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Serum Ferritin and Hepcidin as Biomarkers of Liver Fibrosis in Chronic Hepatitis C: Pathophysiological and Clinical Implications

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Abstract

Chronic hepatitis C (CHC) is characterized by a unique dysregulation of iron metabolism that significantly accelerates liver fibrosis and increases the risk of hepatocellular carcinoma (HCC). This review explores the pathophysiological and clinical implications of serum ferritin and hepcidin as non-invasive biomarkers in CHC. HCV infection promotes hepatic iron accumulation through a dual mechanism: viral-induced oxidative stress suppresses hepcidin transcription via histone deacetylase activity, while the NS3-4A protease directly cleaves the iron exporter ferroprotein. Elevated serum ferritin serves as an independent predictor of advanced fibrosis and reflects a complex metabolic-inflammatory phenotype, often exacerbated by coexisting insulin resistance and steatosis. While hepcidin levels are paradoxically low relative to iron stores in active infection, successful eradication with direct-acting antivirals (DAAs) restores the hepcidin-to-ferritin ratio, signaling a reversal of viral-mediated iron dysregulation. Emerging evidence identifies hepcidin as a direct antifibrotic agent capable of inhibiting hepatic stellate cell activation through the Akt-Smad3 pathway. Despite limitations regarding specificity in the setting of systemic inflammation, the integration of ferritin and hepcidin into multimodal diagnostic frameworks enhances risk stratification beyond traditional elastography. Future therapeutic strategies targeting the hepcidin-ferroprotein axis hold promise for addressing residual fibrotic burden in the post-viral clearance era.

Keywords: Chronic Hepatitis C; Ferritin; Hepcidin; Liver Fibrosis; Iron Metabolism; Direct-Acting Antivirals

Abbreviations: AASLD: American Association for the Study of Liver Diseases; ALT: Alanine Aminotransferase; AOPP: Advanced Oxidation Protein Products; ApoB: Apolipoprotein B; APRI: Aspartate Aminotransferase-to-Platelet Ratio Index; BMP6: Bone Morphogenetic Protein 6; CD2AP: CD2-Associated Protein; CHC: Chronic Hepatitis C; CIDEB: Cell Death-Inducing DFFA-Like Effector B; DAA: Direct-Acting Antiviral; DIOS: Dysmetabolic Iron Overload Syndrome; DMT1: Divalent Metal Transporter 1; EASL: European Association for the Study of the Liver; FIB-4: Fibrosis-4 Index; FPN1: Ferroportin-1; FTN: Ferritin; GLUT2: Glucose Transporter 2; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; HDAC: Histone Deacetylase; HH: Hereditary Hemochromatosis; HIO: Hepatic Iron Overload; HSC: Hepatic Stellate Cell; IRS-½: Insulin Receptor Substrate ½; MASLD: Metabolic Dysfunction-Associated Steatitis Liver Disease; MTP: Microsomal Triglyceride Transfer Protein; NAFLD: Non-Alcoholic Fatty Liver Disease; NAS: NAFLD Activity Score; NASH: Non-Alcoholic Steatohepatitis; ROS: Reactive Oxygen Species; SVR: Sustained Virological Response; T2D: Type 2 Diabetes; TE: Transient Elastography; TGF-β1: Transforming Growth Factor-Beta 1; TFR1: Transferrin Receptor 1; VLDL: Very Low-Density Lipoprotein

Introduction

Chronic hepatitis C (CHC) remains a global health priority, affecting an estimated 50 million people as of 2022 [1-2]. Despite the success of direct-acting antivirals (DAAs), HCV-related mortality remains high due to cirrhosis and hepatocellular carcinoma (HCC) [3]. The natural history of CHC involves progressive fibrosis in 70-

80% of chronically infected individuals, with 10-30% advancing to cirrhosis over two to three decades [1,4-6]. Key accelerators include age, male sex, alcohol use, and metabolic comorbidities [1,6]. Once cirrhosis develops, the annual risks of HCC (2-5%) and hepatic decompensation (3-6%) necessitate early detection [1,5,7]. Staging liver fibrosis is critical for determining treatment urgency and surveillance. While liver biopsy remains the historical reference standard, its invasiveness and sampling errors have catalyzed the shift toward non-invasive biomarkers [8-9]. Current tools like APRI, FIB-4, and elastography are accessible but limited by indeterminate ranges and age-related confounding [8-10]. Consequently, identifying novel biomarkers to refine risk stratification remains a research priority. Iron metabolism dysregulation is a hallmark of CHC. Hepatic iron accumulation accelerates fibrosis and increases HCC risk [11-13]. Serum ferritin has emerged as a key biomarker; elevated levels independently predict advanced fibrosis and treatment failure, with an odds ratio of 2.67 for severe fibrosis [11-12, 14]. Notably, ferritin may reflect inflammation and hepatocellular injury beyond simple iron stores [11-12,15]. This association is driven by iron-catalyzed oxidative stress (Fenton reaction), which activates hepatic stellate cells and promotes collagen deposition [13].

