Expression of hepcidin in hereditary hemochromatosis: evidence for a regulation in response to the serum transferrin saturation and to non–transferrin-bound iron

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Experimental data suggest the antimicrobial peptide hepcidin as a central regulator in iron homeostasis. In this study, we characterized the expression of human hepcidin in experimental and clinical iron overload conditions, including hereditary hemochromatosis. Using quantitative reverse transcriptase–polymerase chain reaction (RT-PCR), we determined expression of hepcidin and the most relevant iron-related genes in liver biopsies from patients with hemochromatosis and iron-stain–negative control subjects. Regulation of hepcidin mRNA expression in response to transferrin-bound iron, non–transferrin-bound iron, and deferoxamine was analyzed in HepG2 cells. Hepcidin expression correlated significantly with serum ferritin levels in controls, whereas no significant up-regulation was observed in patients with hemochromatosis despite iron-overload conditions and high serum ferritin levels. However, patients with hemochromatosis showed an inverse correlation between hepcidin and the serum transferrin saturation. Moreover, we found a significant correlation between hepatic transcript levels of hepcidin and transferrin receptor-2 irrespective of the iron status.

In vitro data indicated that hepcidin expression is down-regulated in response to non–transferrin-bound iron. In conclusion, the presented data suggest a close relationship between the transferrin saturation and hepatic hepcidin expression in hereditary hemochromatosis. Although the causality is not yet clear, this interaction might result from a down-regulation of hepcidin expression in response to significant levels of non–transferrin-bound iron. (Blood. 2003;102:371-376)

Introduction

Abnormal iron homeostasis is found in many common disorders. These disorders include the iron storage disease, hereditary hemochromatosis, chronic viral hepatitis, alcoholic liver disease, chronic inflammation, or anemias with ineffective erythropoiesis such as thalassemia.1-5

Although several new elements of iron metabolism have been characterized over the past years, for most disorders the exact pathophysiology of iron overload is still unclear. It has been shown that the limiting step in iron homeostasis, the intestinal absorption of dietary ferrous Fe[II] iron, seems to be mediated by 2 iron transport proteins. Dietary Fe[II] is transported into the enterocytes by the apical transporter divalent metal ion transporter 1 (DMT1; formerly called Nramp2, DCT1).6,7 The basolateral transporter iron-regulated transporter 1 (IREG1; also known as ferroportin, MTP1) stimulates iron efflux and, therefore, might export the absorbed Fe[II] from the enterocyte into the plasma.8,10 Most absorbed plasma iron then binds to transferrin and circulates as diferric transferrin (Fe[III]2 -Tf).11,12 In addition, a small proportion of iron exported into the plasma is found as non–transferrin-bound iron (NTBI).13

Most of the absorbed iron is used in the bone marrow, where transferrin-bound iron is needed for erythropoiesis and taken up by the classical transferrin receptor 1 (TIR1) pathway. The excess iron is stored in the liver.2,11,12 This cellular iron uptake mechanism might also include the identified transferrin-receptor 2 (TIR2) that shows a high hepatic expression.14-16

The transferrin receptor pathway seems to play a central role in the pathogenesis of the most common iron storage disease, hereditary hemochromatosis. This disorder is associated with a homozygous Cys282Tyr mutation in the hemochromatosis gene HFE.17 The HFE protein is homologous to class I major histocompatibility complex (MHC) molecules and requires β2-microglobulin (β2m) for surface presentation.17,19 Experimental studies have shown that isolated overexpression of wild-type HFE leads to a decreased cellular uptake of transferrin-bound iron by binding to homodimeric TIR1 and lowering the affinity for iron-saturated transferrin.20,21 However, coexpression of both wild-type HFE and β2m has the reverse effect and results in an increase in TIR1-dependent cellular iron uptake.22

The Cys282Tyr substitution in HFE disrupts the association with β2m and, therefore, prevents surface presentation of HFE.18,19 Although the exact mechanism is still incompletely understood, the homozygous Cys282Tyr mutation is associated with an increased intestinal iron absorption, resulting in parenchymal iron overload and the clinical syndrome of hemochromatosis.23

A phenotype similar to classical hereditary hemochromatosis is also observed in individuals with mutations in TIR2 (hemochromatosis type 3)24,25 or IREG1 (autosomal dominant hemochromatosis; type 4).26,27 An identified antimicrobial peptide, named hepcidin, represents another strong candidate putatively involved in the etiology of iron overload syndromes.28-30 Such a hypothesis is supported by the observation that a hepcidin knockout leads to...
severe iron overload and a hepcidin overexpression to severe iron deficiency. In addition, hepcidin mutations were found in 2 families with a new type of juvenile hemochromatosis not linked to chromosome 1q.

