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THE ROLE OF INSULIN RESISTANCE IN THE PATHOGENESIS OF CHRONIC HEPATITIS

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ABSTRACT

Chronic hepatitis remains one of the most pressing issues in modern hepatology, and the role of metabolic factors in its development and progression has been steadily increasing. Epidemiological and clinical studies conducted in recent years indicate that insulin resistance represents an important pathogenetic factor in the development of liver diseases. Disruption of insulin signaling leads to impaired lipid metabolism in hepatocytes, increased triglyceride accumulation, and activation of oxidative stress. These processes promote the production of inflammatory mediators and contribute to the development of hepatic fibrosis. According to data reported in the scientific literature, patients with insulin resistance have a significantly higher risk of developing liver fibrosis, which in turn increases the likelihood of progression to severe forms of chronic hepatitis. This article analyzes the molecular mechanisms, epidemiological aspects, and clinical significance of insulin resistance in the pathogenesis of chronic hepatitis based on contemporary scientific literature.

KEYWORDS

Insulin resistance, chronic hepatitis, metabolic syndrome, hepatic fibrosis, hepatocyte, lipogenesis, oxidative stress, inflammatory cytokines, hepatic steatosis

Introduction

Chronic hepatitis, and chronic viral liver diseases in general, remain among the major global health challenges of the twenty-first century. According to data from the World Health Organization (WHO), as of 2022 approximately 304 million people worldwide were living with chronic viral hepatitis B and C; of these, 254 million individuals were infected with chronic hepatitis B virus (HBV) and 50 million with chronic hepatitis C virus (HCV). In the same year, the number of deaths associated with these two infections reached 1.3 million, with liver cirrhosis and hepatocellular carcinoma being the primary causes of mortality.

Even more concerning is the persistently low coverage of diagnosis and treatment. According to WHO estimates, only 13.4% of individuals living with chronic HBV have been diagnosed and merely 2.6% have received treatment. For HCV infection, diagnostic coverage is estimated at 36.4%, while treatment coverage reaches approximately 20%. These figures indicate that chronic hepatitis should be considered not only as an infectious disease but also as a long-term metabolic and fibrogenic process.

Traditionally, the pathogenesis of chronic hepatitis has been explained primarily by viral replication, immune-mediated inflammation, and hepatocellular injury. However, research over the past two decades has demonstrated that disease progression cannot be adequately explained solely by viral load or the degree of necroinflammation. The rate of hepatic fibrosis progression, the development of steatosis, the likelihood of transition to cirrhosis, and the risk of hepatocellular carcinoma are frequently influenced by the metabolic status of the host organism. In this context, insulin resistance has attracted particular attention as a central factor affecting both the clinical course and morphological progression of chronic hepatitis.

Insulin resistance is defined as a condition in which the sensitivity of peripheral tissues and hepatocytes to insulin is reduced, requiring higher concentrations of insulin to maintain normal glycometabolic responses. This metabolic disturbance is closely associated with metabolic syndrome, abdominal obesity, type 2 diabetes mellitus, and metabolic dysfunction–associated fatty liver disease. At the hepatic level, insulin resistance leads to insufficient suppression of gluconeogenesis, increased de novo lipogenesis, enhanced flux of free fatty acids, and accumulation of triglycerides. As a result, hepatocytes develop steatosis accompanied by mitochondrial dysfunction, oxidative stress, and activation of inflammatory signaling pathways, thereby creating a biological environment conducive to fibrogenesis. For this reason, insulin resistance is increasingly regarded not merely as an endocrine abnormality but also as a structural and progressive biomarker of chronic liver disease.

The association between insulin resistance and chronic HCV infection represents one of the most extensively studied areas in this field. Clinical gastroenterology studies have reported that varying degrees of insulin resistance can be detected in approximately 30–70% of patients with chronic HCV infection. In a classical study conducted by Hui and colleagues involving 260 HCV-infected patients, it was demonstrated that HCV infection may independently promote insulin resistance regardless of the severity of liver disease and that this condition is associated with the progression of hepatic fibrosis. Subsequently, a meta-analysis conducted by Patel and colleagues, which included 14 studies and a total of 3,659 patients, revealed that the presence of insulin resistance in individuals with HCV infection significantly increases the risk of advanced hepatic fibrosis, with a pooled relative risk of 1.63. The association was particularly pronounced in patients infected with HCV genotype 1. These findings suggest that insulin resistance is not merely a comorbid condition in HCV-related liver disease but may represent an active pathogenic factor accelerating fibrogenesis.

