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Organ damage and iron overload

Iron is a metal element essential for life. It is indispensable for several critical functions (O_2 transport and others). The normal iron content of the body is approximately 3 to 4 grams.

In humans iron exists in the following forms:

a. Hemoglobin in circulating red blood cells - about 2.5 gram;
b. Iron containing proteins (myoglobin, cytochromes, and catalase) about - 400 mg;
c. Iron bound to transferrin in plasma - about 3-7 mg;
d. Storage iron.

Storage iron has been precisely calculated by quantitative phlebotomy in healthy, voluntary, subjects and is in the form of ferritin or hemosiderin. Adult men have about 1 gram of storage iron (mainly in liver, spleen, and bone marrow). Adult women have less storage iron, depending upon the extent of menses, pregnancies, deliveries, lactation, and iron intake.[1] Total body iron content in normal adults is the result of the balance between iron losses and iron absorbed from the diet. Increased absorption of dietary iron, or iron from multiple transfusions will ultimately result in iron overload.

Iron toxicity

The iron replete state is characterized by higher production of ferritin to consent adequate storage along with decreased production of the transferrin receptor to minimize further iron entry into the cell. These responses are mediated by the iron responsive element binding protein (IRE-BP).[2] The iron responsive element consists of a loop configuration of nucleotides found on the mRNA for ferritin and the transferrin receptor. In the presence of iron, the IRE-BP detaches from ferritin mRNA, allowing more ferritin to be synthesized. IRE-BP serves a different function on transferrin receptor mRNA, stabilizing it so that more transferrin receptor is synthesized. Thus, detachment of IRE-BP when the cell is iron replete destabilizes the mRNA and reduces transferrin receptor synthesis.

As the body content of iron increases, the saturation of circulating transferrin with iron increases, resulting in the production of increased amounts of non-transferrin-bound iron,[3,4] and the off-loading of iron, especially to cells with high levels of transferrin receptors (heart, liver, thyroid, gonads, and pancreatic islets). The excess iron in these cells may act as a Fenton agent, catalyzing the Haber-Weiss reactions[5]:

$H_2O_2+Fe^{2+}ÆOH^-+Fe^{3+}+OH•$(hydroxyl radical)

O_2^- (superoxide anion) + $Fe^{3+}ÆO_2$+ Fe^{2+}

SUM: $H_2O_2+O_2ÆO_2+OH^-+OH•$

The reactive oxygen species produced by these reactions presumably oxidize lipids, proteins, and perhaps RNA and DNA, thereby causing tissue damage and subsequently fibrosis.[5,6,7] These reactions contribute to the clinical manifestations of the iron overload syndromes which have been best characterized in patients with hereditary hemochromatosis and thalassemia major.

Causes of iron overload

In normal subjects there is no mechanism to regulate iron loss from the body. About 1 mg/day in adult men from shed skin cells, sweat and gastrointestinal losses. Premenopausal adult women lose an additional 0.5-1.0 mg/day because of menses. Therefore, to insure normal stores of iron within the body, iron absorption must be tightly regulated. As a result of the inability to increase iron loss, iron overload is an inevitable response to increased iron entry into the body. This can occur by one of three mechanisms:

- A massive increase in iron intake;
- An increase in iron absorption when iron intake is normal:
- The parenteral administration of iron, as with transfusional overload (eg, sickle cell disease, beta thalassemia major, aplastic anemia, myelodysplasia).

Hereditary iron overload

In patients with homozygous hereditary hemochromatosis the absorption of heme iron is not regulated by the content of iron stores.[8] Subjects with Hereditary Hemochromatosis may absorb 2-4 mg of iron per day from heme and non-heme iron sources, rather than the normal value of 1 mg/day required in males to balance iron loss. An example will make this clear. If iron absorption is increased in an individual by as little as 1.5 mg/day above the amount needed to achieve homeostasis, this will result in the accumulation of 5.5 grams of iron every decade, 16 grams in 30 years and more than 30 grams in 60 years. The latter example corresponds to the amount of iron (30-40 g) usually found in patients with clinically detected hereditary hemochromatosis and explains both the delayed time for the clinical appearance of this disease in men and its rarity in premenopausal women.

