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Patterns of liver iron accumulation in patients with sickle cell disease and thalassemia with iron overload

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Abstract

The rate and pattern of iron deposition and accumulation are important determinants of liver damage in chronically transfused patients. To investigate iron distribution patterns at various tissue iron concentrations, effects of chelation on hepatic iron compartmentalization, and differences between patients with sickle cell disease (SCD) and thalassemia major (TM), we prospectively investigated hepatic histologic and biochemical findings in 44 patients with iron overload (35 SCD and 9 TM). The median hepatic iron content (HIC) in patients with TM and SCD was similar at 12.9 and 10.3 mg Fe/g dry weight, respectively ($P = 0.73$), but patients with SCD had significantly less hepatic fibrosis and inflammation ($P < 0.05$), less hepatic injury, and significantly less blood exposure. Patients with SCD had predominantly sinusoidal iron deposition, but hepatocyte iron deposition was observed even at low HIC. Chelated patients had more hepatocyte and portal tract iron than non-chelated ones, but similar sinusoidal iron deposition. These data suggest that iron deposition in patients with SCD generally follows the traditional pattern of transfusional iron overload; however, parenchymal hepatocyte deposition also occurs early and chelation removes iron preferentially from the reticuloendothelium. Pathophysiological and genetic differences affecting iron deposition and accumulation in SCD and TM warrants further investigation (http://www.clinicaltrials.gov#NCT00675038).

Keywords

liver biopsy; sickle cell anemia; thalassemia; hemosiderosis; liver fibrosis

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Author contributions

Hankins performed research, analyzed and interpreted data, and wrote the manuscript. McCarville and Hillenbrand performed research and wrote the manuscript. Smeltzer performed statistical analysis and wrote the manuscript. Aygun interpreted data and wrote the manuscript. Ware performed research, interpreted data, and wrote the manuscript. Onciu performed research, performed blinded histopathologic review of all liver biopsy samples, and wrote the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Chronic red blood cell transfusions are used to treat hematologic diseases associated with ineffective erythropoiesis such as thalassemia major (TM), myelodysplasia, and Diamond–Blackfan anemia. Patients with sickle cell disease (SCD) receive erythrocyte transfusions to prevent and treat complications such as stroke, acute chest syndrome, and splenic sequestration. With the increased use of blood transfusions to prevent primary stroke, the number of children with SCD receiving chronic blood transfusion therapy has significantly increased in recent years (1–4). Repeated transfusions have therapeutic benefits in these disorders but, when used long-term, inevitably lead to iron accumulation in many organs, especially the liver.

During the process of iron accumulation in non-hereditary forms of hemochromatosis (e.g., transfusion iron overload), most liver iron is initially deposited in the hepatic reticuloendothelial system, particularly the Kupffer cells, while the hepatocyte compartment is largely spared (5). With continued transfusions, iron eventually accumulates in parenchymal cells (hepatocytes), increasing the risk of liver injury with hepatocyte damage, synthetic dysfunction, fibrosis, and eventually cirrhosis (6–11). Most of our understanding of hepatic iron deposition and compartmentalization derives from studies on thalassemia and hereditary hemochromatosis, hence iron accumulation in patients with SCD is less well understood. Iron deposition may be different in SCD than in TM or hereditary hemochromatosis, however. SCD is not primarily characterized by ineffective erythropoiesis and thus does not lead to increased intestinal iron absorption. In addition, circulating levels of hepcidin, which is the main regulator of iron homeostasis, are not as low in SCD as in patients with hereditary hemochromatosis.(12,13) Furthermore, SCD features more inflammation and higher levels of protective antioxidants than TM, which may alter the effects of iron in organs and tissues (14).

Our prospective study had the following goals: (i) to better characterize the pattern of iron distribution in the livers of chronically transfused patients with SCD at various tissue iron concentrations, (ii) to describe the effects of iron chelation on liver iron compartmentalization, and (iii) to contrast the findings in patients with SCD to those with TM. We analyzed liver biopsy material obtained from patients with iron overload who participated in a prospective study comparing quantitative liver biopsy to non-invasive liver iron quantitation using the R2*MRI technique (http://www.clinicaltrials.gov#NCT00675038) (15).

