

# Iron Overload in Dialysis Patients: Rust or Bust?



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A recent study using magnetic resonance imaging (MRI) to assess liver iron content (LIC) by Issad and colleagues provides observational data from prevalent peritoneal dialysis patients, showing that few have iron overload.<sup>1</sup> These results complement earlier MRI studies in hemodialysis patients by Rostoker *et al.* and other groups showing high MRI-estimated LIC in hemodialysis patients and a high incidence of moderate to severe iron overload. The discussions in these reports, and in several editorials and commentaries, have warned that our present i.v. iron use practices are overloading hemodialysis patients and carry great risk.<sup>2–6</sup>

Anemia is a major problem in most patients receiving chronic dialysis, and treatment with i.v. iron was necessary in some even before the approval of epoetin in 1989. Fewer than 10% of patients in this era were transfusion dependent, but over the years these patients developed iron overload. In 1 study of 12 such patients, ferritin ranged from 3000 to 19,360 µg/l, transferrin

saturation (TSAT) ranged from 73% to 100%, liver enzymes were elevated, and these patients' iron burden based on previous transfusions averaged 831 mg/kg of body weight.<sup>7</sup> The very high ferritin and TSAT and the large excess iron stores are similar to those seen in patients with hereditary hemochromatosis or transfusional iron overload from thalassemia major.<sup>8</sup> In these latter disorders, once TSAT is persistently high (> 50%–70%) and the reticuloendothelial (RES) system is loaded with storage iron, excess iron is deposited into tissues, which, over years, can result in organ damage and failure.<sup>8</sup>

Use of epoetin in dialysis patients led to the virtual elimination of transfusion dependence and its consequent iron overload, but created a new problem: widespread overt iron deficiency and so-called functional iron deficiency, which is iron-restricted erythropoiesis. This has led clinicians to prescribe i.v. iron in conjunction with an erythropoiesis-stimulating agent (ESA) routinely. In the United States, more than 80% of dialysis patients each quarter receive an ESA and i.v. iron.<sup>9</sup>

Concerns about the long-term effect of repeated i.v. iron dosing,

including iron overload, have been present for more than 20 years.<sup>10</sup> As the body has no natural way to eliminate iron, excessive i.v. iron can lead to iron overload. MRI-based LIC estimates have been validated by liver biopsy—confirmed LIC in patients with hereditary hemochromatosis and transfusional iron overload disorders. Because phlebotomy may be used to treat their iron overload, we can determine the relationship of total body excess iron to the LIC. In a study of patients with thalassemia major cured by bone marrow transplant, then phlebotomized for iron overload, the following equation was derived:

$$\text{Total body iron (in mg per kg of body weight)} = 10.6 \times \text{liver iron content (mg/g dry weight of liver)}$$

Their analyses showed that “the variation in the hepatic iron concentration accounted for 98 percent of the variation in total iron stores....”<sup>11</sup> Similar analyses in hereditary hemochromatosis patients have estimated that LIC increases by 30 µmol/g (1.68 mg/g) of dry liver for every 1-g increase in total body iron.<sup>12</sup>

Applying this equation to the most iron-overloaded peritoneal dialysis patient in Issad *et al.* (patient 1 in Table 3, LIC 230 µmol/g, or 12.9 mg/g), we would estimate that the patient had 136 mg/kg of excess iron.<sup>1</sup> In a 70-kg person, this is 9.5 g of excess iron. Even the data from hemochromatosis patients would suggest 7.6 g of excess iron (230 µmol/g divided by 30 µmol/g = grams of total body iron). Yet we are told that this woman received only 300 mg of i.v. iron, had a ferritin of 100 µg/l, and had a TSAT of 15%. The patient most certainly is not iron overloaded, and does not have

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9.5 g of excess iron; her liver biopsy results would show virtually no parenchymal iron, and phlebotomy would be malpractice.

In the peritoneal dialysis study by Issad *et al.*, 5 patients had mild iron overload, with MRI-based LIC ranging from 55 to 70  $\mu\text{mol/g}$ .<sup>1</sup> Yet 3 patients had ferritin values  $< 200 \mu\text{g/l}$ , and only 1 patient had a TSAT  $> 35\%$ . Using the above equation and assuming 70 kg weight, we would estimate their total body iron overload at 2.2 to 2.9 g. None received i.v. iron, and 2 did not even take oral iron.