The pathogenetic relationship between HCV infection and insulin resistance can be explained through several molecular mechanisms. HCV proteins are capable of interfering with key components of the insulin signaling pathway, particularly insulin receptor substrates and downstream signaling cascades. In addition, they may enhance the secretion of pro-inflammatory cytokines and increase oxidative stress. Furthermore, HCV-associated steatosis, especially in certain genotypes, forms a bidirectional pathogenic cycle with impaired insulin signaling: the virus exacerbates insulin resistance, while insulin resistance further aggravates steatosis and fibrosis. For this reason, HCV infection has long been discussed in the scientific literature as a potential “metabolic virus.”

Aim of the Study

The aim of this study was to analyze the role of insulin resistance in the pathogenesis of chronic hepatitis based on contemporary scientific literature and to evaluate the mechanisms through which this metabolic disturbance contributes to the development of hepatic fibrosis.

Materials and Methods

The present study was conducted using the method of a scientific literature review. During the research process, scientific articles published in international scientific databases were analyzed. The primary sources included publications indexed in PubMed, Scopus, Web of Science, and ScienceDirect, as well as studies published in leading hepatology journals. For the analysis, clinical studies, systematic reviews, and meta-analyses published between 2015 and 2024 were selected. Priority was given to scientific publications specifically investigating the association between insulin resistance and chronic hepatitis. The obtained data were summarized using analytical and comparative approaches.

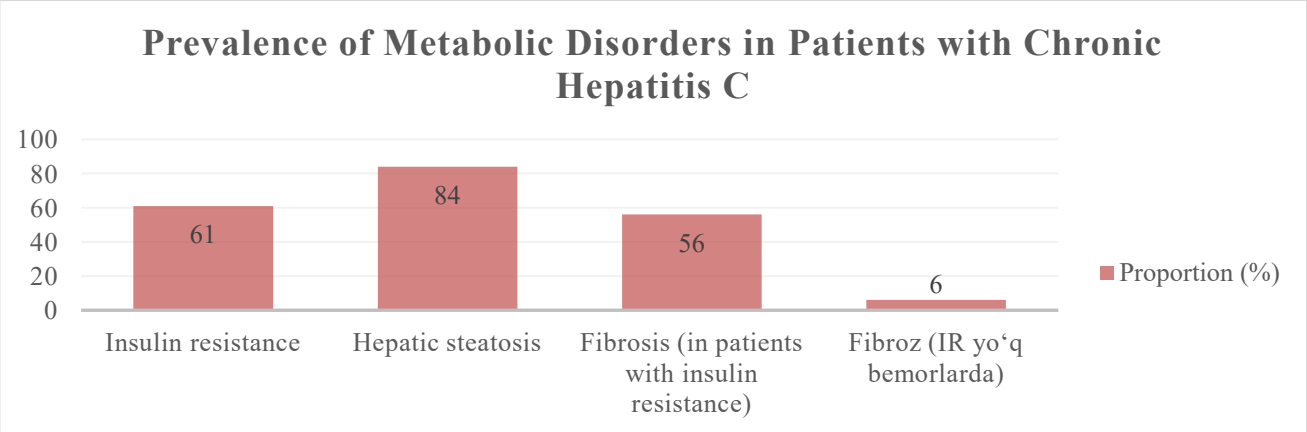
Results

Numerous clinical studies have reported the presence of metabolic disturbances in patients with chronic hepatitis. Among these disturbances, insulin resistance is increasingly considered an important pathogenetic factor contributing to the progression of liver diseases. Epidemiological studies indicate that insulin resistance is detected in a substantial proportion of patients with chronic hepatitis. According to clinical gastroenterology studies, insulin resistance is observed in approximately 30–70% of patients with chronic hepatitis C, which is significantly higher than in the general population.