Methods

Patient selection and data collection

This study was approved by the St. Jude Children's Research Hospital institutional review board. Eligibility criteria have been previously reported (15). In brief, patients were eligible if they were ≥7 yr old and had serum ferritin > 1000 ng/mL within 3 months of enrollment or receipt of ≥18 lifetime erythrocyte transfusions. The transfusion and chelation histories before study enrollment were ascertained by review of the medical records. Of note, in four patients who qualified for the study based on serum ferritin levels, the total number of transfusions was not available and may have been underestimated. Study participants underwent liver biopsy with quantitation of hepatic iron content (HIC), routine histologic examination, and serum ferritin evaluation within 30 d. Study participants or their legal guardians signed informed consent before any study-related activity in accordance with the Declaration of Helsinki; all children signed an assent form.

Liver biopsies

Liver biopsies were performed by an interventional radiologist using either the coaxial percutaneous (transcapsular) or the transjugular technique. In an effort to reduce bleeding during and after the procedure, the latter technique was performed only if study participants had an elevated risk of bleeding (e.g., thrombocytopenia or prolonged clotting time) (16). In addition, the biopsy tracts were embolized with microfibrillar collagen hemostat to prevent local bleeding (16). Two liver specimens at least 5 mm long were obtained: the first was placed in a metal-free vial, refrigerated, and submitted to Mayo Laboratories (Rochester, MN) for HIC quantitation using acid digestion followed by inductively coupled plasma-mass spectrometry analysis; the second was immediately placed in 10% formalin and submitted for histologic review within our institution.

Histologic analyses

All liver histology specimens were reviewed initially by local pathologists and then centrally reviewed by a single pathologist (M.O.) who was blinded to the patients' clinical status, disease severity, and HIC value. Evaluation included examination of sections stained with hematoxylin and eosin, Masson's trichrome, and Perls' iron. Scoring of iron stores was performed using the semi-quantitative Deugnier system of grading iron overload, which assesses iron deposition in the hepatocytes (hepatocytic iron score; HIS), in the Kupffer cells within sinusoidal spaces (sinusoidal iron score; SIS), and in the endothelial cells and connective tissue within the portal space (portal iron score; PIS) (9). These compartments have maximum possible scores of HIS = 36, SIS = 12, and PIS = 12. The sum of the scores from the three compartments (HIS + SIS + PIS) yields a combined overall score (total iron score; TIS) ranging from 0 (absent) to 60 (maximum iron deposition). In addition, the relative iron abundance within each liver compartment was calculated by dividing the actual score by the maximum possible score for that particular compartment, yielding a calculated percentage that indicates the saturation of each liver compartment. Finally, liver fibrosis was scored using a scale from zero (no fibrosis) to six (cirrhosis), and liver inflammation was classified as absent, mild, moderate, or severe (17).

Statistical analyses

Median values for liver compartment scores were compared using the Wilcoxon–Mann–Whitney test. The association between liver compartment scores and HIC or ferritin was investigated using Spearman's rank-order correlation. Clinical parameters were compared between the SCD and TM groups using the Wilcoxon–Mann– Whitney test or Fisher's exact test. The relationship between scores in each liver compartment and HIC was investigated using regression analysis. *P* values were considered significant if <0.05.

Using thresholds with clinical significance, patients were divided into three groups according to their HIC levels: low (HIC < 7 mg Fe/g dry weight), moderate (7–15 mg Fe/g dry weight), and high (> 15 mg Fe/g dry weight). HIC less than 7 mg Fe/g dry weight is the usual goal for chronically transfused patients (18), and higher HIC values (above 7 mg Fe/g dry weight) are linked to complications from iron toxicity, such as liver fibrosis and diabetes mellitus in patients with hereditary hemochromatosis (19). HIC levels above 15 mg Fe/g dry weight are associated with heart disease and early death in patients with TM (20).

