

# Role of Hypoxia-Inducible Factors (HIFs) in Liver Diseases

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## ABSTRACT

Hypoxia-inducible factors (HIFs) are key transcription factors that regulate cellular adaptation to low oxygen conditions. In recent years, their role in the pathogenesis of liver diseases has gained increasing attention. In this study, the role of HIFs in fibrogenesis and disease progression was evaluated based on a clinical case with impaired liver function. The findings suggest that elevated HIF levels are associated with activation of hypoxia-related pathways and enhanced fibrogenic processes in the liver. This case suggests that elevated serum HIF levels may reflect active fibrogenesis and disease progression in liver cirrhosis.

**Keywords:** Hypoxia-inducible factor; liver cirrhosis; hypoxia; HIF-1 $\alpha$ ; HIF-2 $\alpha$

## INTRODUCTION

Hypoxia-inducible factors (HIFs) are considered one of the most important discoveries in molecular biology in recent decades. Because the liver is highly metabolically active and sensitive to oxygen fluctuations, HIF signaling has received increasing attention in the context of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

HIFs are composed of an oxygen-sensitive  $\alpha$  subunit and a constitutively expressed  $\beta$  subunit [1,2]. To date, three  $\alpha$  isoforms have been described — HIF-1 $\alpha$ , HIF-2 $\alpha$ , and HIF-3 $\alpha$  — all of which can dimerize with HIF-1 $\beta$ . Activation is regulated principally via hydroxylation of proline residues within the  $\alpha$  subunits [3]. Tissue distribution differs between isoforms: HIF-1 $\alpha$  is ubiquitously expressed in many organs including the brain, heart, lung, liver, kidney, and pancreas, whereas HIF-2 $\alpha$  expression is more tissue-restricted and demonstrates developmental specificity [4].

HIFs and chronic liver disease

Chronic liver disease (CLD) represents a major public health burden; cirrhosis and its complications, including hepatocellular carcinoma, account for a substantial number of annual deaths worldwide [5]. The rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) contributes to increasing CLD incidence. Despite extensive research, there remains no widely accepted and clinically established antifibrotic therapy.

Both hepatotoxic and cholestatic models indicate that HIF-

1 $\alpha$  and HIF-2 $\alpha$  act as potent stimulators of hepatic stellate cell activation during later stages of hepatocellular injury, promoting metabolic changes, proliferation, angiogenesis, and extracellular matrix production.

In a combined intermittent hypoxia and NASH model, ER stress, inflammation, and angiogenic signaling contributed to accelerated liver fibrosis. Silencing HIF-1 $\alpha$  reduced markers of ER stress, angiogenesis, and inflammation, while attenuating fibrosis progression [6,7].

Other studies have demonstrated significant roles of HIF-1 and HIF-2 in the pathogenesis of nonalcoholic fatty liver disease and progression to fibrosis through dysregulation of lipid metabolism and induction of profibrotic mediators in response to hypoxia. Hepatocyte-specific deletion of HIF-1 $\alpha$  reduced fibrosis in murine models [8].

Interestingly, PHD1 knockout mice exhibit HIF activation with increased tolerance to hypoxia and protection from liver injury. Deletion of PHD genes has also been reported to enhance liver regeneration following 80% hepatectomy [9]. Recent studies have highlighted the role of HIF-2 in steatosis progression. Although HIF activation may exert context-dependent beneficial effects, the overall impact on NAFLD appears detrimental, making HIF signaling a potential therapeutic target [10]. In addition, HIF-2 $\alpha$  has been implicated in promoting hepatocyte apoptosis and facilitating fibrogenesis [11].



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## CASE PRESENTATION

A 61-year-old male patient presented with complaints of generalized weakness and fatigue. The patient had a known history of chronic hepatitis C infection.

Laboratory investigations revealed abnormalities in liver function tests. Alanine aminotransferase (ALT) was 78.2 U/L and aspartate aminotransferase (AST) was 61 U/L. Cholestatic markers were also elevated, with alkaline phosphatase (ALP) at 245 U/L and gamma-glutamyl transferase (GGT) at 139 U/L. Total bilirubin level was 2.7 mg/dL. Serum albumin was reduced at 3.67 g/dL, while the international normalized ratio (INR) was elevated at 1.29. Serum creatinine was within normal limits at 0.92 mg/dL. The Model for End-Stage Liver Disease (MELD) score was calculated as 13.

