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Chronic liver diseases and iron: a concise review with emphasis on hypotransferrinemia and hypohepcidinemia

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Abstract: Iron studies in chronic liver diseases (CLDs) have a long history. Currently we can mention certainties, uncertainties, and hopes related to this topic. It is certain that iron metabolism problems and hepatic siderosis are frequent in CLDs and they get more frequent as CLD progresses, but true iron overload is rare. There are conflicting literature data on the mechanism of siderosis, the role of iron in CLD pathogenesis, and the potential benefits of iron removal. We may hope that pharmacological approaches targeting iron metabolism disorders of CLD will be actively evaluated in the future. In this review, we aimed to present a general outlook of this extensively studied topic.

Key words: Iron, chronic liver disease, siderosis, hepcidin, transferrin

1. Introduction

There are extensive literature data on iron in chronic liver diseases (CLDs). In this review, we intended to summarize current information on hepatic siderosis and changes of iron metabolism seen in CLDs. We aimed to present a general perspective of this wide topic. Although this work is not a systematic review, we undertook a detailed literature review and integrated published research evidence to get answers for some relevant questions. Our literature review was conducted in March 2015 using the PubMed search engine. The following Boolean phrase was searched: "(cirrhosis or hepatitis) and iron". References of the retrieved papers were also considered.

2. The link between liver and iron

The liver is an important organ in iron homeostasis. In addition to its involvement in iron storage, which means the presence of a large quantity of the iron storage protein ferritin within the liver, this organ also produces plasma iron carrier protein transferrin (TF) and the iron-regulatory hormone hepcidin (1,2). Another aspect of the relationship between iron and the liver is that this organ is the first one affected in iron overload disorders (3). Additionally, hepatic siderosis is frequently observed in CLDs.

3. Hepatic siderosis: is it always pathological?

The histological finding of hepatic stainable iron is frequently not associated with systemic overload or even liver iron overload. In fact, minimal hepatic siderosis in otherwise healthy persons is possible, the significance of which is not known (4–6). Some of these cases may have at least some components of the metabolic syndrome, but higher grades of hepatic siderosis are commonly associated with systemic iron overload disorders and CLDs.

4. Hepatic siderosis in CLDs: historical point of view

The frequent appearance of hepatic siderosis/iron overload in nonhemochromatosis CLDs, which increases as liver disease progresses, was first noticed at least 60–70 years ago (7–10). This condition was observed to be most prominent in alcoholic CLD (11). Increased iron absorption (12,13), increased hepatocyte cellular affinity for iron due to liver damage (14), and saturation of total iron-binding capacity (15) were suggested as the possible mechanisms at that time. During succeeding decades the first hypothesis and related issues were worked and discussed actively, but it seems that the issue of saturation of total iron binding capacity has been overlooked.

Studies on iron in liver diseases generally focused on the effect of iron on the progression of liver damage and treatment response in chronic hepatitis C (CHC) during the last decades. Hepcidin studies are another hot topic about hepatic iron overload. After the discovery of this hormone in 2000 (16,17), many studies were published on the status and effect of hepcidin production in CLDs.

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5. Hepatic siderosis in CLDs: hypotheses on the mechanism and its impact on CLD pathogenesis

5.1. Suggested mechanisms for the hepatic siderosis and objections

Although some theories were suggested, as explained above, hepatic siderosis of CLDs has been generally considered to have uncertain pathogenesis (18), but recent papers generally blamed decreased hepcidin production (19–22) and hepatic parenchymal oxidative stress secondary to inciting factors (21). Although there are also some contrary reports (23–27) it has been generally found that serum (pro)hepcidin level and m-RNA expression in the liver are decreased (or lower than expected considering iron load) in CHC (20,28–39), alcoholic liver disease (40–44), and chronic hepatitis B (CHB) (24,36,45). The decreased hepcidin in CLDs has been considered to be due to the parenchymal injury. However, there are conflicting study results regarding the association of the hepcidin level with liver parenchymal health (i.e. inflammatory activity and fibrosis/cirrhosis) (20,24,26,28,31,33,34,36,44,46). These conflicting results in both CHC and CHB may stem from the method of expressing hepcidin level and/or studying patients in different stages of CLD. It has been shown that hepcidin in relation to iron load (hepcidin:ferritin ratio) was reduced with increasing fibrosis in CLD and this ratio might have diagnostic implications as a marker of cirrhosis (36). Alcohol and the hepatitis C virus also may directly suppress hepcidin production independent from liver parenchymal failure (40–43,47). This may be another reason for the absence of a correlation between liver fibrosis and hepcidin level in some studies.

Decreased hepcidin is thought to lead to increased iron absorption and hepatic deposition. However, although a correlation between hepatic siderosis and hepcidin level has been consistently reported (20,26,31,33,36), the direction of this correlation, i.e. negative (36) or positive (20,26,31,33), was not consistent between studies.