Because hepcidin is induced by iron stores and inflammation, it might act as a central iron-regulatory hormone important in the pathogenesis of iron overload and the anemia of chronic disease. Therefore, the aim of the present study was to evaluate the regulation of hepcidin in response to iron loading and its role in hereditary hemochromatosis.

Materials and methods

Cells

HepG2 cells were obtained from DSMZ (Braunschweig, Germany) and grown in RPMI 1640 medium containing 10% fetal calf serum, penicillin (100 U/mL), and streptomycin (100 μg/mL). Incubation was performed with 65 μM Fe-NTA (1:1), 50 μM deferoxamine (DFO), and 2.5 g/L iron-saturated human diferric transferrin (FeIII)-Tf.

Liver biopsies

Liver biopsy samples, obtained for diagnostic purposes, were from 10 patients with iron-overloaded hereditary hemochromatosis (HH) homozygous for the Cys282Tyr mutation in the HFE gene. Samples were obtained in the fasting state at the same time of day. HepG2 cells were cultured in RPMI 1640 medium, penicillin, and streptomycin were from Life Technologies (Paisley, United Kingdom). Ferric nitrate nonahydrate, nitrilotriacetic acid disodium salt (NTA), and iron-saturated diferric transferrin were obtained from Sigma-Aldrich (Steinheim, Germany). Deroxamine was from Novartis (Nuenberg, Germany).

Determination of serum iron parameters

Serum ferritin levels were measured by electrochemiluminescence immunoassay (ECLIA) technology on an Elecsys analyzer (Roche Diagnostics, Mannheim, Germany). Transferrin saturation was calculated from serum iron, determined photometrically on an LX-Analyzer (Beckman-Coulter, Krefeld, Germany), and serum transferrin, determined by nephelometry on a BN110 analyzer (Dade-Behring, Schwalbach, Germany). Serum samples derived from 20 patients (7 with isolated liver biopsy. Samples were stored at −20°C in RNAlater solution (Ambion, Austin, TX) prior to RNA isolation. The study was approved by the local ethics committee of the University of Heidelberg. Informed consent was obtained from all patients.

Chemicals

RPMI 1640 medium, penicillin, and streptomycin were from Life Technologies (Paisley, United Kingdom). Ferric nitrate nonahydrate, nitrilotriacetic acid disodium salt (NTA), and iron-saturated diferric transferrin were obtained from Sigma-Aldrich (Steinheim, Germany). Deroxamine was from Novartis (Nuenberg, Germany).

Quantitative RT-PCR

Total RNA was isolated from liver biopsies and from cell culture using the RNAsasy Mini Kit (Qiagen, Hilden, Germany) including DNase digestion according to manufacturer’s instructions. Real-time quantification of mRNA transcripts was performed with a 2-step reverse transcriptase–polymerase chain reaction (RT-PCR) using the LightCycler system and Relative Quantification Software Version 1.0 (Roche Molecular Biochemicals, Mannheim, Germany). In a first step, DNA synthesis was performed with the First Strand cDNA Synthesis Kit for RT-PCR (Roche Molecular Biochemicals) according to manufacturer’s instructions. In a second step, transcripts of hepcidin (Hepc), transferrin receptor 1 (TfR1), transferrin receptor-2 (TfR2), iron-regulated transporter (IREG1), the IRE and non-IRE splice variant of the divalent metal-ion transporter (DMT1-IRE, DMT1-nonIRE), and ceruloplasmin (Cp) were amplified in duplicates with specific sense and antisense primers (Table 2). All transcripts were detected using SYBR Green I according to manufacturer’s instructions and were normalized to actin (β-actin) as internal control. Therefore, actin transcripts were amplified in duplicates with sense primer ACTB-502 (5'-AGG ATG CAG AAG GAG ATC ACT G' and antisense primer ACTB-302 (5'-GGG TGT AAC GCA ACT AAG TCA TAG) and detected using SYBR Green I. Hepc/Actin, TfR1/Actin, TfR2/Actin, IREG1/Actin, DMT1-IRE/Actin, DMT1-nonIRE/Actin, and Cp/Actin ratios were calculated using LightCycler Relative Quantification Software Version 1.0 (Roche Molecular Biochemicals), which provides a fully automated, efficiency-corrected, relative quantification normalized to calibrators. According to manufacturer’s instructions, calibrators for Hepc, TfR1, TfR2, IREG1, DMT1-IRE, DMT1-nonIRE, Cp, and β-actin were generated from expressed sequence tag (EST) cDNA sequences (obtained from RZPD, Berlin, Germany, by sequence analyses to verify the proposed insert). In addition, standard curves were prepared according to accurately determined dilutions of the plasmids containing cDNA sequences of Hepc, TfR1, TfR2, IREG1, DMT1-IRE, DMT1-nonIRE, Cp, and β-actin as templates. Plasmid dilutions covered a dynamic range of 5 logarithmic orders.