Hepcidin, the master regulator of iron homeostasis, further links these processes [16-17]. In CHC, hepcidin is paradoxically suppressed by HCV-induced oxidative stress despite hepatic iron loading [18-21]. Conversely, higher serum hepcidin levels within CHC cohorts correlate with increased necroinflammation and fibrosis, perhaps reflecting a secondary response to inflammatory signaling [19]. Emerging evidence even suggests hepcidin may exert direct antifibrotic effects by modulating the Akt-Smad3 pathway [23]. The multifaceted rationale for investigating these markers rests on their mechanistic link to HCV pathology, ease of measurement via standardized serum assays, and potential to complement existing non-invasive panels [11-13,15,19]. This review synthesizes the pathophysiological interplay between ferritin, hepcidin, and CHC-related fibrosis to evaluate their utility in modern clinical practice.

Iron Metabolism and Hepatic Physiology

Iron is essential for oxygen transport, DNA repair, and enzymatic reactions, owing to its ability to cycle between ferrous (Fe2+) and ferric (Fe3+) states [24]. Dietary iron absorption occurs primarily in the duodenum, where ferric iron must be reduced to its ferrous form for uptake via divalent metal transporter 1 (DMT1) [24-25]. Intracellularly, iron is either stored in ferritin (FTN) or exported into circulation through ferroportin-1 (FPN1), the only known mammalian cellular iron exporter [25].

The Hepcidin-Ferroportin Axis

Systemic iron balance is primarily governed by hepcidin, a 25-amino-acid hepatic peptide. Hepcidin limits iron entry into the blood by binding to FPN1, inducing its internalization and degradation [25]. Its expression is upregulated by high iron levels via the BMP6-SMAD signaling pathway and suppressed by erythropoietic demand through erythroferrone [25, 27]. Dysregulation of this axis, such as mutations in HFE or TFR2, leads to hereditary hemochromatosis and pathological iron overload [25, 27].

Ferritin: Beyond Iron Storage

Ferritin serves as a spherical nanocage for safe iron sequestration, preventing oxidative damage via Fenton and Haber-Weiss reactions [26]. Beyond storage, it acts as an acute-phase reactant. The ferritin heavy chain (FTH) can activate NF-κB signaling in hepatic stellate cells, promoting proinflammatory mediators [26]. Consequently, serum ferritin is a recognized biomarker for systemic inflammation and immune activation [26].

Hepatic Iron Handling

The liver is the central hub for iron sensing. Hepatocytes acquire iron mainly through transferrin receptor 1 (TFR1)-mediated endocytosis of diferric transferrin [28]. In the acidic environment of the endosome, iron is released, and the receptor-apotransferrin complex recycles to the cell surface [28]. This tightly regulated uptake and the subsequent production of hepcidin ensure that systemic iron levels remain within physiological limits [27-28].

Iron Overload in Chronic Hepatitis C

Iron overload is a hallmark of chronic hepatitis C (CHC), affecting 30–40% of patients through elevated serum iron, transferrin saturation, and ferritin [1,12]. Although hepatic iron accumulation is often mild to moderate, its deposition in hepatocytes and Kupffer cells carries significant pathophysiological weight, correlating with accelerated fibrosis, increased risk of hepatocellular carcinoma (HCC), and poor response to historical therapies [3, 29].

Mechanisms of Viral-Mediated Iron Accumulation

HCV disrupts iron homeostasis through a sophisticated dual mechanism involving both transcriptional and post-translational pathways:

Hepcidin Suppression: Despite potential induction by ER stress via CREBH, the net effect of HCV infection is a profound suppression of hepcidin [22]. HCV-induced reactive oxygen species (ROS) increase histone deacetylase (HDAC) activity, leading to hypoacetylation of the hepcidin promoter [18, 20, 30]. This inhibits the binding of positive transcription factors like C/EBPα and STAT3 [30]. Reduced hepcidin levels subsequently upregulate ferroprotein in the duodenum and liver, increasing systemic iron absorption [31-32].

