

Hepcidin and other iron regulating proteins in thalassemia

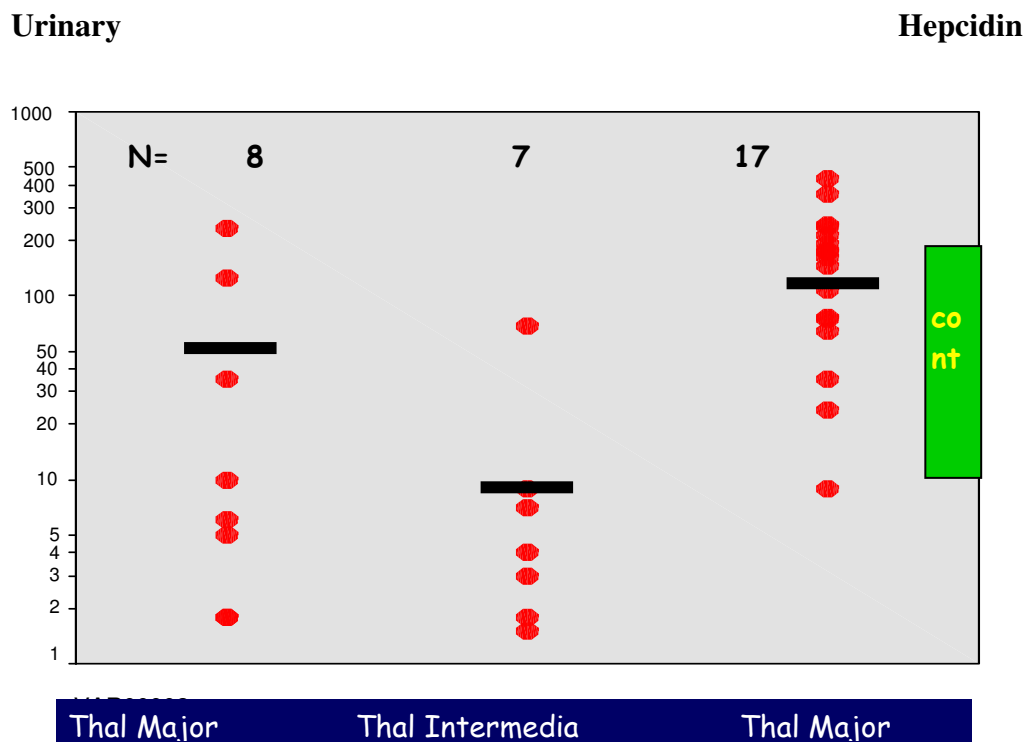
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Iron homeostasis is tightly regulated in the human body mainly by adjusting iron absorption from the gastrointestinal tract, as there are no efficient mechanisms for excretion of body excess iron. Many exciting data on the mechanisms of iron homeostasis have recently emerged.

Heme iron is absorbed from the gastrointestinal tract through the action of heme carrier protein 1, while non-heme iron is absorbed through the action of membrane transporter for bivalent iron (DMT-1) and after been reduced by duodenal cytochrome α -D (Dcytb). From the enterocytes iron enters the microvasculature through the action of ferroportin / hephaestin. Transferrin binds iron and transfers it to the target cells. Diferric transferrin forms a complex with transferrin receptor and then they internalize by endocytosis. Iron exits the endosome through DMT-1. In the cytoplasm it is either used directly especially on the mitochondria or it is stored in ferritin molecules.

The iron of the senescent erythrocytes is recycled in the macrophages. The efflux of iron from the macrophages takes place through ferroportin. Iron homeostasis is tightly balanced as iron is both an essential metal participating in many cellular functions and a potential toxic element. Hepcidin, a small polypeptide synthesized in the liver, seems to play key orchestrating role in iron metabolism. Increased hepcidin levels lead to decrease iron absorption and iron recirculation from the reticulo-endothelial system. Hepcidin production is regulated mainly by body iron stores, degree of erythropoiesis and inflammation. In patients with thalassemia massive erythroid proliferation leads to a 5-10 fold increase in erythroid iron demands leading to the paradoxical phenomenon of iron deficient erythropoiesis in the

presence of enlarged iron stores. Anemia and ineffective erythropoiesis influence hepcidin expression in an opposite way than iron overload in these patients. Hepcidin mRNA expression was found decreased in the liver of C57Bl/6 Hbb^{th3/+} mice (murine model of human thalassemia) [Adamsky et al, 2004] and urinary hepcidin was found suppressed in thalassemia major and thalassemia intermedia patients [Papanikolaou et al, 200; Kearney et al, 2005; Kattamis et al, 2005]. The ratio of urinary hepcidin over ferritin, which in normal individuals is around 1, was significantly decreased in patients with thalassemia. Of note is that, urinary hepcidin levels before and after transfusions have been shown to vary significantly with a median magnitude of 164% [Kearney et al, 2005].



We evaluated the effect of iron overload and of ineffective erythropoiesis in hepcidin expression in 19 patients with thalassemia major, by estimating liver mRNA and urinary hepcidin levels. Liver hepcidin mRNA levels correlated to hemoglobin

and inversely correlated to sTfR, EPO and non-transferrin-bound iron. They did not correlate to indexes of iron load. Urinary hepcidin levels were disproportionately suppressed in regards to iron burden.

Based on our results and the ones reported by other investigators the following hypothesis may explain the absence of correlation and iron overload in patients with thalassemia. Tissue hypoxia triggers the production of EPO, which results in pronounced erythroid proliferation accompanied by increased sTfR levels. Hypoxia and yet-undefined signals from the robust erythroid activity down-regulate hepcidin production, counteracting the up-regulating effect of iron overload. Low hepcidin levels result in increased iron absorption and greater release of stored iron into the circulation, leading to high transferrin saturation and NTBI formation.

HFE is an HLA class I atypical protein, which binds β 2-microglobulin and competes in vitro with transferrin for TFR1 binding. Mutations at the HFE gene are responsible for hereditary hemochromatosis, which is a common autosomal recessive disorder, leading to progressive iron overload caused by increased iron absorption from the gastrointestinal tract.

Co-existence of HFE mutations and thalassemia mutations may enhance iron absorption from the gastrointestinal tract aggravating iron overload. β –thalassemia heterozygous patients had increased ferritin levels when they also carry the H63D mutation of the HFE gene (Melis et al., 2002). Patients with hereditary hemochromatosis had more severe clinical phenotype when they carry also a β –thalassemia mutation (Piperno et al, 2000). On the other hand, ferritin levels in patients with either sickle/ β –thalassemia or thalassemia intermedia did not differ with the coexistence of the H63D mutation of the HFE gene (Politou et al, 2004). Unpublished data from our group showed the incidence of HFE mutations in patients with thalassemia intermedia and elevated ferritin levels were similar to the reference population. The correlation of ferritin levels and indexes of

erythropoiesis in this group of patients was statistically significant only if patients with HFE mutations were excluded from analysis. Finally, although coexistence of thalassemia major and HFE mutations did not seem to affect iron overload indexes, sporadic cases of unusually persistent severe iron overload despite intensive iron chelation in these patients have been reported.

In conclusion, iron regulating proteins seem to play a significant role in the pathogenesis of iron overload in patients with thalassemia. Altered function of HFE protein may result in unusually severe siderosis. Erythropoietic activity is the main regulator of hepcidin, while inappropriate hepcidin levels may further contribute to iron toxicity. Understanding the mechanisms of dysregulated iron homeostasis in patients with thalassemia is of great significance in planning novel treatments and preventing iron toxicity.