

Iron Toxicity and Clinical Sequelae

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Iron overload may result from two underlying mechanisms. The first is non-transfusional loading, with increased iron absorption through the gastrointestinal tract. This includes various forms of genetic haemochromatosis, as well as acquired loading due to inappropriately high dietary iron intake. In genetically determined forms of dietary iron loading, hepcidin plays an important role, most forms being associated with inappropriately low synthesis of hepcidin by the liver. The second mechanism is transfusional iron overloading. This is seen in a variety of chronic anaemias such as thalassaemia major, sickle cell disease, myelodysplasia (MDS), and other anaemias.

Because the body has no mechanism for clearing excess iron, patients requiring repeated transfusions of red blood cells quickly develop iron loading. This can result in complications and increased risk of early death. The rate of iron loading and risk of end-organ complications varies according to condition. Iron loading rate may be estimated using the simple method, of 200mg per unit of blood. A more precise measure of transfusional loading is calculated by multiplying the volume transfused by Hct of the blood product and then by 1.08.

When iron levels in the body become too high, this leads to saturation of transferrin, and non-transferrin-bound iron (NTBI) species circulate in the plasma. Uptake of NTBI uptake, if uncontrolled, may cause excess iron loading in susceptible tissues in the liver, heart, and endocrine system. Unbound iron within cells or in plasma is labile and able to redox cycle between Fe^{2+} and Fe^{3+} , thereby generating reactive oxygen species (ROS), leading to lipid peroxidation and organelle damage that ultimately result in cell death.

The characteristic pattern of iron deposition with repeated transfusions initially involves iron storage as ferritin and haemosiderin in macrophages of the spleen, liver, and bone marrow. This is followed by iron accumulation elsewhere, mainly in hepatocytes, but also in endocrine glands, anterior pituitary, and myocardium. The brain and skeletal

muscle are spared. Deposition in the anterior pituitary in childhood results in hypogonadotropic hypogonadism with poor growth and sexual development. Myocardial iron deposition causes cardiomyopathy, the commonest cause of death in thalassaemia major. Hypothyroidism, hypoparathyroidism, and diabetes may also occur. Liver cirrhosis and hepatoma are late consequences of chronic transfusional overload. An important therapeutic objective in patients receiving regular transfusions is to control the buildup of body iron and maintain levels below those where iron can be distributed to tissues such as the heart and endocrine system.

Suggested Reading

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