In addition to the above-mentioned conflicting reports on hepcidin production and its correlations with liver parenchymal health and siderosis, the following subjects also raise suspicion about a primarily hepcidin-dependent mechanism in CLD-related hepatic siderosis: normal serum iron level and cellular distribution of hepatic siderosis in CLDs are not compatible with a hepcidin-dependent mechanism. Hereditary hemochromatoses (HHs) types I–III, including HFE-associated HH (type I HH), are associated with inadequately decreased production of hepcidin. In consequence, the decreasing inhibitory effect of hepcidin on duodenal iron absorption leads to clinical iron overload. In this disease, hepcidin is not produced adequately in spite of iron overload due to a defect in the body's iron-sensing mechanism (48). Serum iron level is almost always elevated in HFE-associated iron overload. As the iron overload is related to increased intestinal absorption, iron comes to the liver through the portal vein and typically there is a decreasing gradient of iron staining from periportal to centrilobular areas until late stages (49,50). The hepatic siderosis of CLD does not fit this example. Serum iron level is frequently not increased and cellular distribution of hepatic iron staining pattern is mixed, indicating a complex mechanism (including release of iron from damaged hepatocytes) instead of a hepcidin-related mechanism (49,51).

The hepatic siderosis observed in nonhemochromatosis CLDs is frequently not associated with systemic or even hepatic iron overload. Systemic iron load is very low even in alcohol-related cirrhosis with prominent hepatic siderosis compared to hemochromatosis (11,52–55). Appearance of hepatic siderosis in spite of low iron load in CLDs suggests that the mechanism of siderosis is not an increased iron entrance into the body, but improper management of iron and/or the tendency of the diseased liver to accumulate iron.

5.2. Impact of siderosis in CLD pathogenesis and objections

Iron-related tissue damage has long been known (56). Animal experiments and studies in hereditary and secondary iron overload states proved that increased hepatocellular iron load may cause lytic necrosis of the hepatocytes and mild chronic inflammation (57–61). These necroinflammatory changes may progress to fibrosis and cirrhosis. Removal of excess iron before the cirrhotic stage may result in regression of the fibrosis (62–65). What about nonhemochromatosis CLDs? Many studies (66–80) concluded that hepatic siderosis is associated with worse necroinflammatory activity, and excessive iron in CHC is probably a cofactor supporting the progression of liver parenchymal damage and increasing fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Many researchers have also found that hepatic iron accumulation has a negative correlation with response to antiviral therapy (74,81–99). Iron elimination by phlebotomy improves elevated serum aminotransferase levels (83,84,100–117), histopathology (100,118–122), and enhanced lipid peroxidation (123); increases the probability of response to antiviral treatment (84,106,114,118,120,124,125); and decreases HCC risk in CHC patients (119,126,127).

Hepatic iron also enhances liver lesions caused by alcohol (128). Alcohol catabolism in the liver by cytochrome p450, subfamily IIE (CYP2E1), results in generation of reactive oxygen species, such as hydrogen peroxide (H_2O_2) (129). H_2O_2 is poorly reactive in the absence of transition metal ions, such as iron. Iron catalyzes the Fenton reaction, which leads to conversion of H_2O_2 to hydroxyl radical. Hydroxyl radical, which is indiscriminately reactive, causes tissue injury and fibrosis (129,130).

Hepatic siderosis is also common in CHB, including noncirrhotic patients (131,132). Liver iron deposits in CHB are associated with higher necroinflammatory activity and fibrosis, too. Therefore, it has been suggested that excess iron might be a factor contributing to the aggressive disease course also for CHB (131,132).

Histological evaluation of the liver in insulin resistance-associated iron overload showed a good correlation between fibrosis and iron accumulation, too (5,133).

In addition to fibrosis and cirrhosis, hepatic iron overload in CLD is also associated with porphyria cutanea tarda (134) and HCC (22,135–137).

Some objections can also be proposed against the above-mentioned considerations related to the role of siderosis in the pathogenesis of CLD: iron overload has a benign course in primary hemochromatosis (138). Practically there is no cirrhosis risk if the serum ferritin level is below 1000 mg/L (139). Thus, the siderosis of CLD, which is generally not associated even with hepatic iron overload, should be just a contributing factor if it is not only a consequence of the disease. There are conflicting reports related to the effect of hepatic siderosis on the course of CHC. Although many studies have suggested that excessive iron is a cofactor promoting progression of liver damage and increasing the risks of fibrosis, cirrhosis, and HCC, as summarized above, some contrary reports have also been published (54,140–155). D'Souza et al. (142) reported that hepatic siderosis, which is quite common in CHC, had no effect on disease progression. Consequently, it should be a result instead of a reason in the disease pathogenesis. Thorburn et al. (143) concluded that neither the concentration of liver iron nor associated hereditary hemochromatosis had significant roles in the progression of HCV-related liver injury. Sajjad et al. (156) could not observe a correlation between hepatic iron and fibrosis.

