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Iron Overload in Patients With Chronic Liver Disease

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G&H How common is iron overload in patients with chronic liver disease?

KK Some degree of iron overload is present in anywhere from 10% to 30% of patients with chronic liver disease. We previously published a paper showing that increased iron was present in the liver of up to one-third of patients with nonalcoholic fatty liver disease. In certain liver diseases, such as alcoholic liver disease, increased hepatic iron is very common. Iron overload is also relatively common in chronic hepatitis C virus and has been shown to be associated with mutations in hemochromatosis genes. Increased liver iron is more common in these liver diseases than in others such as autoimmune or cholestatic liver diseases (eg, primary biliary cholangitis). In advanced liver disease, the likelihood of finding excess iron in the liver can be as high as 8%. We previously showed that 30% of patients with end-stage liver disease have elevated serum iron studies suggestive of hemochromatosis. Thus, patients with liver disease are much more likely to have iron overload, even in the absence of hemochromatosis.

G&H What are the manifestations or clinical features of iron overload in these patients?

KK As shown in a series of studies in patients with liver disease (both early- and end-stage), iron overload may result in increased infections following liver transplant. Patients who are homozygous (C282Y+/+) or compound heterozygous (C282Y/H63D) for *HFE* mutations have reduced survival following liver transplant. Iron overload may lead to increased infectious or cardiac complications after liver transplant.

Increased iron stores in the setting of end-stage liver disease can also mimic hemochromatosis, even in patients who do not have the genetic mutations.

In patients who do not have end-stage liver disease or cirrhosis but have a chronic liver disease that is compensated, increased iron in the liver could significantly accelerate the progression of fibrosis or scarring in the liver. In a paper that my colleagues and I published in *Gastroenterology*, the progression of scarring was dramatically higher in hepatitis C virus–infected patients who had extra iron in the liver compared with those who did not.

Similarly, in nonalcoholic fatty liver disease, my colleagues and I found that increased iron, particularly in macrophages, appears to activate these cells and may also activate stellate cells, which are responsible for scarring or fibrosis in the liver.

G&H Does iron play a role in the pathophysiology of liver disease, or does the disease cause iron overload?

KK Regulation of iron absorption is carefully orchestrated because, for millennia, the challenge in human nutrition has been iron deficiency more than iron overload. Thus, the body has a good mechanism for retaining iron, but not for eliminating it. The mechanism by which iron is absorbed in the gut is tightly controlled. In states of iron deficiency, iron absorption is increased. When the deficiency is resolved, iron absorption falls to reflect the positive iron balance. Iron absorption is up- and downregulated by a hormone made in the liver called hepcidin. Hepcidin is a small circulating peptide that is secreted from the liver in response to circulating iron

signals. Receptors on hepatocytes sense the amount of iron in circulation and accordingly up- or downregulate the production of hepcidin. Hepcidin binds to the basolateral transporter (ferroportin), following which ferroportin is internalized and then degraded by lysosomes. Consequently, the iron export out of the gut epithelium is reduced, leading to secondary reduction in iron import at the level of the gut on the absorptive side.

Thus, hepcidin has a negative feedback loop. Liver injury could potentially lead to a reduction in the production of hepcidin from hepatocytes or a reduction in the sensing of iron by the liver. Therefore, less hepcidin is made and more iron is absorbed. This explains how increased iron buildup could be caused in the liver secondary to liver disease.

However, iron can also accumulate in the liver because of liver injury. Once liver cells undergo necrosis, they are scavenged by macrophages in the liver. Thus, part of what might lead to excess iron in the liver could be absorption or scavenging of dying hepatocytes by Kupffer cells. Once this process occurs and these macrophages become iron-loaded, a secondary process of liver injury and more damage may be precipitated.

Therefore, in the relationship between iron overload and liver disease, it is unclear which comes first. There is no question that excess iron in the liver can occur independent of liver damage, or due to liver damage, and that iron buildup in the liver can also be secondary to more advanced liver disease.

G&H Does the presence of mutations such as *HFE* predict liver disease or more severe or rapid progression of disease?

KK Several groups have examined this issue both in the setting of hepatitis C virus and in nonalcoholic steatohepatitis (NASH). Our team found that *HFE* mutations were associated with more advanced fibrosis in both diseases as well as with increased iron. Increased iron due to *HFE* mutations (not necessarily homozygous mutations, but even just the carrier state) may be enough to lead to increased iron absorption as a consequence of reduced hepcidin production, and that could then lead to more accelerated liver damage. However, whether that is true in nonalcoholic fatty liver disease or NASH is less clear. Several studies by our team and others have shown that patients who are carriers for *HFE* mutations in NASH accumulate more iron in hepatocytes selectively. However, iron in hepatocytes may or may not be as important as iron in Kupffer cells or macrophages. We have shown in several publications that Kupffer cell iron loading, particularly in nonalcoholic fatty liver disease, is associated with significant progression of liver disease.

