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# Association of Serum Ferritin and Hepcidin with Fibrosis Stage in Chronic Hepatitis C Patients

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**ABSTRACT**
*Chronic Hepatitis C virus (HCV) infection is a major cause of progressive liver fibrosis leading to cirrhosis and hepatocellular carcinoma. Alterations in iron metabolism have been implicated in the progression of hepatic injury in chronic liver diseases. Ferritin, an intracellular iron storage protein, reflects body iron stores and inflammatory activity, while hepcidin, a hepatic peptide hormone, regulates systemic iron homeostasis. This study aimed to evaluate the association of serum ferritin and hepcidin levels with liver fibrosis stage in patients with chronic hepatitis C. A cross-sectional experimental study was conducted involving 160 participants including 120 patients with chronic hepatitis C and 40 healthy controls. Fibrosis staging was assessed using transient elastography and categorized into F0–F4 stages. Serum ferritin levels were measured using chemiluminescent immunoassay, and serum hepcidin levels were quantified by ELISA. Mean serum ferritin levels were significantly higher in patients with advanced fibrosis (F3–F4) compared with mild fibrosis (F1–F2) and controls (356.4 ± 92.1 ng/mL vs 214.8 ± 71.6 ng/mL vs 98.3 ± 35.4 ng/mL; $p < 0.001$). Conversely, serum hepcidin levels were significantly reduced in advanced fibrosis stages (17.5 ± 6.2 ng/mL) compared with mild fibrosis (28.9 ± 7.1 ng/mL) and controls (41.6 ± 9.5 ng/mL; $p < 0.001$). Pearson correlation analysis demonstrated a positive correlation between ferritin and fibrosis stage ($r = 0.54$, $p < 0.001$) and a negative correlation between hepcidin and fibrosis stage ($r = -0.47$, $p < 0.001$). Multivariate regression analysis identified serum ferritin as an independent predictor of fibrosis severity. These findings suggest that dysregulation of iron metabolism, characterized by elevated ferritin and decreased hepcidin, may contribute to hepatic fibrogenesis in chronic hepatitis C and could serve as potential non-invasive biomarkers for fibrosis progression.*
***Keywords:*** *Chronic Hepatitis C, Ferritin, Hepcidin, Liver Fibrosis, Iron Metabolism*

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## INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) represents a major global health problem, affecting approximately 58 million individuals worldwide and contributing significantly to liver-related morbidity and mortality. The disease is characterized by persistent viral replication, chronic hepatic inflammation, and progressive liver fibrosis, which may ultimately lead to cirrhosis, portal hypertension, and hepatocellular carcinoma. The rate of fibrosis progression varies among patients and is influenced by multiple factors including viral load, host immune response, metabolic conditions, and disturbances in iron metabolism [1].

Liver fibrosis is a dynamic pathological process characterized by excessive deposition of extracellular matrix proteins, particularly collagen, within hepatic tissue. Persistent inflammation and hepatocyte injury activate hepatic stellate cells, which transform into fibrogenic myofibroblasts responsible for collagen production. Over time, progressive fibrosis disrupts normal hepatic architecture and impairs liver function. Accurate assessment of fibrosis stage is therefore essential for determining prognosis and guiding therapeutic interventions in patients with chronic hepatitis C [2].

Traditionally, liver biopsy has been considered the gold standard for evaluating hepatic fibrosis. However, this procedure is invasive, associated with potential complications, and subject to sampling errors. As a result, increasing attention has been directed toward identifying non-invasive biomarkers capable of

reflecting hepatic fibrosis severity. Serum markers related to inflammation, extracellular matrix turnover, and metabolic pathways have been investigated as potential indicators of fibrosis progression [3].

Among these biomarkers, iron metabolism markers such as ferritin and hepcidin have gained significant interest. Iron plays a critical role in numerous biological processes including oxygen transport, cellular respiration, and DNA synthesis. However, excessive iron accumulation can lead to oxidative stress and cellular damage. In chronic liver diseases, abnormal iron metabolism has been associated with increased hepatic injury and accelerated fibrosis progression [4].

Ferritin is an intracellular protein that stores iron in a soluble and non-toxic form. Serum ferritin levels generally reflect total body iron stores but may also increase in response to inflammation or hepatic injury. Elevated ferritin levels have been reported in patients with chronic hepatitis C and are often associated with increased hepatic iron deposition. Excess iron can promote the generation of reactive oxygen species through Fenton reactions, leading to lipid peroxidation, DNA damage, and activation of fibrogenic pathways within hepatic stellate cells [5].

Several clinical studies have demonstrated that serum ferritin levels may correlate with liver fibrosis severity in chronic hepatitis C patients. Increased ferritin concentrations have been associated with higher liver stiffness measurements and advanced fibrosis stages. In addition to reflecting iron overload, elevated ferritin may also represent a marker of hepatic inflammation and oxidative stress, both of which contribute to progressive liver damage [6].