Although many studies (including 4 randomized controlled studies and one metaanalysis) have indicated an enhanced response to antiviral treatment with phlebotomies in CHC as mentioned before (84,114,118,120,124,125,157), contrary reports (including 3 randomized controlled studies) are also frequent (100,103,106–108,158–163). The effect of iron removal on CHB has been rarely investigated. Bayraktar et al. (164) reported better biochemical, histological, and serological response in CHB cases treated with interferon plus iron chelator deferoxamine compared to a group receiving only interferon.

6. Hypotransferrinemia as a cause of hepatic siderosis in CLDs

Nonhemochromatosis cirrhosis, especially in advanced stages, is known to frequently cause a hemochromatosis-like phenotype both histologically and also in serum iron tests (i.e. increased transferrin saturation and ferritin) (10,165–169). An autopsy study showed that the iron overload of advanced cirrhosis might even cause cardiac and pancreatic siderosis in some cases (170). The iron overload phenotype of advanced cirrhosis is closely associated with hypotransferrinemia (166). In these cases the main reason for the increased TF saturation is not an elevated serum iron level, but rather the diminished serum TF (i.e. total iron-binding capacity) level. It was shown that as hepatic parenchymal failure progresses, serum total iron binding capacity (i.e. TF activity) decreases (166,171–175) and consequently TS increases. Increased TS was found to be a good predictor of the status of hepatic iron deposits (and fibrosis) in CHC (34,71,176,177). As there is a correlation between iron accumulation and fibrosis (66,67,70,178–184), which is the hallmark of hepatic cirrhosis, it can be concluded that hepatic siderosis might be both a contributing factor for and an indirect consequence of hepatic parenchymal fibrosis (due to decreased synthesis capacity) (166).

7. More on atransferrinemia/hypotransferrinemia, and nontransferrin-bound iron

Congenital atransferrinemia (hypotransferrinemia) (OMIM 209300) is a very rare recessive disorder caused by mutation in the TF gene on chromosome 3q22.1 (185,186). Only 11 cases had been described by 2007 (187). Serum TF level is severely depressed, approximately 1/10 to 1/20 of normal. It is characterized by microcytic anemia and iron overload. The first known case was described by Heilmeyer et al. in 1961 (188). Death occurred from heart failure in this case. Severe hemosiderosis of the heart and liver was found at autopsy.

Besides TF iron, which is the normal form of circulating iron, nontransferrin-bound iron (NTBI) has been identified in the plasma of patients with various diseases in which TF saturation is significantly increased (189). When the carrying capacity of TF is exceeded (due to increased serum iron and/or decreased TF), NTBI appears in the plasma. In hypotransferrinemic mice, the liver and pancreas rapidly cleared absorbed or injected NTBI, suggesting the existence of NTBI uptake system(s) (190). We could not find any published study on NTBI in CLDs or cirrhosis. The lowered serum TF level and the consequent increased TF saturation in cirrhosis may result in the appearance of plasma NTBI, which is avidly taken up by the hepatocytes.

8. Treatments directed toward hepatic siderosis: could TF or hepcidin be treatment agents?

There are experiences indicating the potential benefit of iron removal in CLDs. As stated above, nearly all related studies have concluded that phlebotomy with or without iron restriction was effective in reducing serum transaminase levels in patients with CHC (83,84,100–117). Hepatic iron removal may also improve liver histopathology (100,118–122) and HCC risk (119,126,127).

Could TF and/or hepcidin be used as treatment agents for the hepatic siderosis in CLD/cirrhosis? Human and murine atransferrinemia/hypotransferrinemia cases showed us that TF can be replaced by plasma infusions or by using the purified molecule. TF has a plasma half-life of 8–10 days, which makes the replacement relatively easier (191). Whether TF or hepcidin replacements could be useful in CLD/cirrhosis is an exciting question, but hepcidin has a relatively short half-life, and with present technologies, it is very expensive to produce it at the doses required. Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice. They have been shown to prevent iron overload in a hepcidin-deficient mouse model of severe hemochromatosis (192,193).

9. What further studies related to iron in CLD are needed with priority?

1. NTBI in CLD and its association with hepatic siderosis and serum iron tests would be an interesting study topic. A correlation between NTBI and hepatic siderosis proves that the excess liver iron comes from the blood. 2. If NTBI is elevated in CLD, how does transferrin replacement by plasma infusions (or probably minihepcidins in future) change serum iron tests and NTBI level? The findings may provide clues regarding potential roles of transferrin and hepcidin analogs in the treatment of hepatic siderosis.

In conclusion, although the topic of CLDs and iron has been extensively studied, the studies have been repetitively focused on a relatively narrow scope of this wide subject. There is a high level of conflicts in some issues. There are enough data to accept that iron metabolism problems and hepatic siderosis get more frequent/severe as CLD progresses. The mechanism of hepatic siderosis in CLD, the role of iron in the disease pathogenesis, and potential benefits of its removal are contradictory issues. There have been ongoing efforts to develop drugs that mimic hepcidin activity. In the future, such agents targeting iron metabolism defects should also be evaluated in hepatic siderosis related to CLDs.

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