Results

Patient characteristics

Forty-four participants, including 35 with SCD (34 with hemoglobin SS disease and one with hemoglobin S β°-thalassemia) and nine with TM (six with β°β° and three with hemoglobin Eβ°-thalassemia), had liver biopsy performed with iron quantitation and

histologic assessment. The clinical and histologic findings of these two groups of patients are summarized in Table 1. Patients with TM had a median age of 26 yr (range, 15.5–36.8 yr), a median of 195 months of transfusions, and typically received chelation therapy. By contrast, patients with SCD were significantly younger (median age 13 yr, $P < 0.0001$), with a shorter duration of transfusions (median 51 months), and less exposure to chelation. The most commonly used iron chelator was deferoxamine. Patients with SCD had similar HIC (median 10.3 mg Fe/g dry weight) compared to those with TM (median 12.9 mg Fe/g dry weight, $P = 0.73$), but had a higher serum ferritin value trend (Table 1).

Liver histology

There was no significant difference in the average total iron score (TIS) between patients with SCD and TM (TIS = 23 vs. 26, $P = 0.20$), and the proportion of total liver iron corresponding to iron deposited within hepatocytes (HIS) was also similar (64% vs. 69%, $P = 0.43$; Table 1). In patients with SCD with low levels of iron accumulation (HIC < 7 mg Fe/g dry weight), iron was found in all compartments but primarily within the sinusoidal spaces (Fig. 1). The SIS was almost 50% saturated at low HIC, much more than the % maximum scores for HIS and PIS. As iron levels increased, HIS was predominantly affected, increasing its % maximum score from 22% to 55% at the highest HIC values (Fig. 1). At the highest HIC (> 15 mg Fe/g dry weight), both the SIS and HIS were approximately 60% saturated, much more than PIS. In contrast, patients with TM tended to have iron preferentially deposited in hepatocytes rather than in the reticuloendothelial system; HIS was almost twice as saturated as SIS at lower iron burdens and equivalently saturated at higher HIC (data not shown). Overall, the TIS was significantly associated with HIC (correlation coefficient = 0.79, $P < 0.0001$) and serum ferritin (correlation coefficient = 0.37, $P = 0.0131$).

Hepatic fibrosis was not commonly observed in SCD (Table 1). Among patients with SCD, 28 of 35 had either none or grade 1 fibrosis; 6 had grade 2 or 3, and only 1 had grade 5 fibrosis. The median (range) fibrosis among patients with SCD with low, moderate, and high HIC levels was 1 (0–3), 1 (0–5), and 1 (0–3), respectively. Further, most patients with SCD had only mild hepatic inflammation. In contrast, moderate inflammation was more common among patients with TM (Table 1).

To evaluate the relative contribution of each liver compartment to increasing HIC values in patients with SCD, the percentage of TIS corresponding to SIS, HIS, and PIS was plotted as a function of HIC (Fig. 2). Sinusoidal iron represents approximately 50% of the TIS at the lowest HIC values and decreased with increasing iron burden, indicating that iron deposited in the sinusoids decreased proportionally as more iron was deposited in hepatocytes. At higher HIC values, approximately 70% of the TIS was because of hepatocyte iron deposition, indicating that this compartment was preferentially affected by higher iron burdens.

The iron distribution patterns within the liver were then compared between 16 patients with SCD who received iron chelation and 19 patients who never received chelation therapy. The median age of chelated and non-chelated patients was similar (13.1 and 12.7 yr, $P = 0.64$). As expected, chelated patients with SCD had longer exposure to blood transfusion (duration of transfusion 64 vs. 32 months, $P = 0.0048$); however, their HIC values were comparable (9.5 vs. 12.6 mg Fe/g of dry weight of liver, $P = 0.11$). The serum ferritin for chelated and non-chelated patients was 1696 ng/mL (578–7450 ng/mL) and 3555 ng/mL (743–5850 ng/mL), respectively. The median TIS was significantly higher among chelated in comparison with non-chelated patients (scores 26 vs. 21; $P = 0.008$), likely reflecting an incomplete chelation effect because of the relative short duration of chelation. The median SIS between chelated and non-chelated patients with SCD was similar (scores 7 vs. 6, $P = 0.11$), but

chelated patients had higher median HIS and PIS than non-chelated patients (HIS scores 18 vs. 13, $P = 0.032$, and PIS scores 2 vs. 1, $P = 0.014$).