Metabolic alterations associated with hepatitis C virus infection are closely related to hepatic steatosis, fibrosis, and disturbances in glucose metabolism. Several clinical investigations have demonstrated that viral infection itself can interfere with insulin signaling pathways, thereby reducing peripheral glucose utilization. As a consequence, insulin resistance becomes more pronounced, which subsequently activates fibrogenic processes within hepatic tissue.

Association between insulin resistance and hepatic fibrosis. Clinical evidence suggests that hepatic fibrosis progresses more rapidly in patients with insulin resistance. In a systematic review and meta-analysis conducted by Patel and colleagues, data from 3,659 patients with chronic hepatitis C were analyzed. The results demonstrated that the risk of developing hepatic fibrosis was significantly higher among patients with insulin resistance, and the association was found to be statistically significant.

Prevalence of insulin resistance among patients with chronic hepatitis C. In one clinical study, 44 patients with untreated chronic hepatitis C were examined. According to the results, insulin resistance was detected in 61% of patients, while hepatic steatosis was observed in 84%. Furthermore, hepatic fibrosis was identified in 56% of patients with insulin resistance, compared to only 6% among those without insulin resistance. These findings indicate that metabolic disturbances play a significant role in the development and progression of hepatic fibrosis.



The results demonstrate a strong clinical association between insulin resistance and hepatic fibrosis.
Insulin resistance and the development of steatosis. Hepatic steatosis is also frequently observed in patients with chronic hepatitis. Insulin resistance increases the release of free fatty acids from adipocytes. These fatty acids accumulate in hepatocytes and are converted into triglycerides, leading to the formation of hepatic steatosis.
Metabolic dysfunction–associated fatty liver disease is currently the most prevalent liver disorder worldwide, affecting approximately 25–38% of the global population. Insulin resistance is considered one of the central mechanisms in the pathogenesis of this disease.
Insulin resistance and metabolic diseases. Epidemiological studies also indicate an association between chronic hepatitis infection and the development of type 2 diabetes mellitus. Several investigations have reported that hepatitis C virus infection may increase the risk of developing type 2 diabetes. In this process, viral infection together with metabolic inflammation disrupts insulin signaling pathways, resulting in impaired glucose metabolism.
Furthermore, elevated glucose levels have been associated with more rapid progression of hepatic fibrosis. These findings suggest that insulin resistance and other components of metabolic syndrome may contribute to a more severe course of chronic liver diseases.

Discussion

The analysis of the obtained results indicates that insulin resistance in the pathogenesis of chronic hepatitis should not be regarded as a secondary, incidental, or merely comorbid condition. Rather, it represents an important pathogenetic link that accelerates both the clinical and morphological progression of the disease. Chronic viral hepatitis continues to impose a significant global burden: in 2022, approximately 304 million people worldwide were living with hepatitis B and C, and deaths associated with these infections reached 1.3 million in the same year. These figures demonstrate that chronic hepatitis should be interpreted not only as an infectious process but also as a complex pathological condition in which metabolic, inflammatory, and fibrotic mechanisms intersect.
The findings presented in the literature review, particularly those related to HCV infection, confirm the close association between insulin resistance and the severity of liver damage. In the meta-analysis conducted by Patel and colleagues, a statistically significant association was identified between insulin resistance and advanced hepatic fibrosis. Importantly, insulin resistance does not merely coexist with fibrosis; rather, it creates a biological environment that promotes fibrogenesis. Consequently, metabolic indicators such as HOMA-IR may reflect not only endocrine risk but also the hepatic prognosis in patients with chronic hepatitis.
One of the most notable observations from the results is the formation of a “pathological triad” consisting of insulin resistance, steatosis, and fibrosis. In chronic hepatitis, impairment of insulin signaling enhances de novo lipogenesis in hepatocytes, reduces fatty acid oxidation, and increases triglyceride accumulation. Therefore, hepatic steatosis should be considered not merely a morphological finding but also the starting point for subsequent oxidative stress and lipotoxicity. According to the review by Kukla and colleagues, HCV exerts both direct and indirect effects on intracellular insulin signaling pathways, leading to a mutually reinforcing cycle between insulin resistance and steatosis. Under such conditions, the acceleration of hepatic fibrosis becomes a predictable consequence.