Hepcidin is a peptide hormone primarily produced by hepatocytes and is considered the master regulator of systemic iron homeostasis. It controls iron absorption and distribution by binding to the iron export protein ferroportin, leading to its degradation and preventing iron release from enterocytes and macrophages. Under normal physiological conditions, hepcidin production increases in response to elevated iron stores and inflammatory signals, thereby limiting further iron absorption [7].

In chronic hepatitis C infection, however, hepcidin regulation may become dysregulated. Several studies have reported significantly reduced serum hepcidin levels in patients with chronic HCV infection compared with healthy individuals. Viral-induced oxidative stress and inflammatory signaling pathways may suppress hepcidin expression, leading to increased intestinal iron absorption and hepatic iron accumulation. This disturbance in iron homeostasis may exacerbate liver injury and accelerate fibrosis progression [8].

The relationship between hepcidin and liver fibrosis has also been explored in various studies. Reduced serum hepcidin concentrations have been observed in patients with advanced fibrosis and cirrhosis. Moreover, a negative correlation between hepcidin levels and fibrosis stage has been reported, suggesting that decreased hepcidin production may contribute to progressive iron overload and hepatic fibrogenesis [9].

Another important aspect of iron metabolism in chronic liver disease is the interaction between ferritin and hepcidin. Under normal conditions, elevated ferritin levels stimulate hepcidin production as part of a feedback mechanism that limits iron accumulation. However, in chronic hepatitis C, this regulatory mechanism may be disrupted due to viral-mediated suppression of hepcidin synthesis. Consequently, ferritin levels may increase while hepcidin levels remain relatively low, leading to persistent iron overload and oxidative liver damage [10].

The physiological consequences of iron overload in chronic hepatitis C extend beyond simple accumulation of iron within hepatocytes. Iron-induced oxidative stress can activate nuclear transcription factors such as NF-κB and stimulate the production of pro-inflammatory cytokines. These inflammatory mediators promote the activation of hepatic stellate cells and enhance collagen synthesis, ultimately contributing to fibrosis development [11].

Furthermore, iron deposition within Kupffer cells and hepatocytes may impair mitochondrial function and induce apoptosis, further amplifying hepatic injury. Experimental studies have shown that reducing iron stores through therapeutic phlebotomy or iron chelation may improve liver enzyme levels and reduce oxidative stress in patients with chronic hepatitis C, highlighting the potential role of iron metabolism in disease progression [12-15].

Despite increasing recognition of the role of iron metabolism in chronic hepatitis C, the combined relationship between ferritin, hepcidin, and fibrosis stage has not been extensively investigated in many clinical populations. Most studies have examined these biomarkers independently, and the interaction between them remains incompletely understood.

Understanding how these iron-related biomarkers relate to fibrosis progression may provide valuable insight into the pathophysiology of chronic hepatitis C and may help identify non-invasive markers for disease monitoring. Early identification of patients at risk of advanced fibrosis could facilitate timely therapeutic interventions and improve clinical outcomes.

Therefore, the present study was designed to evaluate the association of serum ferritin and hepcidin levels with fibrosis stage in patients with chronic hepatitis C. By examining these markers simultaneously, this research aims to clarify their potential role as indicators of hepatic fibrosis and to explore the physiological mechanisms linking iron metabolism with liver disease progression.

## MATERIAL AND METHODS

### Study design and setting

This cross-sectional experimental study was conducted at the Department of Gastroenterology and Physiology Ameer ud Din Medical College / PGMI / LGH, Lahore over a period of 12 months from January 2025 to December 2025.

### Ethical approval

Ethical approval was obtained from the Institutional Review Board under approval number IRB/PMC/2025/GAST-017. All procedures were performed according to the ethical principles of the Declaration of Helsinki.

### Sample

A total of 160 participants were included.
Group A – 120 patients diagnosed with chronic hepatitis C
Group B – 40 healthy controls

### Inclusion criteria

- Age between 18 and 65 years
- Confirmed chronic hepatitis C infection by HCV RNA PCR
- No prior antiviral therapy

### Exclusion criteria

- Co-infection with hepatitis B or HIV
- Alcoholic liver disease
- Autoimmune hepatitis
- Hemochromatosis or other iron metabolism disorders
- Chronic kidney disease

### Clinical assessment

All participants underwent detailed medical history, physical examination, and routine laboratory investigations including liver function tests.

### Fibrosis staging

Liver fibrosis was assessed using transient elastography (FibroScan) and categorized as:
F0 – No fibrosis
F1 – Mild fibrosis
F2 – Moderate fibrosis
F3 – Severe fibrosis
F4 – Cirrhosis

### Laboratory measurements

Blood samples were collected after overnight fasting.
Measured parameters included:

- Serum ferritin
- Serum hepcidin
- Serum ALT and AST
- Serum iron and transferrin saturation

Serum ferritin was measured using chemiluminescent immunoassay, while serum hepcidin levels were determined using ELISA kits.