Ferroprotein Cleavage: Independent of hepcidin levels, the HCV NS3-4A protease directly cleaves ferroprotein 1 [22]. This impairs cellular iron efflux, forcing intracellular accumulation even when regulatory signals attempt to increase export [22].

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The Synergistic Role of Oxidative Stress

The interaction between iron and HCV creates a lethal "vicious cycle." HCV increases ROS production via NADPH oxidase proteins (Nox1, Nox4) and mitochondrial dysfunction [33-34]. This baseline oxidative stress is amplified by the Fenton reaction, where accumulated iron catalyzes the formation of highly reactive hydroxyl radicals ($\cdot OH$) [29, 35]. These radicals drive lipid peroxidation, DNA damage, and protein modification, directly correlating with viral load and disease severity [35].

Pathogenic Implications

Chronic oxidative stress and iron accumulation serve as primary drivers of fibrogenesis. ROS promote the activation of hepatic stellate cells and upregulate TGF-β1, the master regulator of fibrosis [36-37]. Furthermore, the resulting genomic instability and chronic inflammation provide the ideal substrate for hepatocarcinogenesis, underscoring why managing iron dysregulation is vital for long-term prognosis [33, 37].

Ferritin and Fibrosis Progression

Clinical Correlation Across Liver Pathologies

In metabolic dysfunction-associated steatitis liver disease (MASLD), serum ferritin is a recognized, albeit modest, marker of histological severity. Kowdley et al. demonstrated that ferritin levels >1.5 times the upper limit of normal are independently associated with advanced fibrosis (OR 1.66) and non-alcoholic steatohepatitis (NASH) [38]. Prospective cohorts and meta-analyses involving nearly 50,000 patients confirm that hyperferritinemia predicts a higher incidence of hepatic events (HR 2.02) [39-42]. However, in chronic hepatitis C (CHC), ferritin's role is more complex. While it reflects metabolic phenotypes and iron deposition, its capacity to independently stratify fibrosis stages (F0–F4) is inconsistent and must be integrated with validated tools like FIB-4 or elastography [11, 44]. In contrast, for hereditary hemochromatosis (HH), the correlation is more direct; ferritin levels >1,000 $\mu g/L$ serve as a critical threshold for suspected cirrhosis, while levels <1,000 $\mu g/L$ have a 94% negative predictive value for advanced fibrosis [43].

Ferritin as a Marker of Necroinflammation

Ferritin functions as an acute-phase reactant released during hepatocellular necrosis. In MASLD, elevated ferritin correlates with higher NAFLD Activity Scores (NAS) and hepatocellular ballooning [38, 45]. Conversely, data from CHC cohorts suggest that ferritin may not independently reflect neuroinflammatory activity (p=0.3), instead predominantly indicating a metabolic phenotype of iron deposition and established fibrosis [44]. This duality underscores that circulating ferritin depends on both the total tissue iron burden and the degree of active cellular injury [43, 46].

Confounding Factors: Inflammation and Metabolic Syndrome

Interpreting hyperferritinemia requires careful consideration of systemic "noise." Metabolic hyperferritinemia, driven by insulin resistance and obesity, often coexists with advanced fibrosis, creating an apparent association mediated by shared metabolic dysfunction rather than primary iron overload [41-42,44]. Systemic inflammation can elevate ferritin independently of liver-specific pathology, potentially leading to an overestimation of the fibrotic stage [43]. Therefore, a comprehensive assessment must integrate transferrin saturation and metabolic markers to differentiate between primary iron-driven damage and secondary inflammatory elevation [39, 43].

Hepcidin and Fibrogenesis

Hepatic iron overload (HIO) occurs in 10–36% of chronic hepatitis C (CHC) patients and serves as a significant co-carcinogenic factor for hepatocellular carcinoma (HCC) [22,47]. While HIO usually triggers hepcidin expression via the BMP signaling pathway to limit iron absorption, this regulatory axis becomes "uncoupled" in CHC [21, 22].

The Dysregulated Axis in CHC

Hepcidin typically acts as a type II acute-phase reactant, upregulated by cytokines like IL-6 to induce functional iron deficiency during inflammation [21]. However, CHC patients exhibit paradoxically low hepcidin levels relative to their hepatic iron stores compared to patients with HBV or non-viral liver diseases [21, 48]. This virus-specific suppression occurs even in the presence of systemic inflammation. One proposed mechanism involves TNF-α-mediated inhibition of the BMP6/hemojuvelin axis, which downregulates hemojuvelin transcription and blunts the iron-sensing signal [47].

