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THE IMPACT OF METABOLIC DYSFUNCTION ON THE COURSE AND FIBROGENESIS IN CHRONIC HEPATITIS B (Literature Review)

B. M. Tadjiev, G. A. Mirzaeva
Tashkent State Medical University, Tashkent, Republic of Uzbekistan

Abstract

Background. Given the rising global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), its impact on the natural course of chronic hepatitis B (CHB) has become an issue of growing clinical relevance; comorbidity rates range from 14% to 70% across cohorts. This review summarizes current data on the pathogenetic mechanisms linking HBV infection and metabolic dysfunction, the role of the gut microbiota and gut–liver axis in liver fibrogenesis, and the clinical outcomes of this comorbidity, including the risk of cirrhosis, hepatocellular carcinoma (HCC), and cardiovascular events. The relationship between steatosis and viral replication appears bidirectional and context-dependent: hepatic steatosis may suppress HBsAg secretion and HBV replication, while concurrent metabolic dysfunction can accelerate fibrogenesis through chronic inflammation, oxidative stress, and gut dysbiosis. The potential of microbiome- and metabolome-based biomarkers for disease monitoring is discussed, along with unresolved questions warranting further study, including in cohorts with HBV/HDV coinfection.

Keywords: chronic hepatitis B; metabolic dysfunction-associated steatotic liver disease; fibrogenesis; gut microbiota; liver cirrhosis; gut–liver axis.

Introduction

Chronic hepatitis B remains one of the leading causes of liver cirrhosis, liver failure, and hepatocellular carcinoma worldwide, with the number of chronically infected individuals currently estimated to exceed 250–296 million [1]. Concurrently, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is rapidly rising globally, including among patients with chronic HBV infection. MASLD is defined as hepatic steatosis confirmed by imaging or biopsy in combination with at least one of five cardiometabolic risk factors: overweight/obesity, type 2 diabetes mellitus, arterial hypertension, hypertriglyceridemia, or reduced high-density lipoprotein cholesterol levels [2].

Given the high prevalence of both conditions, their coexistence is frequent: 14% to 70% of patients with CHB exhibit evidence of concurrent steatotic liver disease [2]. This poses a fundamental question for clinicians and researchers: how does metabolic dysfunction modify the natural history of CHB, the rate of fibrogenesis, and the risk of adverse hepatic and extrahepatic outcomes? The answer remains subject to ongoing debate, as published data are often conflicting and vary depending on study design, steatosis diagnostic modalities, and patient virological status.

The gut microbiota plays a crucial role in this cross-talk; in recent years, gut dysbiosis has come to be recognized as an independent link between metabolic disorders and the progression of chronic liver diseases, including those of viral etiology [1, 3, 4]. The overall burden of chronic viral hepatitis remains a critical public health challenge, underscoring the need for an integrated, multidisciplinary approach to managing patients with virus-associated liver disorders [5].

The aim of this review is to systematize current evidence regarding the pathogenetic mechanisms and clinical outcomes associated with concurrent chronic hepatitis B and metabolic dysfunction, with a primary focus on hepatic fibrogenesis and the gut–liver axis.

Materials and Methods

A comprehensive search of original research and review papers was conducted across PubMed, Google Scholar, and peer-reviewed journals (*Frontiers in Cellular and Infection Microbiology*, *Frontiers in Microbiology*, *World Journal of Hepatology*, *Microorganisms*, etc.) covering the period 2011–2026. The search utilized keywords and combinations including: "hepatitis B", "MASLD/MAFLD/NAFLD", "gut microbiota", "liver fibrosis", "gut-liver axis", "hepatocellular

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carcinoma", and "cirrhosis". In addition to primary search results, reference lists of identified review articles were evaluated to trace assertions back to primary sources and prevent secondary citation distortions. The analysis included studies reporting quantitative risk metrics (odds ratios, adjusted hazard ratios) alongside data on clinical outcomes, pathogenetic pathways, and microbiome/metabolome profiles in patients with chronic hepatitis B.

