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Transfusion-Induced Iron Overload

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Background

The human body has no active mechanism for the excretion of iron.^[1] Iron homeostasis thus relies on the amount that is absorbed from the small intestine.^[2] During normal physiology, the amount of iron absorbed (1-2 mg/d) is lost by sloughing of intestinal mucosa and skin, as well as small amounts in the urine and bile. The day-to-day iron requirements, as iron is needed by virtually all body cells and especially erythrocytes, are met by recycling between various compartments.

In some patients, noticeably those with [thalassemia major](#), [sickle cell disease](#), [myelodysplastic syndrome](#), [aplastic anemia](#), [hemolytic anemia](#), and refractory [sideroblastic anemias](#), who may become transfusion-dependent and receive excess iron with each transfusion (that the body has no means to excrete), iron gradually accumulates in various tissues, causing morbidity and mortality. Each unit of transfused blood has approximately 250 mg of iron.^[3]

Pathophysiology

The dynamics of iron regulation in the body is multifaceted and is altered in transfusion-induced iron overload.

Hepcidin, a peptide synthesized in liver, is also known as the "iron hormone."^[4] Circulating hepcidin reduces iron export into the plasma by binding to the iron export protein ferroportin 1 (FPN1) on the surface of enterocytes, macrophages, and other cells and causing its internalization and degradation. Thus, iron-deficiency states exhibit reduced hepcidin and iron-excess states have high levels of hepcidin to maintain the amount of iron secreted into the circulation.^[5] Several factors can influence hepcidin production, including the *HFE* gene, hypoxia, and increased erythropoietin production.^[6] Most forms of hereditary [hemochromatosis](#) exhibit a deficiency of hepcidin.^[7]

In some disorders, such as β -thalassemia, excessive intestinal absorption also adds to the transfusion-induced iron overload. In [thalassemia intermedia](#), high erythropoietic drive causes hepcidin deficiency. The lack of hepcidin results in hyperabsorption of dietary iron and body iron overload. In contrast, in thalassemia major, transfusions decrease erythropoietic drive and increase the iron load, resulting in relatively higher hepcidin levels. In the presence of higher hepcidin levels, dietary iron absorption is moderated and macrophages retain iron, but body iron stores increase due to the inability to excrete iron in transfused red blood cells.^[8]

When the plasma iron-binding protein transferrin is oversaturated, as in transfusion-induced iron overload, the excess iron circulates as relatively free non-transferrin-bound iron (NTBI). This NTBI is rapidly taken up by liver and other tissues. Transferrin-bound iron (TBI) is also taken up by these cells through the hepcidin mechanism, which is increased in such states.^[9] It is this excessive iron that damages tissues.

A specific portion of NTBI is the chelatable labile plasma iron (LPI), which is not found in healthy individuals.^[10] This is the most toxic component due to high reduction-oxidation (redox) potential that generates oxygen-free radicals such as superoxide anion in the cells, which damages DNA, proteins, and membrane lipids in the cell.^[11]

Hemosiderin is an abnormal, insoluble form of iron storage. It consists of ferritin trapped in lysosomal membranes.^[12] Unlike ferritin, it does not circulate in blood but is deposited in tissues and is unavailable when cells need iron.^[13]

Major organs affected by this surplus iron include the heart, lung, liver, and endocrine glands.

Cardiac involvement is a major determinant of the prognosis in iron-overload states.^[14] Hypertrophy and dilatation are common. Abnormal cardiac function can be observed in the absence of overt **heart failure**.^[15] The average time for the development of heart failure in transfused, unchelated patients is 10 years.^[16] Iron chelation can reverse cardiac changes and improve performance.^[17]

Pulmonary hypertension appears to be less common in thalassemia major patients who undergo transfusion, probably due to the correction of hypoxia, and it is more common in the less transfused thalassemia intermedia patients.^[18] More than one third of transfusion-dependent patients with β -thalassemia major exhibit a restrictive lung function defect, which may improve with chelation therapy.^[19]

Liver involvement is common in those who undergo long-term transfusions. Early cirrhotic changes can be observed as early as age 7 years in some people with thalassemia.^[20] Upregulation of the transport of NTBI is observed in cultured hepatocytes and is likely to occur in vivo.^[21] Once cirrhosis develops, the risk of hepatocellular carcinoma (HCC) is increased.

Endocrine dysfunction affects virtually all glands. Pituitary involvement causes delayed puberty in more than 50% of patients.^[22] Up to 14% may develop insulin-dependent diabetes mellitus (IDDM).^[23] Even those without diabetes have impaired insulin secretion.^[24] **Thyroid**, parathyroid, and exocrine pancreas are also affected.^[25]

Neutrophils from patients with secondary iron overload have an increased iron and ferritin content and a phagocytosis defect.^[26] *Yersinia enterocolitica* seems to have affinity for those loaded with iron, causing abdominal infections^[27] and hepatic abscesses.^[28] Deferoxamine seems to worsen the infection and should be discontinued in cases in which active abdominal symptoms are present.^[29]

Degenerative arthropathy in thalassemia is also a sequela of iron overload.^[30]

Epidemiology

Frequency

United States

Amongst 342 patients with transfusion-dependent thalassemia in the National Institutes of Health (NIH) registry, 23% had iron overload as documented by a liver iron concentration of 15 mg/g dry weight or greater.^[31] Around 15,000 patients with sickle cell disorder and estimated and 5,000 with myelodysplastic syndromes and other acquired refractory anemias require blood transfusions.^[32]

International

In a Japanese cohort of transfusion-dependent patients with myelodysplastic syndrome and aplastic anemia, one third of all deaths were attributable to iron overload (97% of the deceased had a serum ferritin >1000 ng/mL).

Cardiac failure was responsible for 24% and liver failure for 7% of all deaths. On average, each patient was transfused with more than 60 units of red blood cells per year.^[33]

In a Greek population of thalassemia major patients who were transfusion dependent, 51% had moderate (defined as serum ferritin >2000 mcg/L) to severe iron overload (defined as serum ferritin >4000 mcg/L).^[34]

Mortality/Morbidity

Mortality in chronically transfused patients with thalassemia and sickle cell disease is 3 times that of the general United States population. The most common cause of morbidity is cardiomyopathy (30%) that is induced by iron overload.^[35]

Race

The prevalence of mild to moderate iron overload was similar in black and white veterans in one autopsy study that evaluated the hepatic iron concentration of 256 specimens.^[36]

Sex

An analysis of data from 1861 patients with β -thalassemia major from Italy showed that failure of puberty was the major clinical endocrine problem in these patients, and it was present in 51% of boys and 47% of girls, all older than 15 years. Secondary amenorrhea was recorded in 23% of the patients with β -thalassemia major.^[37]

Age

Several distinct groups can be recognized in terms of the initiation of transfusion therapy. The average age of patients undergoing transfusion initiation is 4 years in thalassemia and 13 years in sickle cell disease^[35]; in adults, the average age at transfusion initiation is in the 40s for aplastic anemia,^[38] and in the 60s for myelodysplasia.^[39]

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