and oxidative stress.

These changes, which can be observed using light and electron microscopy, are crucial indicators of liver injury and disease progression. In chronic hepatitis B (CHB), hepatocytes frequently exhibit ground-glass appearance, which is due to the accumulation of hepatitis B surface antigen (HBsAg) within the endoplasmic reticulum. This is often accompanied by cytoplasmic swelling, increased eosinophilia, and fine granular cytoplasmic inclusions.

Ballooning degeneration, characterized by swollen hepatocytes with rarefied cytoplasm and indistinct cell borders, is another common feature, especially in advanced inflammatory stages. Inflammatory infiltrates, predominantly composed of lymphocytes and plasma cells, surround the portal tracts and interface zones, contributing to piecemeal necrosis and apoptotic cell death. In chronic hepatitis C (CHC), hepatocytes display a broader range of morphological abnormalities. Steatosis, or fatty change, is a hallmark feature and is present in up to 50% of patients, particularly those with HCV genotype 3. The accumulation of lipid droplets within the cytoplasm results from viral-induced disruption of lipid metabolism and mitochondrial dysfunction. Other notable features include cytoplasmic vacuolization, acidophilic bodies (apoptotic hepatocytes), and the presence of Mallory-Denk bodies, which are aggregates of misfolded cytoskeletal proteins. Nuclear changes such as irregular nuclear contours, binucleation, and chromatin margination also reflect hepatocyte stress and regenerative activity.

Both CHB and CHC are associated with varying degrees of necrosis, apoptosis, and regeneration, leading to architectural disruption over time. The presence of mitotic figures, anisocytosis, and increased nuclear-cytoplasmic ratio may indicate regenerative hyperplasia or, in some cases, pre-neoplastic transformation. The chronicity of these infections perpetuates the cycle of injury and repair, which contributes to fibrogenesis and the eventual development of cirrhosis. Staging of liver disease using histopathological scoring systems enables correlation of these morphological findings with clinical outcomes and informs decisions regarding treatment urgency and surveillance strategies. The integration of histological examination with clinical and virological parameters enhances the understanding of disease behavior and response to antiviral therapy.

Diagnostic and histopathological assessment of hepatocyte injury

Accurate diagnosis and evaluation of hepatocyte injury in chronic viral hepatitis require a multidisciplinary approach that integrates clinical, biochemical, virological, imaging, and histopathological data to determine disease severity, progression, and therapeutic strategy. Serum biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin levels, and viral load quantification (HBV DNA or HCV RNA) provide preliminary information about liver inflammation and viral activity but are insufficient to capture the full extent of cellular and structural damage. Imaging modalities such as ultrasound, transient elastography (FibroScan), and magnetic resonance elastography are useful non-invasive tools to assess liver stiffness and fibrosis, though they cannot directly visualize hepatocyte morphology. Histopathological examination of liver biopsy remains the gold standard for assessing the degree of hepatocellular damage, necroinflammation, steatosis, and fibrosis. Under light microscopy with hematoxylin and eosin staining, hepatocyte injuries are revealed as ballooning degeneration, acidophilic (Councilman) bodies, cytoplasmic inclusions, ground-glass appearance, and nuclear pleomorphism, each representing different stages and mechanisms of cellular insult.

Special stains such as Masson's trichrome or Sirius Red help evaluate the extent of fibrosis, while periodic acid–Schiff (PAS) and reticulin staining assist in detecting structural alterations in the hepatocellular framework. Immunohistochemical techniques enhance diagnostic precision by detecting viral antigens (e.g., HBsAg, HBcAg) or apoptotic markers (e.g., caspase-3), providing insight into the localization and activity of viral replication and immune-mediated apoptosis. Furthermore, electron microscopy enables visualization of subcellular changes including mitochondrial swelling, dilated rough endoplasmic reticulum, and disruption of desmosomal junctions, offering a deeper understanding of the ultrastructural damage occurring within infected hepatocytes. Standardized scoring systems such as the METAVIR, Ishak, and Knodell indices allow quantification of necroinflammatory activity and fibrosis stage, which are crucial for predicting prognosis and determining eligibility for antiviral treatment or liver transplantation. Advances in digital pathology and artificial intelligence-driven histological analysis are further refining diagnostic accuracy and enabling more objective assessment of hepatocellular injury patterns. Therefore, comprehensive diagnostic and histological evaluation not only informs individualized treatment planning but also enhances our understanding of the pathogenesis and progression of chronic HBV and HCV infections.