Epidemiology of Coexistent Chronic Hepatitis B and Metabolic Dysfunction

Aggregated literature indicates that MASLD prevalence among CHB patients spans 14% to 70%, driven largely by regional population characteristics, diagnostic criteria for steatosis, and the age distribution of studied cohorts [2]. In a large retrospective cohort study encompassing 8,052 CHB patients, concurrent MASLD was identified in 19.98% of cases [6]. Notably, patients with coexistent CHB and MASLD differed significantly from those without metabolic disturbances: they were younger, predominantly male, had higher rates of arterial hypertension and diabetes mellitus, and exhibited typical atherogenic dyslipidemia—elevated total cholesterol, triglycerides, and low-density lipoprotein cholesterol paired with decreased high-density lipoprotein cholesterol [6]. These distinct demographic and metabolic traits mandate a risk-stratified management strategy in this cohort.

Pathogenetic Mechanisms of HBV and Metabolic Dysfunction Interaction

Impact of Steatosis on Viral Replication and Antigen Expression

The liver is an immune-privileged organ with specialized microvasculature and an immune cell repertoire comprising Kupffer cells, natural killer cells, and CD4+ and CD8+ lymphocytes [2]. Hepatocyte steatosis suppresses hepatitis B surface antigen (HBsAg) secretion at the cellular level by triggering endoplasmic reticulum stress; specifically, the accumulation of stearic and oleic acids in HepG2.2.15 cell cultures significantly inhibits both HBV DNA and HBsAg secretion [7]. A meta-analysis pooling 28,648 patients across 54 studies confirmed an inverse association between hepatic steatosis and HBeAg positivity (odds ratio [OR] 0.82; 95% CI: 0.75–0.91) [8].

Adiponectin plays an important role in this inverse relationship; while it suppresses hepatic steatosis, it can concurrently promote viral DNA replication. In stable HBV-expressing HepG2 cell assays, elevated adiponectin levels correlated with augmented viral replication [9]. Simultaneously, saturated fatty acids activate toll-like receptor 4 (TLR4), whose signaling cascade can suppress HBV replication, whereas peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α)—a transcription factor that ordinarily enhances HBV transcription—is downregulated in MASLD, further contributing to viral suppression [6].

Immune-Mediated Mechanisms and HBsAg Clearance

HBsAg loss involves an intricate equilibrium between viral replication and host immunity. Obesity and hepatic steatosis can trigger CD8+ T-cell activation, potentially facilitating HBsAg clearance, albeit at the cost of exacerbated hepatocyte inflammation [2, 10]. A prospective cohort study demonstrated that combined HBV and MASLD was associated with elevated pro-inflammatory cytokines, correlating with lower classic viral marker levels ($p<0.01$), but simultaneously with heightened HBV surface gene diversity ($p=0.02$) and a greater frequency of immune-escape variants—which may influence progressive liver injury up to HCC development [2].

At the tissue level, TLR4 activation on Kupffer and hepatic stellate cells driven by bacterial lipopolysaccharides (LPS) and pathogen-associated molecular patterns (PAMPs) stimulates pro-inflammatory and profibrotic cytokines—including TNF-α, IL-1, IL-6, and TGF-β. This promotes hepatic stellate cell transdifferentiation, accelerating fibrosis toward cirrhosis and HCC, as directly demonstrated in gut microbiota-driven hepatocarcinogenesis models [1, 11].

The Gut–Liver Axis and Gut Dysbiosis as a Pathogenic Link

The concept of the "gut–liver axis" reflects the close anatomical and functional integration between the intestine and the liver: approximately 70% of hepatic blood flow originates from the portal vein, delivering not only nutrient products but also microbial antigens [1]. Disruption of the intestinal epithelial barrier permits bacterial components and metabolites to translocate into the portal circulation, activating hepatic innate immunity and triggering inflammatory and profibrotic signaling cascades [1].

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Foundational studies in cohorts with liver cirrhosis of diverse etiologies first established reproducible shifts in the intestinal microbiome during progressive hepatic injury [12, 13], which were subsequently validated and detailed specifically for HBV-related cirrhosis.

