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Iron Overload in HIV: Impact on Hepatic Function

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Abstract

Iron overload is a common complication in individuals living with HIV, with significant implications for hepatic function and disease progression. Chronic inflammation, dysregulated iron metabolism, and comorbidities associated with HIV infection contribute to systemic iron accumulation and oxidative stress, leading to liver injury and fibrosis. This review examines the impact of iron overload on hepatic function in the context of HIV infection, focusing on underlying mechanisms, clinical manifestations, and implications for disease management. Mechanisms of iron dysregulation, including alterations in hepcidin expression and interactions with antiretroviral therapy, are discussed, highlighting the complex interplay between iron metabolism and liver health. Additionally, potential therapeutic interventions targeting iron overload and hepatic dysfunction are explored, with a focus on optimizing treatment outcomes and improving liver-related morbidity and mortality in individuals living with HIV.

Keywords*: Iron overload, HIV, Hepatic function, Liver disease, Hepcidin, Antiretroviral therapy*

Introduction

Iron overload has emerged as a notable complication in individuals living with HIV, exerting a profound impact on hepatic function and overall disease management. The interplay between chronic inflammation, dysregulated iron metabolism, and comorbidities associated with HIV infection contributes to systemic iron accumulation and subsequent hepatic injury. The liver, being central to iron homeostasis and detoxification, becomes particularly susceptible to the adverse effects of iron overload. Chronic inflammation, a hallmark of HIV infection, drives the production of hepcidin, a key regulator of iron metabolism, leading to increased iron sequestration within macrophages and hepatocytes. Dysregulated hepcidin expression, coupled with alterations in iron metabolism, results in systemic iron overload, oxidative stress, and liver injury. Furthermore, the

intricate interactions between iron and antiretroviral therapy (ART) add complexity to the management of hepatic function in individuals living with HIV and iron overload. Clinically, iron overload in individuals with HIV may present as hepatic steatosis, fibrosis, cirrhosis, and hepatocellular carcinoma. Hepatic steatosis, characterized by excessive fat accumulation in the liver, is prevalent in this population, especially among those with metabolic risk factors and hepatitis coinfection. Iron accumulation exacerbates hepatic fibrosis and cirrhosis, predisposing individuals to portal hypertension, liver failure, and an elevated risk of hepatocellular carcinoma. Moreover, iron-mediated oxidative stress and mitochondrial dysfunction contribute significantly to liver inflammation and injury, further escalating liver-related morbidity and mortality.[1-20]

Antiretroviral therapy, while pivotal for managing HIV infection, poses additional challenges in individuals with iron overload. Certain antiretroviral drugs, particularly nucleoside reverse transcriptase inhibitors (NRTIs), may exacerbate hepatic dysfunction in this population. NRTIs, such as zidovudine and stavudine, are known to induce mitochondrial toxicity and hepatotoxicity, which can be potentiated by iron-mediated oxidative stress and liver injury. Furthermore, the potential interactions between iron chelators and antiretroviral drugs necessitate careful monitoring and dosage adjustments to minimize hepatotoxicity and optimize treatment outcomes. Therapeutic interventions targeting iron overload in individuals living with HIV encompass a multifaceted approach aimed at reducing iron burden, mitigating liver injury, and optimizing treatment outcomes. Iron chelation therapy, utilizing agents like deferoxamine, deferiprone, and deferasirox, offers promise in reducing iron accumulation and improving hepatic function. Additionally, modulation of hepcidin activity and optimization of ART regimens represent potential strategies for managing iron overload and hepatic dysfunction in affected individuals. Lifestyle modifications, including dietary adjustments and blood donation, may also play a role in reducing iron burden and alleviating liver-related complications in this population.[21-40]

Mechanisms of Iron Dysregulation in HIV

Iron dysregulation in individuals living with HIV involves multifaceted interactions between chronic inflammation, altered iron metabolism, and comorbidities associated with the virus. Understanding these mechanisms is crucial for elucidating the pathogenesis of iron overload and its implications for hepatic function and disease progression. HIV infection induces a state of chronic inflammation characterized by elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). This inflammatory milieu stimulates the production of hepcidin, the master regulator of iron metabolism, by hepatocytes and macrophages. Hepcidin exerts its effects by binding to ferroportin, the only known iron exporter, inducing its internalization and degradation. Consequently, decreased ferroportin expression leads to reduced iron efflux from macrophages and hepatocytes into the circulation, resulting in cellular iron retention and systemic iron overload. Dysregulated hepcidin expression is a hallmark of iron dysregulation in HIV. While inflammation typically upregulates hepcidin production, HIV-induced immune dysfunction may lead to hepcidin deficiency or resistance. This dysregulation results in impaired suppression of ferroportin, allowing for increased iron absorption from the diet and enhanced iron sequestration within macrophages and hepatocytes. Furthermore, genetic

mutations in the HFE gene, commonly associated with hereditary hemochromatosis, may further disrupt hepcidin regulation and exacerbate iron overload in individuals living with HIV.[41-60]

