# Iron Overload in Thalassemia and Related Conditions: Therapeutic Goals and Assessment of Response to Chelation Therapies

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**KEYWORDS**

• Chelation • Iron • Deferiprone • Deferoxamine • Deferasirox
• Thalassemia • Sickle

## FACTORS CONTRIBUTING TO IRON OVERLOAD AND ITS DISTRIBUTION

With regular blood transfusion, iron stores increase to many times the norm unless chelation treatment is given. Approximately 200 mg of iron is present in a unit (420 mL) of donated blood, or approximately 1.08 mg of iron per 1 mL of pure red blood cells (ie, hematocrit 1.0).[1] Mean transfusional loading in thalassemia major (TM) is 0.4 mg/kg/d,[2] but this varies. In 20% of patients, this is less than 0.35 mg/kg/d, approximately 60% receive 0.3 to 0.55 mg/kg/d, and a further 20% receive greater than 0.5 mg/kg/d.[2] This transfusional loading is less in sickle cell disease (SCD; 0.22 mg/kg/d)[3] than in TM and is further decreased by approximately 60% when using manual exchanges, whereas neutral iron balance can be achieved with automated exchanges.[4] In myelodysplastic syndromes (MDS), the average rate of iron loading (0.28 mg/kg/d) is less on average than TM.[5] Iron loading may worsen from increased iron absorption caused by increased rates of ineffective erythropoiesis. Thus, iron absorption in thalassemia intermedia (TI) can be up to 5 to 10 times normal, or 0.1 mg/kg/d.[6,7] Splenectomy seems to increase the rate of gastrointestinal hyperabsorption

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in TI[8] and other conditions, such as pyruvate kinase deficiency,[9] but interestingly patients with hyposplenic SCD do not hyperabsorb iron.

Tissue iron uptake, in the absence of iron overload, is determined by the distribution of transferrin receptors and by transferrin saturation. However, once transferrin becomes saturated, and with the appearance of plasma iron species that are not bound to transferrin (so-called plasma nontransferrin bound iron [NTBI]), the pattern of tissue iron uptake differs considerably and uptake is mediated through different pathways, such as calcium[10] and zinc channels.[11]

The pattern of tissue iron distribution resulting from transfusional iron overload is best described in TM, in which without chelation therapy, death from iron-induced cardiac failure was usual from the second decade.[12] Postmortem examination in the prechelation era showed high concentrations in liver, heart, and endocrine glands, little in striated muscle, and none in the brain and nervous tissue.[13] Cardiac iron overloading occurred after approximately 70 to 100 units of blood (containing 14–20 g iron) across a range of diagnoses, including MDS.[14,15] Although cirrhosis has been found in approximately 50% of patients with TM at postmortem, particularly when chronic hepatitis is present, this has historically been an uncommon cause of death, because cardiac disease typically develops first. However, as patients live longer with improved chelation, cirrhosis and hepatocellular carcinoma[16] are likely to increase. Hypogonadism historically occurred in more than half of patients older than 12 years old,[17] leading to disturbances of growth and sexual maturation.

In patients with multitransfused SCD, liver disease is common with cirrhosis in nearly half of the patients who died with severe liver siderosis.[18] By contrast, extrahepatic iron distribution may be delayed in transfused SCD, with MRI showing a lower incidence of myocardial iron deposition,[19,20] although cardiac iron may be visible postmortem.[18] Lower rates of endocrine complications at matched levels of iron loading to those of patients with TM have also been noted.[21,22] Possible mechanisms for the lower extrahepatic iron distribution in SCD include lower transfusion rates, less ineffective erythropoiesis, higher plasma hepcidin values,[23] chronic inflammation, and lower NTBI[24] values at matched levels of body iron to those of TM.

## GOALS OF CHELATION THERAPY

The primary objective is to maintain body iron at safe levels at all times. Iron stored as ferritin or hemosiderin is not chelated directly at clinically useful rates, so that once accumulated, iron removal is slow and inefficient, relying on the tiny fraction of labile iron that is available for chelation at any moment, either from the breakdown of red cells in macrophages or from the turnover of tissue iron stores in lysosomes. Ideally, chelation therapy therefore should begin before clinically significant iron loading develops. Ample evidence shows that the age at which chelation is started in TM is a key factor in survival,[17,25,26] although this is often not accounted for in the retrospective analysis of survival data.

In practice, chelation with deferoxamine (DFO) has traditionally been started only after 2 to 3 years of transfusion or when ferritin exceeds 1000 g/L, for fear of the unwanted effects of overchelation at low levels of body iron (see later discussion). Whether chelation can be safely started earlier with other iron chelators remains to be seen, but this would be desirable. What constitutes safe levels of body iron burden is debated. It may differ depending on the underlying diagnosis and the chelation therapy being used. Preventing the primary accumulation of iron overload in hepatocytes should avoid secondary distribution of iron to endocrine organs and the heart.