Statistical analysis

Statistical analysis of quantitative variables was performed using the nonparametric Mann-Whitney test. To study the linear relationship between continuous variables, Pearson correlation coefficients were calculated. P < .05 was considered significant. All statistical analyses were performed using StatView Version 5.0 (SAS Institute, Cary, NC).

Results

Transcript levels of iron-related genes in liver biopsies from patients with HH and iron-stain–negative control subjects

Hepatic expression of the iron-related genes Hepc, TfR1, TfR2, IREG1, DMT1-IRE, DMT1-nonIRE, and Cp normalized to actin transcript levels was analyzed in liver biopsy samples from patients with untreated hereditary hemochromatosis and in liver biopsy samples from control individuals negative for iron staining (Table 1). Differences between patients with HH and control subjects were found for the mean TfR1/Actin ratio. As expected, the TfR1/Actin ratio was significantly decreased in patients with untreated HH (P < .001) (Figure 1). In contrast, mean ratios (± standard deviation) for Hepc/Actin (0.53 ± 0.26 versus 0.47 ± 0.52) (Figure 1), TfR2/Actin (0.90 ± 0.37 versus 0.73 ± 0.18), IREG1/Actin × 10 (1.35 ± 0.30 versus 1.27 ± 0.26), DMT1-IRE/Actin × 10^2 (0.99 ± 0.56 versus 0.87 ± 0.49), DMT1-nonIRE/Actin × 10^2 (3.45 ± 0.72 versus 4.62 ± 1.75), and Cp/Actin (0.50 ± 0.21 versus 0.62 ± 0.24) did not differ significantly between patients with HH and control subjects.

Hepatic expression of hepcidin in relation to serum ferritin levels and the transferrin saturation

In control individuals, the hepatic Hepc/Actin ratio correlated significantly with serum ferritin levels (r = 0.713, P < .001)
transferrin saturation above 80% showed a strong inverse correlation with HRE/Actin, and 

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The mean values are shown (Hepc/Actin (Figure 2A). In contrast, an inverse correlation between the hepatic 

Hepc/Actin with iron overloaded HH (r = −0.715, P < .05) (Figure 2B). We also analyzed the association between the hepatic Hepc/Actin ratio and the serum transferrin saturation. Patients with HH with a transferrin saturation above 80% showed a strong inverse correlation between the Hepc/Actin ratio and the serum transferrin saturation (r = −0.861, P < .01) (Figure 3B); no significant correlation was found in control patients with a transferrin saturation between 4% and 51% (Figure 3A).

Because the hepatic Hepc/Actin ratio was found to correlate with serum ferritin levels and the transferrin saturation, multiple regression analyses were performed. These analyses confirmed the significant correlation between the Hepc/Actin ratio and serum ferritin levels in control individuals (P < .001) (Figure 2A) and the significant inverse correlation between the Hepc/Actin ratio and the serum transferrin saturation in patients with untreated HH (P < .05) (Figure 3B). The inverse correlation between the Hepc/Actin ratio and serum ferritin levels in patients with HH (Figure 2B) did not remain statistically significant using multiple regression analysis. As the serum ferritin levels correlate with the serum transferrin saturation in our patients with HH (r = 0.662, P < .05), the impaired Hepc/Actin ratio in patients with HH with high serum ferritin levels (Figure 2B) might be indeed related to a high transferrin saturation.