Seven patients with SCD were splenectomized: three before starting transfusions and four after a median of 20 months of chronic transfusions. The median duration of transfusions among non-splenectomized and splenectomized patients was not significantly different (56 vs. 61 months, $P = 0.64$), nor was their median HIC (10.3 vs. 10.5 mg Fe/g dry weight, $P = 0.93$).

Discussion

As chronic transfusions are more frequently provided to patients with SCD, iron overload becomes an increasingly important problem because the degree of iron overload may be significant and lead to morbidity and organ dysfunction. Patients with SCD accumulate liver iron to the same degree as patients with TM (6), although the patterns of hepatic iron deposition seem to be different with respect to sinusoidal iron accumulation and the development of liver fibrosis and inflammation. Ghugre *et al.* (21) recently showed that patients with SCD have more sinusoidal deposition than patients with TM, and our data confirm relative sparing of the hepatocytes from iron overloading in SCD, with predominant iron deposition within the reticuloendothelial system. This finding is particularly important, because the parenchymal hepatocytes are the most potentially damaging location for iron accumulation (22).

The pattern of deposition from transfusional iron overload is typically observed in the sinusoids because of destruction of senescent transfused erythrocytes by the macrophages, whereas in hereditary hemochromatosis the iron is predominantly hepatocytic (9). Prati *et al.* (23) recently challenged the notion that the hepatic iron distribution in patients with TM follows that of classical transfusional overload, reporting significant hepatocytic iron deposition in more than 200 patients. Our findings corroborate these observations, with substantially more hepatocytic iron deposition than sinusoidal iron found in patients with TM. Hepatocytic deposition in thalassemia can be explained by a dual source of iron intake: accumulation from repeated blood transfusions and increased fractional uptake of intestinal iron in response to ineffective bone marrow erythropoiesis (24,25).

Although our data suggest that the iron in patients with SCD initially accumulates preferentially in the sinusoidal spaces, all three liver compartments began loading iron even at low total iron levels. With continued loading and an increasing iron burden, accumulation appeared to plateau in the sinusoidal spaces but continued in hepatocytes (Fig. 1). At high total iron levels (above 15 mg Fe/g dry weight), hepatocytic accumulation accounted for approximately 70% of the total, while sinusoidal loading fell to about 25% of the total (Fig. 2).

The duration of chelation therapy was relatively short in our patients with SCD (median 8 months), but most of the iron was likely mobilized from the reticuloendothelial compartment, as chelated patients had the same amount of iron accumulation within the sinusoidal space, but significantly higher hepatocytic and portal tract iron scores than those who did not receive iron chelation. This observation suggests that in SCD, iron deposited in the sinusoids and macrophages was mobilized faster by chelation with deferoxamine. Although having a very efficient hepatocytic excretion of iron, deferoxamine also has the ability of excreting iron from the reticuloendothelium, primarily eliminating the recycled iron from senescent red blood cells (26).

The spleen has been proposed to act as an ‘iron buffer’ by storing iron as part of the reticuloendothelial spleen, thereby protecting the liver and other tissues from toxic

accumulation. However, in contrast to previous reports, our splenectomized patients with SCD did not have a higher iron burden than non-splenectomized patients (8,27–29). Because some of our patients underwent surgical splenectomy after initiation of transfusion therapy, a partial buffering effect could have occurred before splenectomy, to some extent minimizing the hepatic burden.

It is difficult to compare patients with SCD and TM directly, because of large demographic and ethnic differences, as well as medical variability related to transfusion and chelation practices. In our cohort, the observed differences in fibrosis and inflammation could reflect the longer exposure to transfusions alone; however, a recent study with balanced young TM and SCD populations still showed significantly more fibrosis among patients with TM (21).