G&H Does iron overload increase the risk of liver cancer?

KK There is a good deal of evidence that in hemochromatosis, which is associated with very high levels of iron, liver cancer risk is significantly increased. Iron is known to directly cause DNA damage, and it may have an effect on tumor suppressor genes. In *Liver International*, Dr Cynthia Ko and colleagues reported findings from a survey of liver pathology reports that patients who had iron in the liver were much more likely to have liver cancer than patients without iron.

In addition, there are epidemiologic associations and pathophysiologic evidence that by causing direct DNA damage and by inactivating tumor suppressor genes, extra iron may lead to increased risk of cancer in the liver.

G&H How is iron overload diagnosed in liver disease patients? Is a liver biopsy required?

KK Liver biopsy is needed much less often than in the past. To determine whether a patient has increased iron, the first test should be a circulating serum test, which looks for serum iron, total iron-binding capacity, and ferritin. Patients with iron overload have increased transferrin-iron saturation, which is calculated by serum iron divided by total iron-binding capacity. Normal saturation is less than 40%, and normal ferritin levels are usually less than 300 ng/mL in men and less than 200 ng/mL in women.

An elevated ferritin level and/or transferrin-iron saturation should lead to suspicion of iron overload. However, there are several caveats. Ferritin is a marker for inflammation throughout the body. Therefore, a high ferritin level does not always mean that there is iron overload. Similarly, because transferrin-iron saturation is a ratio, if the denominator (total iron-binding capacity) is reduced, the saturation may be falsely elevated, suggesting iron overload when there is not any.

Historically, a liver biopsy was also required to determine the presence of increased iron in the liver. Now there are several alternative tests that use magnetic resonance imaging (MRI) technology. Doctors can perform a MRI T2* or a FerriScan (Resonance Health), which uses the paramagnetic properties of iron in the liver. With a MRI, doctors can quantify relaxation time (by looking at this measure after a radiofrequency pulse) and plot it out against expected relaxation time to identify the presence of increased iron.

When there is concern regarding the presence of cirrhosis in addition to iron overload, a liver biopsy is often performed. This procedure remains important to assess the amount of liver damage for many patients. However,

information can still often be obtained without a biopsy because in addition to measuring iron via MRI, the amount of scarring or stiffness of the liver can be determined via MR elastography. Using the T2* technique, doctors can obtain information about liver stiffness as well as liver iron and fat. This noninvasive technology can be used as a first-line test in patients with suspected iron overload.

G&H Should all liver disease patients be evaluated periodically for iron overload?

KK In any patient with a known diagnosis of liver disease, iron testing, namely for transferrin-iron saturation and ferritin, must be routinely performed to screen for iron overload. Even in a patient with a specific known cause of liver disease such as hepatitis C or B, nonalcoholic fatty liver disease, alcoholic liver disease, or end-stage liver disease, it is important to include iron testing as part of the standard evaluation. Hemochromatosis is one of the most common genetic conditions. One in 250 whites is homozygous, and in certain populations of Northern European descent, the carrier rate may be as high as 10%. Because nonalcoholic fatty liver disease, hepatitis C virus, and alcoholic liver disease are all quite common, iron as a cofactor or cause of liver disease should always be considered.

G&H How should iron overload be treated in patients with liver disease?

KK If a patient has hereditary hemochromatosis with mutations in the *HFE* gene or if he or she has iron overload that is significant in the absence of hemochromatosis genes, there is general agreement that the patient should undergo phlebotomy. However, it is unclear what defines significant iron overload. If a patient has *HFE* hemochromatosis and is homozygous for the C282Y mutation or compound heterozygous for C282Y and H63D, any elevation of ferritin should raise consideration of phlebotomy. Certainly if the patient's ferritin level is greater than 500 ng/mL or if the patient has elevated liver enzymes or symptoms, phlebotomy should be initiated.

For patients who have suspected hemochromatosis who do not have *HFE* mutations, either a liver biopsy or MRI is needed to diagnose iron overload. If the liver biopsy or MRI shows that the hepatic-iron concentration is more than 2 to 2.5 times the upper limit of normal (eg, 4000 µg/g dry weight or >70 umol/g dry weight), most doctors would agree that iron depletion is needed. For patients who are not anemic and can tolerate phlebotomy, that is the easiest therapy, and it can be performed by draining blood or by bloodletting of the venous approach. Generally, phlebotomy is performed by drawing 400 to 500 cc of blood at any given time weekly or every other week until the patient has a normal ferritin level.