Patients with chronic HBV infection, and particularly those with HBV-related cirrhosis, display hallmark alterations in gut microbiome composition. An investigation of 83 patients with HBV-related cirrhosis versus 40 healthy controls revealed significant decreases in alpha-diversity, depletion of short-chain fatty acid (SCFA, notably butyrate)-producing taxa including *Alistipes*, *Lachnospira*, *Parabacteroides*, and *Agathobacter*, and an overgrowth of potentially pathogenic genera such as *Klebsiella* and *Streptococcus* [3]. These alterations correlated with clinical indices of disease severity, including Child-Turcotte-Pugh class, MELD score, total bilirubin, and prothrombin time [3]. Metabolomic profiling revealed depleted levels of tocopherols and 21-hydroxypregnenolone, which correlated with diminished *Alistipes* and *Lachnospira* abundance, alongside significant enrichment of linoleic acid metabolism and unsaturated fatty acid biosynthesis pathways, suggesting disrupted lipid homeostasis as a driver of cirrhosis progression [3].

Crucially, the gut microbiota influences antiviral immunity in addition to fibrogenesis. In murine experiments, antibiotic-mediated microbiome depletion impaired HBV-specific T-cell responses and promoted viral persistence, whereas microbiota reconstitution restored immune clearance capacity—a phenomenon providing insight into age-dependent HBV persistence in infants [14].

Particular consideration is warranted for patients with virologically suppressed HBV infection (undetectable HBV DNA on antiviral therapy) who display persistent liver enzyme elevations. In this subset, contrary to the classical paradigm of reduced microbial diversity in progressive liver disease, a paradoxical increase in alpha-diversity was observed. However, this was accompanied by functional dysbiosis: depletion of SCFA producers (*Blautia*) and expansion of TLR4-agonist taxa (*Escherichia-Shigella*) [4]. These patients also showed significant reductions in hepatoprotective bile acids—ursocholic acid (UCA) and taurocholic acid (TCA)—which inversely correlated with AST, total bilirubin, and alkaline phosphatase levels [4]. These findings indicate that gut–liver axis dysfunction driven by aberrant bile acid metabolism and oxidative stress can sustain subclinical hepatic inflammation independent of active viral replication [4].

Impact of Metabolic Dysfunction on Hepatic Fibrogenesis

Evidence regarding the cumulative impact of concomitant MASLD on fibrogenesis in CHB remains heterogeneous. In a retrospective cohort of 18,980 individuals (excluding significant alcohol intake and HCV coinfection), patients with both MASLD and chronic HBV exhibited higher inflammation and fibrosis scores than those with MASLD alone; among HBV-infected individuals, coexistent pathology was accompanied by more pronounced necroinflammation compared to isolated CHB [15].

Conversely, in a cohort of 8,052 CHB patients, concurrent MASLD was independently associated with a 39% lower risk of severe liver disease (adjusted hazard ratio [aHR] 0.61; 95% CI: 0.49–0.76), with similar protective associations observed for cirrhosis (aHR 0.61) and HCC (aHR 0.57) [6]. This protective trend was most evident in HBsAg-positive patients with low HBV DNA loads or HBeAg-negative status [6]. The authors hypothesized that hepatic steatosis may facilitate HBsAg clearance and suppress HBV replication via the aforementioned molecular pathways, thereby indirectly lowering progression risk [6]. This aligns with a 15-year prospective study of 4,084 untreated HBeAg-negative patients, in whom steatosis correlated with higher rates of HBsAg seroclearance and seroconversion [16]. Nevertheless, in patients who have already achieved HBsAg seroclearance, persistent metabolic inflammation driven by unresolved MASLD can turn into an independent driver of hepatic disease progression [6].

These discordant findings are partly attributable to differences in study designs. An individual patient data meta-analysis demonstrated that in cohorts utilizing liver biopsy, patients with CHB and concurrent fatty liver disease had an approximately 70% higher baseline prevalence of cirrhosis than those without steatosis. Conversely, in cohorts evaluated using non-invasive imaging, no significant

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difference in cirrhosis distribution was detected, pointing to potential selection bias in biopsy-based cohorts [17]. Consequently, the effect of metabolic dysfunction on CHB fibrogenesis appears stage-specific and context-dependent, shaped by the interplay among virological status, the duration and severity of metabolic derangements, and gut microbiota integrity.

Clinical Outcomes

Liver Cirrhosis and Hepatocellular Carcinoma

In the large cohort study cited above, the protective association of MASLD against severe liver outcomes persisted after adjusting for age, sex, BMI, hypertension, and diabetes, remaining statistically significant for both cirrhosis and HCC [6]. Interaction analysis revealed a synergistic protective association between HBsAg positivity and MASLD regarding HCC development: HCC risk in HBsAg-positive patients with MASLD was lower than in HBsAg-positive patients without MASLD and HBsAg-negative patients with MASLD [6].