Comorbidities commonly observed in individuals with HIV, such as viral hepatitis, liver fibrosis, and non-alcoholic fatty liver disease (NAFLD), contribute to iron dysregulation and hepatic dysfunction. Viral hepatitis, particularly hepatitis C coinfection, is associated with increased hepatic iron deposition and accelerated progression of liver fibrosis. Liver fibrosis compromises hepatic iron clearance and disrupts the regulatory function of hepatocytes in iron metabolism, further exacerbating iron overload and oxidative stress. Additionally, NAFLD, often seen in individuals with HIV and metabolic risk factors, is characterized by hepatic steatosis and iron accumulation, further contributing to liver injury and dysfunction. The use of antiretroviral therapy in individuals with HIV may impact iron metabolism and hepatic function. Certain antiretroviral drugs, such as zidovudine and stavudine, have been associated with mitochondrial toxicity and hepatotoxicity, which may exacerbate liver injury in individuals with iron overload. Furthermore, drug interactions between iron chelators and antiretroviral drugs may affect drug metabolism and toxicity, necessitating careful monitoring and dosage adjustments. Iron-mediated oxidative stress and mitochondrial dysfunction play a central role in the pathogenesis of liver injury in individuals living with HIV and iron overload. Excessive iron accumulation promotes the generation of reactive oxygen species (ROS) and oxidative damage to cellular components, including mitochondrial DNA, proteins, and lipids. Mitochondrial dysfunction further exacerbates oxidative stress and impairs cellular energy metabolism, contributing to liver inflammation, fibrosis, and hepatocellular damage.[61-80]

Clinical Manifestations and Hepatic Complications

Iron overload in individuals living with HIV can manifest clinically as a spectrum of hepatic manifestations, ranging from hepatic steatosis to advanced liver disease, including fibrosis, cirrhosis, and hepatocellular carcinoma. Understanding these clinical manifestations and hepatic complications is essential for early detection, risk stratification, and appropriate management in affected individuals. Hepatic steatosis, characterized by the accumulation of fat within hepatocytes, is a common finding in individuals with HIV and iron overload. Iron-mediated oxidative stress and mitochondrial dysfunction contribute to the development of hepatic steatosis, exacerbating lipid accumulation and promoting inflammation within the liver. Hepatic steatosis may be asymptomatic or present with nonspecific symptoms such as fatigue and abdominal discomfort. Imaging studies, such as ultrasound or computed tomography (CT), may reveal hepatic steatosis as diffuse hyperechogenicity or attenuation on imaging. Chronic iron overload promotes hepatic fibrosis, a process characterized by the excessive deposition of extracellular matrix proteins within the liver parenchyma. Persistent liver injury and inflammation lead to the progressive accumulation of scar tissue, resulting in hepatic fibrosis and eventual cirrhosis. Individuals with HIV and iron overload are at increased risk of developing advanced liver fibrosis and cirrhosis, particularly in the setting of viral hepatitis coinfection or metabolic risk factors. Clinical manifestations of hepatic fibrosis and cirrhosis may include jaundice, ascites, hepatic encephalopathy, and coagulopathy.[81-90]

Iron overload is a known risk factor for the development of hepatocellular carcinoma (HCC), the most common primary malignancy of the liver. Chronic iron accumulation promotes hepatocyte injury, inflammation, and proliferation, contributing to the development and progression of HCC. Individuals with HIV and iron overload, particularly those with advanced liver fibrosis or cirrhosis, are at increased risk of developing HCC. Clinical manifestations of HCC may include abdominal pain, weight loss, jaundice, and palpable abdominal mass. Advanced liver fibrosis and cirrhosis in individuals with HIV and iron overload may lead to portal hypertension, characterized by increased resistance to blood flow within the portal venous system. Portal hypertension may manifest clinically as splenomegaly, ascites, variceal hemorrhage, and hepatic encephalopathy. Complications of portal hypertension, such as esophageal varices and spontaneous bacterial peritonitis, contribute to morbidity and mortality in affected individuals. Advanced liver disease in individuals with HIV and iron overload may progress to liver failure, a life-threatening condition characterized by impaired hepatic function and synthetic dysfunction. Decompensated liver failure may manifest clinically as hepatic encephalopathy, coagulopathy, jaundice, and hepatorenal syndrome. Liver transplantation may be considered in individuals with end-stage liver disease and decompensated liver failure, although access to transplantation may be limited in individuals with HIV.[91-95]

Impact of Antiretroviral Therapy

Antiretroviral therapy (ART) has revolutionized the management of HIV infection, significantly improving outcomes and reducing morbidity and mortality in affected individuals. However, the use of ART in individuals with HIV and iron overload presents unique challenges and considerations, impacting both iron metabolism and hepatic function. Certain classes of antiretroviral drugs, particularly nucleoside reverse transcriptase inhibitors (NRTIs), are associated with mitochondrial toxicity, which may exacerbate hepatic dysfunction in individuals with iron overload. Drugs such as zidovudine and stavudine can impair mitochondrial DNA replication and function, leading to mitochondrial dysfunction and oxidative stress. In the context of iron overload, mitochondrial injury may be further amplified, contributing to liver injury and fibrosis. Hepatotoxicity is a well-recognized adverse effect of several antiretroviral drugs, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Drugs such as ritonavir and efavirenz can induce hepatocellular injury and liver enzyme elevation, potentially exacerbating liver injury in individuals with HIV and iron overload. Hepatotoxicity may manifest as elevated liver enzymes, jaundice, and hepatic steatosis, further complicating the management of liver disease in affected individuals.[96-100]