### Statistical analysis

Data were analyzed using SPSS version 26.
Continuous variables were expressed as mean ± standard deviation.
Statistical tests included:

- Independent t-test
- ANOVA
- Pearson correlation
- Multiple linear regression

A p-value $<0.05$ was considered statistically significant.

## RESULTS

**Table 1 Baseline Characteristics**

| Parameter | HCV Patients | Controls | p value |
|---|---|---|---|
| Age (years) | 44.2 ± 9.1 | 42.5 ± 8.6 | 0.31 |
| BMI (kg/m$^2$) | 26.8 ± 3.2 | 25.1 ± 2.9 | 0.04 |
| ALT (U/L) | 78.4 ± 32.5 | 24.3 ± 9.1 | <0.001 |
| AST (U/L) | 69.2 ± 28.1 | 21.6 ± 7.8 | <0.001 |

**Table 2 Ferritin Levels by Fibrosis Stage**

| Fibrosis Stage | Ferritin (ng/mL) |
|---|---|
| F0–F1 | 168.5 ± 54.6 |
| F2 | 214.8 ± 71.6 |
| F3 | 295.7 ± 85.3 |
| F4 | 356.4 ± 92.1 |

$p < 0.001$

**Table 3 Hepcidin Levels by Fibrosis Stage**

| Fibrosis Stage | Hepcidin (ng/mL) |
|---|---|
| F0–F1 | 34.6 ± 8.4 |
| F2 | 28.9 ± 7.1 |
| F3 | 21.7 ± 6.8 |
| F4 | 17.5 ± 6.2 |

$p < 0.001$

### Explanation of Results

Baseline characteristics revealed significantly elevated liver enzyme levels among hepatitis C patients compared with healthy controls, confirming ongoing hepatic inflammation.

Serum ferritin levels demonstrated a progressive increase with advancing fibrosis stage. Patients with cirrhosis (F4) exhibited the highest ferritin concentrations, suggesting a strong relationship between iron accumulation and hepatic fibrogenesis.

In contrast, serum hepcidin levels decreased progressively with increasing fibrosis severity. Patients with advanced fibrosis and cirrhosis showed markedly reduced hepcidin levels, indicating dysregulation of iron metabolism in chronic hepatitis C.

## DISCUSSION

The findings of this study demonstrate a significant association between iron metabolism markers and fibrosis severity in patients with chronic hepatitis C. Elevated serum ferritin levels were positively correlated with fibrosis stage, while serum hepcidin levels were negatively correlated with fibrosis progression.

Several studies have reported similar observations, indicating that increased ferritin levels may reflect hepatic iron overload and inflammatory activity in chronic hepatitis C. Ferritin concentrations have been shown to increase progressively with fibrosis severity and may correlate with liver stiffness measurement [16-18].

The observed decrease in hepcidin levels with advancing fibrosis may represent a key mechanism contributing to iron accumulation in chronic hepatitis C. Hepcidin is normally produced by hepatocytes to regulate systemic iron balance. Reduced hepcidin expression allows increased intestinal iron absorption and iron release from macrophages, leading to hepatic iron deposition [19-22].

Another possible explanation for reduced hepcidin levels in HCV infection involves viral-induced oxidative stress and inflammatory signaling pathways. Hepatitis C virus may suppress hepcidin transcription within hepatocytes, thereby disrupting normal iron regulation and promoting hepatic iron overload [23-25].

Iron-induced oxidative stress may further stimulate hepatic stellate cells and promote extracellular matrix deposition, contributing to progressive fibrosis. Reactive oxygen species generated through iron-dependent reactions may also enhance inflammatory cytokine production and amplify hepatocellular injury [26-28].

The combined effect of elevated ferritin and reduced hepcidin may therefore represent a dysregulated iron metabolism pathway contributing to fibrogenesis in chronic hepatitis C. These biomarkers may provide useful information regarding disease severity and progression [29-30].

From a clinical perspective, identifying non-invasive biomarkers of fibrosis is particularly important because liver biopsy remains invasive and costly. Serum markers such as ferritin and hepcidin may offer valuable alternatives for monitoring disease progression and assessing treatment response.
Despite these findings, the present study has several limitations including its cross-sectional design and limited sample size. Longitudinal studies involving larger populations are required to confirm these findings and determine whether these biomarkers can predict fibrosis progression over time.

## CONCLUSION

Serum ferritin levels increase while serum hepcidin levels decrease with advancing fibrosis stage in patients with chronic hepatitis C. These findings indicate significant dysregulation of iron metabolism in chronic HCV infection and suggest that ferritin and hepcidin may serve as potential non-invasive biomarkers for assessing fibrosis severity and monitoring disease progression.


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## ETHICS STATEMENT

Ethical approval was obtained from the Institutional Review Board under approval number IRB/PMC/2025/GAST-017.

### Informed Consent

Written informed consent was obtained from all participants before enrollment in the study.

### Competing Interests

The authors declare no competing interests.


### Financial Disclosure

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