However, earlier biopsy-validated cohorts have reached opposite conclusions: a retrospective cohort of 1,613 CHB patients found that biopsy- and imaging-confirmed steatosis was associated with an increased risk of HCC, independent of overweight status and cardiometabolic risk factor count [18]. These discrepancies underscore the need for cautious data interpretation and future prospective trials employing standardized steatosis assessment protocols.

Cardiovascular Outcomes

Beyond hepatic sequelae, cardiovascular risk assessment is vital in coexistent CHB and MASLD. In the cohort of 8,052 CHB patients, MASLD was associated with an increased overall risk of cardiovascular disease (aHR 1.16), with the sharpest rise seen in coronary heart disease risk (aHR 1.91; 95% CI: 1.34–2.74) [6]. This vulnerability was particularly pronounced in patients with high viral loads (HBV DNA ≥ 2000 IU/mL), where concurrent MASLD significantly heightened risks of both coronary heart disease and cerebrovascular events [6]. Therefore, even if MASLD confers potential hepatic benefits via viral suppression, cardiovascular risks in this cohort remain substantial and require systematic monitoring within comprehensive clinical care plans.

Therapeutic Approaches and Perspectives

Given the central role of gut dysbiosis and disrupted bile acid profiles in sustaining hepatic inflammation and fibrogenesis in CHB, microbiota-targeted strategies represent a promising therapeutic avenue. In patients with HBV-related cirrhosis and minimal hepatic encephalopathy, probiotic supplementation (*Clostridium butyricum* combined with *Bifidobacterium infantis*) significantly increased dominant commensals (*Clostridium* cluster I, *Bifidobacterium*) while reducing *Enterococcus* and *Enterobacteriaceae* abundance, leading to reduced venous ammonia levels, restored mucosal barrier integrity, and improved neurocognitive function [19]. Fecal microbiota transplantation (FMT) has similarly shown promise, inducing HBeAg clearance in a subset of patients with persistent HBeAg positivity despite long-term entecavir or tenofovir therapy [20], while also improving hepatic encephalopathy outcomes in non-viral cirrhosis cohorts [1].

Nucleos(t)ide analog therapies (entecavir, tenofovir) can partially restore HBV-induced microbial dysbiosis, illustrating the link between virological suppression and gut microbiome health [1]. However, as demonstrated in patients with complete virological response but ongoing transaminase elevations, viral suppression alone may not fully reverse microbial and metabolomic dysregulation. This supports exploring adjunct therapies—such as bile acid modulation (e.g., farnesoid X receptor agonists) and antioxidant regimens—to quell residual inflammation [4].

Another promising direction is the validation of non-invasive microbial and metabolomic biomarkers (e.g., UCA and TCA levels, tocopherols, and alpha/beta-diversity metrics) for early detection of fibrosis progression and personalized treatment stratification in patients with CHB and concurrent metabolic dysfunction [3, 4].

Conclusion

The interaction between chronic HBV infection and metabolic dysfunction is multifaceted, bidirectional, and context-dependent. Hepatic steatosis can inhibit HBV replication and HBsAg

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secretion through mechanisms involving endoplasmic reticulum stress, adiponectin modulation, and TLR4 signaling pathways. In several large cohorts, this has correlated with reduced risks of cirrhosis and HCC, particularly among HBsAg-positive individuals with low viral loads. Conversely, coexisting metabolic dysfunction can fuel necroinflammation, promote fibrogenesis, and increase cardiovascular disease risks; following HBsAg seroconversion, it can emerge as an autonomous driver of liver injury. Intestinal dysbiosis and associated disruptions in bile acid, SCFA, and antioxidant metabolism along the gut–liver axis play an important and underrecognized role in sustaining these pathologies independent of viral replication levels.

Current evidence is derived largely from single-center, cross-sectional studies in Asian populations, limiting causal inference and generalizability. Prospective, longitudinal multi-omics studies featuring serial bio-sampling across distinct disease stages are needed. Finally, the impact of metabolic dysfunction on clinical course, fibrogenesis, and gut microbiome architecture in HBV/HDV coinfection remains virtually unexplored, outlining an important avenue for future dedicated research.

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