Molecular Variability and Viral Influence

The regulation of hepcidin (encoded by the HAMP gene) in CHC is highly context-dependent, influenced by specific viral proteins and disease stages:

a) HCV Core Protein: Has been shown to activate the HAMP promoter in certain models [49].

b) NS5A Protein: Conversely suppresses HAMP promoter activity, contributing to the net reduction of circulating hepcidin [49].

This molecular tug-of-war, combined with the duration of infection and the varying inflammatory milieu, determines the net hepcidin output. The resulting inappropriate hepcidin response facilitates persistent iron maldistribution and creates a self-reinforcing loop of hepatic injury, making hepcidin a central mechanistic link between metabolic dysregulation and fibrotic progression [22, 47-48].

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Interaction with Metabolic Syndrome and Steatosis

Chronic hepatitis C (CHC) is as much a metabolic disease as a viral one. The convergence of HCV and metabolic syndrome creates a synergistic environment that accelerates fibrogenesis and increases the risk of hepatocellular carcinoma (HCC) [1,2]. While the virus directly perturbs glucose and lipid homeostasis, pre-existing metabolic disorders further enhance HCV virulence and chronicity [2].

Insulin Resistance: The Central Link

HCV-infected patients face an 80% higher risk of developing type 2 diabetes (T2D) [3, 4]. This is driven by both direct and indirect mechanisms:

I. **Direct Viral Effects:** HCV downregulates the glucose transporter GLUT2 and promotes the degradation of insulin receptor substrates (IRS-1 and IRS-2) via the PI3K/Akt pathway [3, 6, 50]. Specifically, the upregulation of CD2-associated protein (CD2AP) facilitates IRS-1 degradation, simultaneously impairing insulin signaling and creating lipid droplets for viral assembly [50].

II. **Peripheral Resistance:** Hepatic dysfunction and systemic inflammation (TNF-α, IL-6) induce whole-body insulin resistance [3, 7]. Notably, successful viral clearance with direct-acting antivirals (DAAs) significantly improves glycemic control and reduces the incidence of new-onset T2D [3, 5].

Genotype-Specific Steatosis

HCV-induced steatosis follows two distinct patterns. Genotype 3 exerts a direct cytopathic effect, where the viral core protein reduces VLDL assembly by inhibiting microsomal triglyceride transfer protein (MTP) and induces lipogenesis via SREBP-1c [3, 8]. In other genotypes, steatosis is primarily "metabolic," though HCV still contributes by inducing the oxidation and proteasomal degradation of Apolipoprotein B (ApoB) and attenuating mitochondrial β-oxidation [51-53].

The Iron-Metabolic Interface

The interplay between iron and metabolic factors adds a final layer of complexity. In metabolic syndrome/MASLD, hepcidin is typically elevated in proportion to iron stores (Dysmetabolic Iron Overload Syndrome - DIOS) [54, 55]. Conversely, HCV suppresses hepcidin, leading to iron accumulation that exacerbates insulin resistance and oxidative stress [7, 18]. When both conditions coexist, the viral suppression of hepcidin often overrides metabolic signals, creating a highly profibrogenic environment [55].

Clinical Considerations

Management of CHC must include lifestyle interventions identical to those for metabolic syndrome [7]. While DAAs effectively achieve viral clearance regardless of steatosis, metabolic comorbidities remain a long-term risk for HCC even after a sustained virological response (SVR) [1,5].

Diagnostic and Prognostic Implications

Historically, liver biopsy has been the gold standard for staging fibrosis, yet its invasiveness and sampling variability have paved the way for non-invasive alternatives [1, 56]. Transient elastography (TE) currently leads clinical practice, offering high diagnostic accuracy for advanced fibrosis with sensitivities near 89% and specificities exceeding 90% in HCV cohorts [57]. However, emerging serum biomarkers like ferritin and hepcidin offer a cost-effective, accessible complement that reflects the dynamic interplay of iron dysregulation and inflammation.

Clinical Utility of Ferritin and Hepcidin

Serum ferritin serves as an independent predictor of advanced fibrosis across various chronic liver diseases, including CHC, NAFLD, and autoimmune hepatitis [13, 58]. Levels 1.5 times above the upper limit of normal (>300 ng/mL in women; >450 ng/mL in men) correlate with severe histological damage and can even predict mortality in decompensated cirrhosis [58-59]. Hepcidin's utility is increasingly recognized through the hepcidin-to-ferritin ratio. This ratio typically decreases as fibrosis progresses, providing a performance comparable to established indices like APRI [13, 60]. Unlike biopsy or elastography, these markers capture the metabolic "state" of the liver, offering prognostic value beyond simple architectural staging [58].