Let's examine the hemodialysis patients with severe iron overload in another publication that uses the same MRI-LIC techniques.<sup>6</sup> These patients had LIC values between 210 and 340  $\mu\text{mol/g}$  dry liver. Assuming that they weighed 70 kg, this suggests 8.7 to 14.1 g of excess iron, yet the median ferritin was 446  $\mu\text{g/l}$  (range 55–1299  $\mu\text{g/l}$ ) and TSAT 30.9% (range 8%–72.1%).<sup>6</sup> If they had this much excess iron, and if iron losses via hemodialysis are 100 to 200 mg per month, then LIC should fall at 3 to 6  $\mu\text{mol/g}$  dry liver per month, given that 1 g of total body iron = 30  $\mu\text{mol/g}$  dry liver. Yet we are told that when i.v. iron was stopped, LIC fell by 17.9  $\mu\text{mol/g}$  dry liver per month.<sup>6</sup> Either these hemodialysis patients were losing large amounts of blood, or MRI-estimated LIC is overestimating total body iron burden in hemodialysis patients by 3- to 6-fold.

The largest issue with the use of MRI to diagnose iron overload in dialysis patients is whether LIC estimated by MRI indicates the same degree of total body iron observed in patients with hereditary hemochromatosis or transfusional iron overload, which is the implication of many editorials warning of massive iron overload

in dialysis patients. Based on the available data, I conclude that it clearly does not.

So what is going on, and what needs to be done to advance the science? First, MRI-estimated LIC is validated in hereditary hemochromatosis and transfusional iron overload by comparing results to liver biopsy results and total iron burden. Neither validation has been done in dialysis patients. Also, some data suggest the MRI-based LIC method used by Issad *et al.* may overestimate liver biopsy LIC, especially in the normal to mildly elevated range.<sup>13</sup> Second, i.v. iron products are iron cores surrounded by carbohydrates. They are taken into the RES, which is predominantly in the liver and spleen. When iron-deficient patients are given i.v. iron, it fills the RES, and then “bleeds” out via ferroportin to circulating transferrin to maintain erythropoiesis over months. The high retention in the RES is likely a product of the dose, nature of i.v. iron metabolism, functional iron deficiency, and inflammatory blockade. In contrast, the traditional iron overload syndromes accumulate iron slowly throughout the body, first filling the RES, then pathologically depositing into parenchymal cells; thus the relationship of LIC to total body iron differs.<sup>8</sup>

Some i.v. iron products are paramagnetic and will give even more misleading results.<sup>14</sup> The effect of each i.v. iron product on MRI-estimated LIC needs validation. Research studies involving liver biopsy are needed to determine how much i.v. iron is in the parenchymal (where it does harm) rather than RES, and to determine whether it is associated with fibrosis or cirrhosis—suggesting end-organ damage. Although claims of harm from iron overload are frequently made, a new or

worsening clinical problem from overload remains unidentified. With severe, prolonged iron overload, cardiac iron deposition can occur and can lead to heart failure, but reports of cardiac MRI iron content in dialysis patients are scant, perhaps because the scans do not show iron deposition.<sup>15</sup>

Finally, we need clinical evidence of harm from the i.v. iron that we give.<sup>16</sup> We know that i.v. iron use reduces ESA doses and maximizes hemoglobin, whereas conversely maintaining a very low ferritin, as some recommend, will cost more and expose patients to higher ESA doses.<sup>17–20</sup> Excessive administration of i.v. iron to dialysis patients can and does occur,<sup>21</sup> and could be prevented by following guidance from 1997: stop giving i.v. iron when the TSAT is greater than 50%.<sup>22</sup> Most hemodialysis patients should receive maintenance iron to replace ongoing losses. We also are awaiting the completion of the Proactive i.v. iron therapy for hemodialysis (PIVOTAL) trial, which randomized 2142 hemodialysis patients to lower or higher ferritin goals (generally i.v. iron only if ferritin  $< 200 \mu\text{g/l}$  vs. maintain ferritin  $> 700 \mu\text{g/l}$ ). This event-driven trial is not expected to end until mid-2018.