Therapeutic implications and prognostic significance of hepatocyte damage in chronic viral hepatitis

The extent and nature of hepatocyte injury in chronic viral hepatitis have direct therapeutic implications and serve as critical indicators of disease prognosis. In patients with chronic HBV or HCV infection, the degree of hepatocyte degeneration, necroinflammatory activity, and fibrosis progression fundamentally influence clinical decision-making, including the timing of antiviral therapy initiation, treatment modality, and monitoring strategies. For HBV, the presence of significant hepatocellular damage, as evidenced by elevated ALT levels and histological activity, necessitates the use of potent nucleos(t)ide analogues such as tenofovir or entecavir, which effectively suppress viral replication and mitigate further hepatocyte destruction. In the case of HCV, direct-acting antiviral agents (DAAs) offer high cure rates regardless of fibrosis stage; however, patients with advanced hepatocyte damage and cirrhosis may require extended treatment duration and careful post-treatment surveillance.

Histopathological findings of ballooning, apoptosis, and Mallory-Denk bodies often indicate ongoing oxidative stress and endoplasmic reticulum dysfunction, which correlate with poor therapeutic response and elevated risk of hepatocellular carcinoma (HCC). Moreover, the identification of ground-glass hepatocytes in HBV or steatosis in HCV patients may suggest specific viral genotypes or coexisting metabolic liver disease, necessitating a personalized treatment approach. The degree of hepatocyte damage is also a key determinant of liver regeneration capacity and informs eligibility for liver transplantation in end-stage disease. Prognostically, the presence of extensive hepatocyte apoptosis, bridging necrosis, and regenerative nodules correlates with faster fibrosis progression, reduced response to antiviral therapy, and higher incidence of cirrhosis and HCC. Regular monitoring using non-invasive biomarkers, imaging, and, when needed, follow-up biopsy is essential to assess treatment efficacy and adjust therapy. Future directions in the management of chronic hepatitis will likely focus on targeting intracellular pathways responsible for hepatocyte injury, such as

mitochondrial protection, oxidative stress modulation, and immune checkpoint regulation. Thus, comprehensive understanding of hepatocyte damage is not only pivotal for guiding current therapeutic strategies but also for developing novel interventions aimed at preserving liver architecture and function, ultimately improving long-term clinical outcomes in chronic viral hepatitis.

Conclusion: Chronic viral hepatitis caused by HBV and HCV remains a global public health burden due to its progressive hepatocellular injury, leading to fibrosis, cirrhosis, and hepatocellular carcinoma. The detailed understanding of hepatocyte damage mechanisms—ranging from viral cytopathic effects and immune-mediated apoptosis to oxidative stress-induced degeneration—forms the cornerstone for accurate diagnosis, risk stratification, and personalized treatment strategies. Diagnostic approaches that integrate histopathological assessment with non-invasive markers offer critical insights into the extent of liver damage and facilitate timely therapeutic interventions. The histological identification of specific injury patterns such as ballooning, necrosis, and steatosis not only reflects disease activity but also predicts response to antiviral therapy and long-term outcomes. As antiviral regimens evolve and curative therapies become more accessible, the recognition of histological and molecular determinants of hepatocyte injury gains even greater significance in optimizing care. Furthermore, the prognostic implications of hepatocellular damage necessitate lifelong monitoring and proactive management to prevent irreversible liver failure and malignancy. Advancements in digital pathology, molecular diagnostics, and targeted therapies promise to further refine our ability to detect, treat, and reverse hepatocyte damage in chronic viral hepatitis. Therefore, a comprehensive, multidisciplinary understanding of hepatocyte injury not only enhances clinical practice today but also paves the way for innovation in the prevention and management of liver disease globally.

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