From this perspective, insulin resistance participates in the pathogenesis of chronic hepatitis at two principal levels. The first is the metabolic level, where disturbances in glucose and lipid metabolism lead to lipid accumulation in hepatocytes and increased mitochondrial stress. The second is the immuno-inflammatory level, characterized by activation of pro-inflammatory mediators such as TNF-α and IL-6, increased oxidative stress, and subsequent activation of hepatic stellate cells, which results in enhanced collagen synthesis. These processes are not independent; rather, they function synergistically as a persistent driver of fibrogenesis. In scientific terms, insulin resistance serves as a mechanistic bridge linking intracellular metabolic imbalance within hepatocytes to structural remodeling at the tissue level.

This relationship is most clearly observed in the case of HCV infection. HCV has long been described in the scientific literature as a potential "metabolic virus," as it not only induces inflammation but also interferes with insulin signaling pathways. As a result, insulin resistance occurs more frequently in patients with HCV infection than in the general population and is associated with the progression of hepatic fibrosis. Thus, in chronic hepatitis C, insulin resistance is not merely a reflection of general metabolic disturbances associated with obesity or diabetes but often represents a direct component of the virus-related pathogenic process. Clinically, this observation is highly relevant: even when transaminase levels or viral load appear relatively moderate, a high metabolic risk may still lead to active and accelerated fibrosis progression.

Data concerning hepatitis B virus infection are less consistent than those for HCV, yet they do not exclude the involvement of metabolic mechanisms. Experimental studies have demonstrated that the HBV X protein can reduce the expression of insulin receptor substrate-1 (IRS-1), an important component of the insulin signaling pathway, while increasing the expression of suppressor of cytokine signaling-3 (SOCS3), thereby weakening insulin signaling within hepatocytes. These findings suggest that although insulin resistance may not be uniformly expressed in all patients with HBV infection, the virus itself has the potential to interfere with metabolic signaling pathways. Therefore, considering metabolic screening as a secondary issue in patients with chronic hepatitis B would be inappropriate. Virological control is essential, but without metabolic control it cannot constitute a comprehensive management strategy.

Conclusion

The findings of this literature review indicate that insulin resistance represents one of the key metabolic components involved in the pathogenesis of chronic hepatitis. It not only aggravates disturbances in carbohydrate and lipid metabolism but also promotes inflammatory processes, hepatic steatosis, and fibrosis within liver tissue.

1. The reviewed scientific evidence confirms a close association between insulin resistance and metabolic imbalance in hepatocytes. Impairment of insulin signaling leads to increased *de novo* lipogenesis in hepatocytes, enhanced influx of free fatty acids, and accumulation of triglycerides. As a result, hepatic steatosis develops, which subsequently creates favorable conditions for oxidative stress and cellular injury. Thus, insulin resistance can be regarded as one of the primary metabolic triggers initiating structural and functional alterations in liver tissue in the context of chronic hepatitis.

2. The analyzed data demonstrate that insulin resistance accelerates inflammatory and fibrogenic processes in chronic hepatitis. Activation of pro-inflammatory cytokines, increased oxidative stress, and stimulation of hepatic stellate cells lead to enhanced collagen synthesis and accelerated progression

of hepatic fibrosis. In particular, numerous clinical studies and meta-analyses have confirmed the association between insulin resistance and significant fibrosis in patients with chronic hepatitis C. These findings suggest that insulin resistance may act as an independent prognostic factor influencing the rate of progression of liver disease.

3. From the perspective of modern clinical practice, assessment and management of chronic hepatitis should not be limited solely to virological or biochemical indicators. Evaluation of metabolic status, particularly insulin sensitivity, is essential for determining disease prognosis, identifying high-risk patient groups, and developing individualized preventive and therapeutic strategies. Early detection and correction of insulin resistance may contribute to slowing the progression of hepatic fibrosis and reducing the risk of steatosis and other metabolic complications. Therefore, metabolic monitoring should be considered an essential component of the comprehensive management of chronic hepatitis.

A comprehensive understanding of the pathogenesis of chronic hepatitis requires viewing it as a complex pathological process in which viral, inflammatory, and metabolic mechanisms are closely interconnected. Such an integrative approach provides the most appropriate scientific basis for improving early diagnosis, accurate risk stratification, and the development of pathogenetically grounded therapeutic strategies in the future.

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