There is a great deal of controversy regarding whether iron overload that is moderate or mild in patients with other liver diseases, such as NASH or hepatitis C virus, should be treated with phlebotomy or iron depletion. Based on our studies and observations, my colleagues and I believe that excess iron that is more than just trivial may contribute to accelerated progression of liver disease and should be treated with iron depletion. However, some data suggest that iron depletion may not necessarily play a role in patients with a mild to moderate increase in iron stores.

In patients who are anemic in whom phlebotomy cannot be performed or in patients who tolerate phlebotomy poorly, chelating agents such as deferoxamine (also known as desferrioxamine) can be used. This agent has been used for many years to treat thalassemia. However, it is a parenteral therapy that requires an overnight infusion, and patients may experience side effects and may not tolerate it well. For several years now, there has been an alternative approach—the oral medication deferasirox. This agent has been shown in a phase 2 study to be effective for reducing iron levels in hemochromatosis.

G&H Does the presence of cirrhosis affect treatment?

KK The presence of cirrhosis might increase the urgency of treatment or may lead doctors to be more likely to treat patients who would not otherwise be treated because of the evidence that increased iron in a patient with cirrhosis might elevate the risk of cancer. Thus, to reduce the progression of the liver disease and to reduce the risk of cancer in patients who clearly have iron overload, iron depletion may be considered.

However, it should be noted that patients who have more advanced cirrhosis may have low blood pressure and may have a tendency toward anemia. Therefore, these patients may not tolerate treatment well.

G&H Does iron depletion specifically help treat liver disease in addition to iron overload?

KK In hemochromatosis, there is no question that iron depletion is effective in reducing the progression of liver disease and complications of portal hypertension. As shown in a seminal paper in the *New England Journal of Medicine*, patients who were treated with phlebotomy who had not yet developed cirrhosis had a normal life expectancy, whereas patients who were not treated had a reduced life expectancy. In addition, data from Italy have

shown that phlebotomy reduces complications of portal hypertension such as the development of varices and bleeding from varices.

However, there is controversy regarding whether phlebotomy can be helpful in a patient who has extra iron in the liver and has a liver disease such as hepatitis C virus or NASH but does not have advanced disease. Some phlebotomy studies have not shown any improvement in nonalcoholic fatty liver disease. My colleagues and I published a paper on patients infected with hepatitis C virus prior to the availability of the highly effective all-oral medications showing that iron depletion seemed to improve liver enzyme levels. There is some anecdotal evidence that iron depletion may slow progression of liver disease and may reverse liver injury; however, other studies have not shown treatment to be beneficial.

G&H Can treatment for iron overload completely reverse cirrhosis or fibrosis?

KK In hemochromatosis, there are anecdotal observations that long-term phlebotomy therapy and maintaining iron depletion has been shown to reverse cirrhosis. However, whether it actually reverses cirrhosis is difficult to determine because there are no randomized trials in which patients with cirrhosis and iron overload were phlebotomized compared with controls who were not.

G&H Are dietary adjustments or vitamin supplements helpful?

KK Vitamin supplements may be harmful in these patients. Vitamin C significantly increases the absorption of iron by making the duodenum more acidic, therefore driving iron to be absorbed more efficiently. A multivitamin with vitamin C is probably fine, but doses of more than 1 g per day, for example, generally should be avoided in patients with iron overload.

There is no evidence that supplements, nutraceuticals, or naturopathic remedies have any favorable role. Because iron is a potent pro-oxidant and leads to oxidative stress, some doctors support the use of antioxidants. However, iron depletion via phlebotomy is much more effective in removing extra iron and, thus, would still be the favored therapy.

G&H What are the next steps in research?

KK We need further information in 3 areas. One involves hemochromatosis. We know that only a small percentage of patients with hemochromatosis and the homozygous C282Y mutation manifest iron overload, and an even smaller percentage manifest end-organ damage from iron overload. It is important to determine the mechanisms that drive some patients who have the genetic mutations to develop heavy iron loading. Excess alcohol consumption is one mechanism, but there are clearly other genetic factors.

The second area involves nonalcoholic fatty liver disease and NASH and whether increased iron in the liver contributes to disease progression. This is a difficult issue to resolve because it remains unclear whether excess iron increases the risk of advanced liver disease or whether it is a consequence of more aggressive liver disease.

The third area is iron overload following liver transplantation. It is important to determine whether iron overload is associated with increased complication rates following this procedure.

Dr Kowdley has no relevant conflicts of interest to disclose.

Suggested Reading

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