Upper gastrointestinal endoscopy revealed the presence of esophageal varices, indicating portal hypertension.

Serum hypoxia-inducible factor (HIF) level was measured using enzyme-linked immunosorbent assay (ELISA) and was markedly elevated at 510 pg/mL, suggesting activation of hypoxia-related molecular pathways associated with ongoing fibrogenesis.

Overall, clinical, laboratory, and endoscopic findings were consistent with chronic liver disease with evidence of portal hypertension and impaired liver function.

## DISCUSSION

In the present case, elevated serum HIF levels were observed together with biochemical and endoscopic findings indicating chronic liver disease and portal hypertension. Increased ALT, AST, ALP, GGT, bilirubin, and INR levels accompanied by decreased albumin support impaired liver function and ongoing hepatocellular injury. The presence of esophageal varices further indicates portal hypertension.

Chronic liver diseases are associated with structural distortion of hepatic tissue and impaired microcirculation, resulting in reduced oxygen delivery within the liver. Under hypoxic conditions, activation of HIF-1 $\alpha$  and HIF-2 $\alpha$  stimulates hepatic stellate cell proliferation and extracellular matrix accumulation, which play important roles in liver fibrogenesis [12,8,10].

Previous studies have demonstrated that HIF activation increases the expression of profibrotic mediators such as VEGF, PDGF, and TGF- $\beta$ . These mediators enhance collagen synthesis and contribute to progression of liver fibrosis [12,9]. In addition, HIF signaling pathways have also been associated with angiogenesis and inflammatory responses during chronic liver injury.

The markedly elevated serum HIF level observed in this patient may therefore reflect ongoing fibrogenic activity within the liver tissue. Furthermore, portal hypertension and esophageal varices support the presence of chronic hemodynamic alterations and hypoxic stress in the hepatic microenvironment.

Recent studies have reported associations between HIF expression, fibrosis severity, and disease progression in chronic

liver diseases [10,11]. Therefore, serum HIF measurement may potentially serve as an additional biomarker for monitoring disease activity and progression. However, further large-scale clinical studies are required before routine clinical application can be recommended.

Recent studies also suggest that HIFs may have diagnostic, prognostic, and predictive significance in chronic liver diseases. Elevated serum HIF levels may reflect active fibrogenesis and ongoing disease progression, potentially providing additional information regarding disease severity and prognosis. Furthermore, targeting hypoxia-related signaling pathways may represent a novel therapeutic strategy in chronic liver diseases. In patients with markedly elevated HIF levels, anti-HIF therapies may potentially reduce fibrogenic activity and slow disease progression. Therefore, further experimental and clinical studies are required to clarify the potential role of HIF-targeted therapies and their contribution to future treatment approaches in liver fibrosis and cirrhosis.

## CONCLUSION

This case demonstrates elevated serum hypoxia-inducible factor (HIF) levels in a patient with liver cirrhosis and biochemical evidence of impaired hepatic function. The findings suggest that HIF activation is associated with ongoing fibrogenesis and may play a role in disease progression.

Moreover, HIFs may have potential diagnostic, prognostic, and predictive value in chronic liver disease, reflecting disease severity and activity. However, further large-scale clinical studies are necessary to confirm their utility in routine clinical practice.

## Ethics

**Ethical statement:** This case report has a retrospective design. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patient confidentiality was strictly maintained, and all presented data were anonymized to ensure that the patient cannot be identified.

**Informed Consent:** Written informed consent was obtained from the patient for publication of this case report.

**AI statement:** Artificial intelligence tools were used only for minor language editing and grammar correction. The authors are fully responsible for the scientific content of the manuscript.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: N.B., A.I., Concept: N.B., Design: T.A., Data Collection or Processing: A.I., K.H., Analysis or Interpretation: A.I., K.H., Literature Search: T.A., A.I., Writing: K.H., A.I.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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