Hepatic Hepc/Actin ratio correlates significantly with the hepatic TIR2/Actin ratio

To evaluate whether the expression of hepcidin in liver correlates with the expression of iron-related genes, Hepc/Actin ratios of all patients (control subjects and patients with HH) were plotted against TIR2/Actin, Cp/Actin, IREG1/Actin, DMT1-IRE/Actin, DMT1-nonIRE/Actin, and Cp/Actin ratios. These analyses revealed a strong correlation between the Hepc/Actin ratio and the TIR2/Actin ratio (r = 0.777, P < .0001) (Figure 4). In addition, data from control subjects and patients with HH were analyzed separately. These analyses also demonstrated a significant correlation between the Hepc/Actin ratio and the TIR2/Actin ratio in control subjects (r = 0.636, P = .014) and patients with HH (r = 0.823, P < .01). However, no significant correlation between the Hepc/Actin ratio and TIR1/Actin, IREG1/Actin, DMT1-IRE/Actin, DMT1-nonIRE/Actin, and Cp/Actin ratios was found in patients with HH and control subjects.

Hepcidin is down-regulated in HepG2 cells in response to non–transferrin-bound iron but not in response to diferric transferrin

For in vitro analysis of hepcidin regulation in response to iron, HepG2 cells were incubated for 72 hours with different concentrations of non–transferrin-bound ferric iron (Fe-NTA). As demonstrated in Figure 5, the Hepc/Actin ratio decreased after incubation

Figure 2. Linear regression analysis of the correlation between the hepatic Hepc/Actin ratio and serum ferritin levels in control individuals and untreated HH patients. (A) In control individuals, the hepatic Hepc/Actin ratio correlated significantly with serum ferritin levels. (B) In iron overloaded HH patients, an inverse correlation between the hepatic Hepc/Actin ratio and serum ferritin levels was observed. * indicates statistically significant using multiple regression analysis (serum ferritin levels and serum transferrin saturation).

Figure 1. Hepatic TIR1/Actin × 10^8 and Hepc/Actin ratios in patients with HH and control individuals. The mean values are shown (± 95% confidence intervals). The TIR1/Actin × 10^8 ratio differed significantly between patients with HH and control individuals (P < .001).

Table 2. Primers for quantification of Hepc, TIR1, TIR2, IREG1, DMT1-IRE, DMT1-nonIRE, and Cp transcripts using the LightCycler RT-PCR assay