Transfusional iron overload

Iron overload is inevitable in patients requiring chronic transfusion support. Each unit of transfused red cells introduces 200-250 mg of elemental iron into the body. Since iron cannot be actively excreted, and is utilized poorly in patients with ineffective erythropoiesis, the excess iron is deposited in macrophages of the reticuloendothelial system. When iron stores overcome the ability of reticuloendothelial cells to sequester them, parenchymal iron overload develops, leading to end-organ dysfunction, especially in the liver, myocardium, and endocrine organs. Chronic transfusion therapy is the cornerstone of management of children with beta thalassemia major.[9] The typical thalassemic child receiving a hypertransfusion regimen has an intake of 8-16 mg of elemental iron per day.[10] Even if hematopoiesis is partially suppressed by hypertransfusion, accelerated oral iron absorption also contributes to the total iron overload. Chronic transfusional support is also employed in patients with sickle cell anemia, refractory aplastic anemia, myelodysplastic syndrome, and a range of leukemic states.[11] Such patients may receive as many as 100 units of red cells, which contain up to 20-25 g of iron, similar to, or more than, the amount retained in many symptomatic patients with hereditary hemochromatosis. They eventually develop marked elevations in transferrin saturation and serum ferritin concentration and some may develop clinical signs of iron overload (liver dysfunction, heart failure, skin pigmentation, diabetes mellitus, and other endocrinopathies).[12,13]

Liver iron overload and liver disease

In the liver, iron first infiltrates Kupffer cells and then engorges hepatocytes, finally provoking fibrosis and, potentially, end-stage liver disease (in a way analogous to that seen in idiopathic hemochromatosis). In these patients hepcidin levels remain low despite massive iron overload.[14] Serum from thalassemic subjects blocks hepcidin synthesis in cultured liver cells,[15] suggesting that thalassemic serum contains a circulating repressor of hepcidin.[16] The severity of iron related liver disease is strongly influenced by the presence of comorbidities. Both iron overload and HCV infection lead, albeit with different mechanisms, to

hepatocellular necrosis, fibrosis deposition and cirrhosis. A prospective study on thalassemia patients successfully surviving hemopoietic stem cell transplantation has demonstrated with repeated liver biopsies that HCV Infection and iron overload are independent but mutually reinforcing risk factors for fibrosis progression and cirrhosis development. The 10-year probability of fibrosis progression reached 80% in patients with severe iron overload and HCV infection, whereas in patients with good control of iron overload, the rate of fibrosis progression appeared insignificant in HCV-negative patients and limited to approximately 20% in HCV-positive patients in the same period of observation.[17]

Cardiac iron overload and cardiac disease

Cardiac abnormalities are a major feature of transfusional iron overload particularly in thalassemia. Cardiac malfunction (including congestive failure and arrhythmias) are frequent causes of death, and cardiac dilatation secondary to anemia is frequent. Transfusion usually corrects this latter abnormality, but may lead to long-term cardiac hemosiderosis due to deposition of transfused red cell iron in the myocardium. Cardiomegaly and left ventricular dysfunction inevitably appear in unchelated patient with thalassemia major. In transfused patients, cardiac hemosiderosis is the most feared complication. Without early institution of iron chelation therapy, a characteristic iron overload cardiomyopathy develops. These patients can develop a sterile pericarditis, arrhythmias (both supraventricular and ventricular), and end-stage restrictive cardiomyopathy and finally heart failure.[18,19] Fatal ventricular arrhythmias are a frequent cause of death. Rhythm disturbances begin with the characteristic prolongation of the PR interval, then first degree heart block, premature atrial beats, and, later, ST segment depression and ventricular ectopy.

Endocrine and metabolic abnormalities

Endocrine and metabolic abnormalities are quite common in patients with thalassemia major, attributable, at least in part, to chronic iron overload . Defective insulin production is a complication that occurs only during the late stages of development of iron overload.

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