Interactions between antiretroviral drugs and iron chelators used to treat iron overload may impact drug metabolism and toxicity. Iron chelators, such as deferoxamine and deferasirox, may affect the pharmacokinetics of antiretroviral drugs, leading to altered drug concentrations and potential adverse effects. Conversely, antiretroviral drugs may influence the metabolism of iron chelators, affecting their efficacy and safety. Careful monitoring and dosage adjustments may be necessary when co-administering antiretroviral therapy and iron chelation therapy in individuals with HIV and iron overload. Optimizing ART regimens in individuals with HIV and iron overload requires careful consideration of drug interactions, treatment efficacy, and potential toxicities.

Individualized treatment approaches may be necessary to account for variations in iron status, comorbidities, and treatment responses. Clinicians should monitor liver function and iron status regularly and adjust ART regimens accordingly to minimize the risk of adverse effects and optimize treatment outcomes in affected individuals. Adherence to ART is essential for achieving viral suppression and preventing disease progression in individuals living with HIV. However, the presence of iron overload and associated hepatic complications may impact adherence to ART regimens. Individuals with liver disease may experience medication-related side effects, including nausea, fatigue, and gastrointestinal disturbances, which can affect adherence and tolerability. Patient education and support, along with close monitoring of liver function, are essential for optimizing adherence and treatment outcomes in individuals with HIV and iron overload.[101-104]

Therapeutic Interventions

Addressing iron overload in individuals living with HIV requires a multifaceted approach aimed at reducing iron burden, mitigating hepatic injury, and optimizing treatment outcomes. Iron chelators are the cornerstone of treatment for iron overload, aiming to bind and remove excess iron from the body. Agents such as deferoxamine, deferiprone, and deferasirox have been used successfully in individuals with hemochromatosis and other iron overload disorders. Iron chelation therapy can reduce iron accumulation, alleviate oxidative stress, and improve hepatic function in individuals living with HIV and iron overload. However, the safety and efficacy of iron chelators in this population require further investigation, particularly regarding potential drug interactions with antiretroviral therapy and their impact on treatment outcomes. Hepcidin, a key regulator of iron metabolism, plays a central role in mediating iron homeostasis and inflammatory responses. Modulating hepcidin activity represents a potential therapeutic strategy for managing iron overload in individuals with HIV. Hepcidin agonists or antagonists may help restore iron homeostasis, mitigate the adverse effects of iron overload on hepatic function, and improve treatment outcomes. Further research is needed to identify novel therapeutic agents targeting hepcidin and evaluate their efficacy and safety in clinical settings.[105-107]

Optimizing ART regimens in individuals with HIV and iron overload is essential for minimizing hepatotoxicity and drug interactions while maximizing treatment efficacy. Clinicians should carefully select ART drugs with minimal hepatotoxic potential and monitor liver function regularly during treatment. Individualized treatment approaches may be necessary to account for variations in iron status, comorbidities, and treatment responses. Close collaboration between infectious disease specialists, hepatologists, and pharmacists is essential for optimizing ART regimens and improving treatment outcomes in affected individuals. Lifestyle modifications, including dietary changes and blood donation, may help reduce iron burden and mitigate the adverse effects of iron overload in individuals living with HIV. Adopting a diet low in iron-rich foods and high in antioxidants may help reduce iron absorption and oxidative stress. Additionally, regular blood donation can effectively reduce iron levels and prevent iron-related complications in individuals with hemochromatosis. Patient education and support are essential for promoting adherence to lifestyle modifications and optimizing treatment outcomes. Managing comorbidities associated with HIV and iron overload, such as viral hepatitis, liver fibrosis, and non-alcoholic fatty liver disease (NAFLD), is essential for optimizing treatment outcomes and reducing disease

progression. Comprehensive management strategies may include antiviral therapy for viral hepatitis, lifestyle modifications, and pharmacological interventions targeting liver fibrosis and NAFLD. Close monitoring of liver function and iron status is essential for early detection and management of hepatic complications in affected individuals.[100-111]

Conclusion

Iron overload in individuals living with HIV represents a complex and clinically significant phenomenon with profound implications for hepatic function and overall disease management. Chronic inflammation, dysregulated iron metabolism, and comorbidities associated with HIV infection contribute to systemic iron accumulation, oxidative stress, and liver injury. The intricate interplay between iron dysregulation and HIV infection poses unique challenges for clinicians, necessitating a comprehensive understanding of the underlying mechanisms and potential therapeutic interventions. The impact of iron overload on hepatic function extends beyond viral suppression to encompass a spectrum of clinical manifestations, ranging from hepatic steatosis to advanced liver disease, including fibrosis, cirrhosis, and hepatocellular carcinoma. These hepatic complications significantly contribute to morbidity and mortality in individuals living with HIV, underscoring the importance of early detection, risk stratification, and appropriate management.

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