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
<th>Orientation</th>
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<tr>
<td>Cp-501</td>
<td>5′-CTG CAA CCC GAG AGA G-3′</td>
<td>Sense</td>
</tr>
<tr>
<td>Cp-301</td>
<td>5′-GGA ATA AAT AAG GAA GGG AGG G-3′</td>
<td>Antisense</td>
</tr>
<tr>
<td>TIR1-502</td>
<td>5′-TAT AGA AGG TTT GGG GGG TTG G-3′</td>
<td>Sense</td>
</tr>
<tr>
<td>TIR1-302</td>
<td>5′-GAG ACC CTA TGA ACT TTT CCC TAG-3′</td>
<td>Antisense</td>
</tr>
<tr>
<td>TIR2-501</td>
<td>5′-GAT TCA GGG TCA GGG AGG TG-3′</td>
<td>Sense</td>
</tr>
<tr>
<td>TIR2-301</td>
<td>5′-GAA GGG GCT GTG ATT GAA GG-3′</td>
<td>Antisense</td>
</tr>
<tr>
<td>IREG1-501</td>
<td>5′-CTT CAG CCT GGC AAG TTA CAT G-3′</td>
<td>Sense</td>
</tr>
<tr>
<td>IREG1-301</td>
<td>5′-TTC TCA AAG GCA TTT GAA AAG G-3′</td>
<td>Antisense</td>
</tr>
<tr>
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<td>Sense</td>
</tr>
<tr>
<td>DMT-IRE-301</td>
<td>5′-AAA TCT GAG ACT GAC TGG ACC C-3′</td>
<td>Antisense</td>
</tr>
<tr>
<td>DMT-nIRE-502</td>
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<td>Cp-301</td>
<td>5′-GCA TGA ATG TGG TGC TCT AC-3′</td>
<td>Antisense</td>
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with Fe-NTA in a concentration-dependent manner. Fe-NTA led to a significant reduction of the Hepc/Actin ratio at a minimum concentration of 10 μM (P < .01). This down-regulation of hepcidin transcripts was specific for Fe(III), as 65 μM Fe(III) sorbitol citrate produced comparable results, and 65 μM NTA had no effect on the Hepc/Actin ratio (data not shown). To evaluate whether down-regulation of hepcidin is restricted to non–transferrin-bound iron, HepG2 cells were incubated for 24 hours with 65 μM Fe-NTA or 2.5 g/L iron-saturated diferric transferrin (equivalent to 65 μM transferrin-bound Fe(III)). As a positive control, the TfR1/Actin ratio was measured. Although incubation with 50 μM deferoxamine resulted in a significant up-regulation of TR1 transcripts, incubation with 2.5 μg/L diferric transferrin and 65 μM Fe-NTA led to a significantly decreased TfR1/Actin ratio (Figure 6A). The Hepc/Actin ratio significantly decreased after incubation with 65 μM Fe-NTA, whereas incubation with 2.5 g/L diferric transferrin had no effect (Figure 6B), indicating that down-regulation of hepcidin is restricted to non–transferrin-bound iron.

**Discussion**

Previous data indicate that hepcidin mRNA increases in response to exogenous iron loading and is 2-fold up-regulated in 22-microglobulin knockout mice, a model of spontaneous iron loading resembling HH. In addition, Nicolas et al demonstrated a severe iron overload in hepcidin-deficient mice and showed that transgenic mice expressing liver hepcidin develop severe iron-deficiency anemia. Interestingly, identical findings have been recently demonstrated in patients carrying nonsense mutations in the hepcidin gene and in patients with hepatic adenomas that produce inappropriately high levels of hepcidin. Although hepcidin mutations are associated with a new type of severe juvenile hemochromatosis not related to chromosome 1q, patients with adenomas expressing hepcidin developed iron-refractory anemia that spontaneously resolved after resection of the adenomas. On the basis of these observations, hepcidin represents a strong
candidate for a regulatory peptide maintaining iron homeostasis, most likely by down-regulation of intestinal iron absorption.

As the role of hepcidin in HH is still unknown, we investigated hepatic expression of hepcidin mRNA in patients with untreated HH and iron-stain-negative control subjects using quantitative RT-PCR. In control individuals, we found a positive correlation between hepatic hepcidin expression and serum ferritin levels. Although this positive correlation suggests an association between hepcidin expression and increased iron stores, we could not demonstrate an up-regulation of hepcidin expression in patients with iron overloaded HH. However, in patients with untreated HH with transferrin saturations above 80% we found a strong inverse correlation between the hepatic hepcidin expression and the serum transferrin saturation.

The mechanism by which high levels of transferrin saturation interact with hepcidin expression is unclear. In particular, the question arises whether hepcidin is regulated in response to the serum transferrin saturation or whether decreased hepcidin expression is the primary event in HH associated with an increased transferrin saturation. In rats in which an acute-phase response was experimentally induced by injection of Freund complete adjuvant (FCA), hepcidin expression led to a decreased expression of intestinal iron transporters. Remarkably, hepcidin expression changed more rapidly than the expression of intestinal iron transporters and preceded the decline in transferrin saturation. This observation suggests that a change in hepcidin expression is a primary event in the acute-phase response and is in good agreement with the recent finding that hepcidin represents a type II acute-phase protein. However, the regulation of hepcidin expression under conditions of iron overload seems to be a complex process. In mice treated with iron-dextran, phenylhydrazine (PHZ)-induced acute hemolysis inhibits hepcidin expression despite iron overload. A similar phenomenon is seen in hypotransferrinemic hpx/hpx mice. In this murine model of hypotransferrinemia, hepcidin expression is decreased despite significant iron loading of the hepatocytes. Both conditions, acute hemolysis and hypotransferrinemia, are associated with nonphysiologic levels of NTBI. As high levels of NTBI are also found in individuals with untreated HH with transferrin saturations above 80%, a NTBI turnover might explain why we did not find an up-regulation of hepcidin expression despite iron-overload in our patients with HH.