In summary, our data represent one of the largest prospective cohorts of patients with SCD with iron overload reported to date with liver biopsy and histology, with particular emphasis on the deposition of iron within the various liver compartments. Our findings corroborate prior reports that liver iron deposition in SCD follows a traditional transfusional pattern with predominant deposition in the reticuloendothelial system (21,29). Our data suggest, however, a faster rate of iron loading in the liver parenchyma of patients with SCD than previously recognized, with hepatocyte iron loading beginning at even the lowest levels of iron burden. Despite the limitations of our study (small TM cohort with demographic differences from patients with SCD, uncertain chelation compliance, and the use of a semi-quantitative scoring system of histologic iron deposition), these findings have important clinical implications and suggest that chelation therapy in SCD may be underutilized. Because parenchymal iron deposition occurs even at low HIC values, transfusion-associated hepatocyte damage in SCD may begin earlier than previously recognized.

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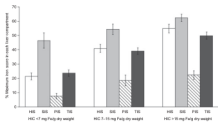

Figure 1.

Iron distribution in the three liver compartments for transfused patients with sickle cell disease according to the hepatic iron burden. The percentage of the maximum iron score was calculated for each of the three liver compartment scores (HIS, SIS, and PIS) and the TIS in patients with low (HIC < 7 mg Fe/g dry weight, *n* = 12), moderate (HIC 7–15 mg Fe/g dry weight, *n* = 13), and high (HIC > 15 mg Fe/g dry weight, *n* = 10). The percentage of the maximum score for all three liver compartments and TIS increased as HIC increased; however, SIS was always higher (i.e., more saturated) than HIS. Results are the mean (±SE) for the % maximum value for each liver compartment. HIC, hepatic iron content; HIS, hepatocytic iron score; PIS, portal iron score; SIS, sinusoidal iron score; TIS, total iron score.

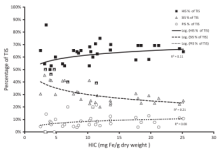

Figure 2.

Relationship of biopsy-proven hepatic iron content and iron scores for all three liver compartments as a percentage of the total histologic iron score in patients with sickle cell disease. Iron saturates the reticuloendothelium (sinusoidal compartment) very fast, with SIS representing approximately 50% of the total iron score (TIS) at lowest iron burden. The amount of iron deposited in hepatocytes increases proportionally with increasing iron burden, so that HIS represents approximately 70% of the TIS at higher iron burdens. HIS, hepatocytic iron score.

Table 1

Patient characteristics

Parameter	SCD (*N* = 35)	TM (*N* = 9)	*P* Value
Age (years)	13.3 (8.0–18.8)	26.4 (15.5–36.8)	<0.0001[1]
Number of females/males	20/15	4/5	0.71[2]
Medical history and laboratory values			
Duration of transfusions (months)	51 (7–162)	195 (2–425)	0.0012[1]
Duration of chelation therapy (months)	8 (1–65)	200 (12–513)	0.0124[1]
# Patients chelated (%)	16 (45.7%)	8 (88.9%)	0.0271[2]
# Patients splenectomized (%)	7 (20%)	7 (78%)	0.0022[2]
Hepatic iron content (mg Fe/g dry weight)	10.3 (2.5–25.2)	12.9 (0.6–38.8)	0.73[1]
Serum ferritin (ng/mL)	2347 (578–7450)	1314 (639–7367)	0.098[1]
Histologic scores			
HIS	15 (6–27)	18 (6–27)	0.23[1]
SIS	7 (0–9)	6 (5–8)	0.13[1]
PIS	1 (0–6)	2 (1–7)	0.27[1]
TIS	23 (7–39)	26 (12–34)	0.20[1]
Proportion of iron corresponding to HIS (%)	64	69	0.43[1]
Inflammation			
Fibrosis score	1 (0–5)	3 (1–6)	0.0185[2]
# Patients with mild inflammation (%)	26 (74%)	3 (33%)	0.0439[2]
# Patients with moderate inflammation (%)	2 (6%)	6 (67%)	0.0003[2]

Results are presented as median (range), unless noted otherwise. SCD, sickle cell disease; TM, thalassemia major; HIS, hepatocytic iron score; SIS, sinusoidal iron score; PIS, portal iron score; TIS, total iron score.

[1] Wilcoxon–Mann–Whitney test for a difference in medians.

[2] Fisher's exact test for association.