



# Understanding Iron Metabolism: Lessons from Transfusion-dependent Thalassemia

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**I**ron metabolism is well regulated in humans by a number of proteins, the most important one being hepcidin.<sup>1,2</sup> Hepcidin inhibits iron absorption at the gastrointestinal (GI) luminal surface through its inhibition of ferroportin.<sup>1</sup> Body iron stores, as well as inflammation, increase the level of hepcidin, thereby leading to decreased GI iron absorption. Additionally, high hepcidin levels lead to immobilization of iron within the reticuloendothelial system, specifically, the spleen and liver.<sup>3</sup> The strict regulation of iron metabolism and the immobilization of iron during inflammation may have developed in animals and humans as a protective mechanism against infection by limiting the availability of iron to the infecting organism. The average daily GI absorption is 1–2 mg, which is similar to the amount shed out by the sloughing of epithelial cells in the GI system. Menstruating females lose an additional 20–40 mg every month. Other than this, humans are not equipped with any other way of removing iron.<sup>4</sup>

Hemosiderosis is a state of iron overload in different tissues and organs of the body.<sup>5</sup> The causes of this are either hereditary (i.e., hereditary hemochromatosis), or iatrogenic as in patients who require frequent blood transfusions.<sup>6</sup> Transfusion-dependent thalassemia (TDT) is a group of genetic disorders characterized by decreased globin chain production of which the commonest is  $\beta$ -thalassemia major ( $\beta$ -TM).  $\beta$ -TM is characterized by the absence or severe reduction of  $\beta$ -globin chain production leading to globin chain imbalance, dyserythropoiesis, and severe anemia.<sup>7</sup> These patients require regular blood transfusion to survive. Unfortunately, the necessary blood transfusions lead to a number of complications particularly iron overload and

transfusion-transmitted viral infections such as hepatitis B and C, in addition to the human immunodeficiency virus.<sup>7</sup>

Animals and humans limit the toxicity of iron by containing it in a storage form to be mobilized when needed.<sup>4</sup> However, when the degree of iron overload is beyond the storage capacity, it becomes freely bioavailable and toxic to different tissues and organs through the formation of free radicals.<sup>4</sup> The cellular damage caused by iron overload in patients with TDT leads to complications such as endocrinopathies, cardiac failure, and hepatic iron overload with subsequent cirrhosis. The development of iron chelators, namely, deferoxamine, deferiprone, and deferasirox (the three chelators currently available in Oman) have led to a marked reduction in the risk of iron-related complications and improved the survival of these patients.<sup>8,9</sup>

The gold standard for the diagnosis of hepatic iron overload is a liver biopsy. However, this is invasive, associated with bleeding and other morbidities and cannot be frequently performed.<sup>10</sup> Although iron-related cardiac disease is the commonest cause of death in TDT, there has, until recently, been no easily and safe way to assess myocardial iron. In 2000, a special sequence of magnetic resonance imaging (MRI) called T2\* was developed as a non-invasive assessment of hepatic and cardiac iron overload.<sup>11</sup> T2\*MRI has become an essential tool in the management of iron overload in TDT, allowing physicians to safely and easily diagnose iron overload in both the liver and the heart, and to institute appropriate chelation strategies.

In this issue of the *Oman Medical Journal*, Soltanpour et al,<sup>12</sup> reported a study that examined the association between cardiac and hepatic T2\*MRI

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in a cross-sectional design. As has been reported by other authors, they found a poor association of iron status between the two organs.<sup>13</sup> The authors rightly concluded that the lack of association is probably related to the different rates of accumulation and clearance of cardiac and hepatic iron. It has been shown in a number of studies that the accumulation and clearance of cardiac iron in patients with TDT is slower than the hepatic clearance.<sup>13</sup> Soltanpour et al,<sup>12</sup> emphasize the importance of cardiac T2\*MRI in the assessment of iron overload in patients with TDT. We agree that the use of T2\*MRI should be the standard of care for these patients and centers should endeavor to make this available for the optimum care of patients with TDT.

The second finding reported in the study by Soltanpour et al,<sup>12</sup> was the association between the human hemochromatosis protein (HFE) gene related mutations and iron overload in patients with TDT. In this study, patients carrying the H63D mutation had a much higher serum ferritin compared to those without the mutation ( $1903 \pm 993$  vs.  $992 \pm 683$ ,  $p < 0.001$ ). They also found that the prevalence of the H63D mutation to be 20% in patients with  $\beta$ -TM. This is higher than expected in this region.<sup>14</sup> However, it has clearly contributed to the increased absorption of GI iron. The mechanism of the increased absorption is, again, related to hepcidin. The HFE protein is an iron-specific adaptor that facilitates communication between transferrin receptor 1 and 2 leading to downward signaling and ultimately increased transcription of hepcidin. Mutations in the HFE gene, namely C282Y and H63D, lead to the disruption of this function, and subsequently, to the decreased level of hepcidin and increased GI iron absorption.<sup>1</sup> This by itself leads to the iron overload in patients with hereditary hemochromatosis. In patients with TDT, iron overload is mainly due to the transfused iron, but increased absorption is an additional factor. The increased GI iron absorption is driven by the increased erythropoietic requirement, a hepcidin related mechanism. Additionally, the disruption of the downward signaling in patients with the HFE mutations further suppresses hepcidin transcription leading to even further increased GI iron absorption. The unexpectedly high rate of the H63D mutation in the sample studied by Soltanpour et al,<sup>12</sup> argues for testing patients with TDT in Oman. However, the impact on therapeutic decision-making is yet to be studied.

In summary, patients with TDT develop iron overload from frequent and necessary blood transfusion in addition to the increased absorption due to the increased erythropoietic requirement and potentially mutations in the HFE gene. Cross-sectional studies are not optimal to study the association between hepatic and cardiac iron overload due to the different rates of iron accumulation and clearance. Further studies are needed to elucidate the prevalence of the HFE mutations in the Omani population.

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