To analyze the interaction between NTBI and hepcidin expression, we incubated human hepatoma cells with increasing concentrations of Fe-NTA, a potent NTBI donor. In these cells, Fe-NTA concentrations as low as 10 μM induced a significant down-regulation of hepcidin mRNA expression. Interestingly, similar observations have been recently made in primary hepatocytes in which iron loading with 10 μM ferric ammonium citrate resulted in a 50% decrease in hepatic hepcidin mRNA. However, we could not demonstrate an effect of iron-saturated differic transferrin on hepcidin expression in our hepatoma cells.

These observations indicate that increasing levels of NTBI induce a down-regulation of hepcidin and, therefore, might explain the following phenomenon in iron metabolism: nonphysiologic levels of NTBI distinguish diseases such as hypotransferrinemia and atransferrinemia, thalassemia, and classical HH. These diseases are also characterized by intestinal hyperabsorption of iron and severe tissue iron overload. The exact mechanism leading to intestinal hyperabsorption in these clinically and pathogenetically different diseases is not yet clear. Most researchers favor the coexistence of a store and an erythropoietic regulator of iron homeostasis. The erythropoietic regulator might play a central rule in the hyperabsorption of iron in hypotransferrinemia, transferrinemia, and thalassemia, as these diseases are characterized by anemia. However, for the hypotransferrinemic hpx/hpx mice, it has been demonstrated that severe iron overload is not solely explained by anemia and the putative erythropoietic regulator. Transferrin levels influence iron absorption (especially mucosal transfer) independently of effects on hemoglobin levels. Thus, it might be speculated that impaired serum transferrin levels and the resulting formation of NTBI down-regulate hepatic hepcidin expression followed by an increase in intestinal iron absorption. This hypothesis is supported by recent findings in hypotransferrinemic hpx/hpx mice in which hepcidin is dramatically down-regulated despite significant iron loading of the hepatocytes, whereas the basolateral iron transporter IREG1 is up-regulated and, therefore, leads to an increased intestinal iron absorption.

As mentioned earlier, the inverse correlation between hepcidin expression and the serum transferrin saturation in our patients with HH might also result from the fact that hepcidin controls transferrin saturation. Therefore, an important question would be whether hepcidin expression influences the expression of additional genes that are involved in iron homeostasis and might, therefore, modify levels of serum transferrin saturation. These iron-related genes include TJP2, REG1, DM1-IRE, DM1-nonIRE, and ceruloplasmin. In the present study, we analyzed whether the expression of hepcidin correlates with the expression of one of these genes. Interestingly, we found a strong correlation between expression of hepcidin and TJP2 in our liver biopsy samples, irrespective of the underlying disease or the iron status. The possible meaning of this correlation is unclear, as there is yet no evidence for a functional relationship between hepcidin and TJP2. However, it is noteworthy that mice with targeted mutations that abrogate expression of HFE show almost the same phenotype with increased transferrin saturations, portal hepatic iron loading, and reticuloendothelial iron sparing. Although these data suggest a close relationship between HFE and TJP2, and hepcidin in the control of iron metabolism, the underlying mechanisms have to be further elucidated.

Taken together, the studies presented here would suggest that hepcidin appears to play different roles in iron homeostasis. The correlation between serum ferritin levels and hepatic hepcidin expression at normal levels of transferrin saturation is in good agreement with previous findings that have demonstrated an up-regulation of hepcidin in response to iron storage and the acute phase. In addition, hepcidin might act as a signaling molecule that modulates intestinal absorption in response to hemolysis, hypotransferrinemia, and high levels of serum transferrin saturation, apparently by a down-regulation of hepcidin expression in response to significant levels of NTBI. These interactions could play an important role in the pathogenesis of several iron-overload disorders, including thalassemia, hypotransferrinemia, atransferrinemia, and hemochromatosis. The recent finding that hepcidin is a type II acute-phase protein also implies a central role of this antimicrobial peptide in the anemia of chronic diseases.

References

5. Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total iron burden...