In summary, the MRI assessment of LIC in hemodialysis and peritoneal dialysis patients is overestimating total iron burden, and has yet to be tied to a disease state in clinical practice. Much more work needs to be done before we can declare that our present practices are resulting in iron overload.

## DISCLOSURE

DWC has been a consultant, speaker, and researcher for IV iron companies in the past.

## REFERENCES

1. Issad B, Ghali N, Beaudreuil S, et al. Hepatic iron load at magnetic resonance imaging is normal in most patients receiving peritoneal dialysis. *Kidney Int Rep.* 2017;2:1219–1222.
2. Rostoker G, Griuncelli M, Loridon C, et al. Maximal standard dose of parenteral iron for hemodialysis patients: an MRI-based decision tree learning analysis. *PLoS One.* 2014;9, e115096.
3. Rostoker G, Hummel A, Chantrel F, et al. [Therapy of anemia and iron deficiency in dialysis patients: an update]. *Nephrol Ther.* 2014;10:221–227.
4. Rostoker G, Vaziri ND, Fishbane S. Iatrogenic iron overload in dialysis patients at the beginning of the 21st century. *Drugs.* 2016;76:741–757.
5. Vaziri ND. Epidemic of iron overload in dialysis population caused by intravenous iron products: a plea for moderation. *Am J Med.* 2012;125:951–952.
6. Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. *Am J Med.* 2012;125:991–999.
7. Stivelman J, Schulman G, Fosburg M, et al. Kinetics and efficacy of deferoxamine in iron-overloaded hemodialysis patients. *Kidney Int.* 1989;36:1125–1132.
8. Fleming RE, Ponka P. Iron overload in human disease. *N Engl J Med.* 2012;366:348–359.
9. DOPPS Practice Monitor. Available at: [http://www.dopps.org/DPM/DPM\\_SlideBrowser.aspx?type=Topic&id=1](http://www.dopps.org/DPM/DPM_SlideBrowser.aspx?type=Topic&id=1). Accessed August 16, 2017.
10. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis.* 1995;26:41–46.
11. Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. *N Engl J Med.* 2000;343:327–331.
12. Barry M. Liver iron concentration, stainable iron, and total body storage iron. *Gut.* 1974;15:411–415.
13. Alustiza Echeverria JM, Castiella A, Emparanza JI. Quantification of iron concentration in the liver by MRI. *Insights Imaging.* 2012;3:173–180.
14. Lu M, Cohen MH, Rieves D, et al. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. *Am J Hematol.* 2010;85:315–319.
15. Tolouian R, Mulla ZD, Diaz J, et al. Liver and cardiac iron deposition in patients on maintenance hemodialysis by magnetic resonance imaging T2. *Iran J Kidney Dis.* 2016;10:68–74.
16. Tangri N, Miskulin DC, Zhou J, et al. Effect of intravenous iron use on hospitalizations in patients undergoing hemodialysis: a comparative effectiveness analysis from the DEcIDE-ESRD study. *Nephrol Dial Transplant.* 2015;30:667–675.
17. Coyne DW, Sims A, Bingel B. Results of an anemia management program to reduce high epoetin doses by targeted use of i.v. ferric gluconate. *Nephrol Nurs. J.* 2008;35:583–587.
18. Kapoian T, O'Mara NB, Singh AK, et al. Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol.* 2008;19:372–379.
19. Coyne DW, Kapoian T, Suki W, et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol.* 2007;18:975–984.
20. Richardson D, Bartlett C, Will EJ. Optimizing erythropoietin therapy in hemodialysis patients. *Am J Kidney Dis.* 2001;38:109–117.
21. Ghoti H, Rachmilewitz EA, Simon-Lopez R, et al. Evidence for tissue iron overload in long-term hemodialysis patients and the impact of withdrawing parenteral iron. *Eur J Haematol.* 2012;89:87–93.
22. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation–Dialysis Outcomes Quality Initiative. *Am J Kidney Dis.* 1997;30(4 suppl 3):S192–S240.