Limitations and Multimodal Approach

Despite their promise, neither marker is currently recommended for standalone use. Ferritin's status as an acute-phase reactant reduces its specificity in the presence of systemic infection or metabolic syndrome [43, 61]. Similarly, hepcidin levels are highly sensitive to iron stores and erythropoietic activity, leading to variability across different populations [13, 61]. The greatest clinical value of these biomarkers lies in a multimodal approach. Integrating serum markers with elastography may significantly enhance diagnostic accuracy and risk stratification [58, 61]. This combined strategy allows clinicians to better identify patients at high risk for disease progression and adjust surveillance and therapeutic interventions accordingly.

Therapeutic Considerations

The introduction of direct-acting antivirals (DAAs) has revolutionized CHC management, with cure rates exceeding 95% [1,62]. Beyond viral clearance, DAAs significantly impact metabolic and iron-related derangements, offering a more rapid and stable reduction in serum ferritin compared to traditional interferon-based regimens [62-64].

Impact of Viral Eradication on Iron Homeostasis

Successful HCV eradication leads to the normalization of the hepcidin-to-ferritin ratio [63]. By removing viral-induced oxidative stress and HDAC activity, DAA therapy restores the liver's ability to regulate hepcidin relative to iron stores [20, 30, 63]. This restoration is further supported by a decrease in erythroferrone,

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suggesting a systemic rebalancing of iron homeostasis after the viral "brake" is removed [63]. However, host genetic factors-specifically polymorphisms in the ferroprotein gene SLC40A1-continue to influence the likelihood of fibrosis regression even after achieving a sustained virological response (SVR) [54, 62].

Adjunctive Iron Reduction Therapy

Phlebotomy remains a viable strategy for patients with persistent iron overload or those unable to achieve SVR. Maintenance phlebotomy has been shown to slow fibrosis progression and reduce ALT levels by depleting the substrate for the Fenton reaction, thereby decreasing hepatic stellate cell (HSC) activation [65, 66]. While current AASLD guidelines do not recommend routine phlebotomy for mild secondary iron overload, it remains a critical tool for patients with significant hepatic iron concentrations (geq 20mu mol/g) who show ongoing neuroinflammatory activity [67, 68].

Novel Targets: The Hepcidin-Ferroportin Axis

Emerging research identifies hepcidin as a direct antifibrotic agent. Hepcidin inhibits TGF-beta-mediated HSC activation through a ferroprotein-dependent mechanism involving Akt-Smad3 signaling [23]. This has sparked the development of:

a) Hepcidin Mimetics: To induce ferroprotein degradation and prevent iron-mediated injury [69].

b) Ferroportin Antagonists: To directly suppress HSC activation, though systemic iron sequestration must be carefully monitored [23, 69].

Future comprehensive management of CHC will likely integrate DAA therapy with metabolic optimization and novel hepcidin modulators to address the residual fibrotic burden in the post-SVR era [62, 69].

Conclusion

The interplay between HCV infection and iron metabolism represents a critical axis in the pathogenesis of liver fibrosis. Ferritin and hepcidin are not merely markers of iron stores but are active participants in a "vicious cycle" of oxidative stress, insulin resistance, and hepatic stellate cell activation. Although the advent of DAA therapy has transformed CHC treatment by effectively eliminating the viral trigger, the residual metabolic and fibrotic damage remains a clinical challenge, particularly in patients with genetic predispositions (e.g., SLC40A1 polymorphisms) or persistent metabolic dysfunction. This review underscores, serum Ferritin should be utilized as a dynamic marker of both metabolic risk and advanced fibrosis, requiring careful interpretation in the context of systemic inflammation. The Hepcidin-to-Ferritin Ratio provides a more accurate reflection of the "uncoupled" iron-sensing machinery in CHC than either marker alone. A Multimodal Approach, combining these biomarkers with transient elastography, offers a superior strategy for non-invasive disease monitoring. Looking forward, the transition from viral eradication to "organ-specific" repair will likely involve the hepcidin-ferroprotein axis. Hepcidin mimetics and ferroprotein antagonists represent a burgeoning frontier in antifibrotic therapy, potentially offering a way to mitigate the long-term risk of HCC and cirrhosis in the millions of patients who have achieved a sustained virological response but carry a legacy of hepatic injury.

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