Hepcidin: another culprit for complications in patients with chronic kidney disease?

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Abstract
Hepcidin has been established as a central regulator of iron metabolism. In most patients with chronic kidney disease (CKD), serum hepcidin levels are relatively high, favoring iron sequestration in several cell types and organs and thereby leading to iron-related complications. In the absence of overt inflammation, serum hepcidin has been found to be most closely associated with serum ferritin in healthy subjects and in CKD patients. Intestinal iron absorption is tightly regulated by both iron stores and hepcidin. The expression of the mammalian iron exporter, ferroportin (FPN), limits the growth of intracellular bacteria by depleting cytosolic iron. An upregulation of hepcidin could diminish FPN and favor bacterial growth. Of note, in patients with hyperferritinemia impaired hepcidin expression caused by a mutation in the hemochromatosis gene associates with an attenuation of atherosclerosis. Thus, hepcidin might accelerate atherosclerosis by preventing iron exit from macrophages or other cells in the arterial wall. High hepcidin levels have also been found to be linked to good erythropoiesis-stimulating agents (ESAs) response, in conjunction with the strong hepcidin–ferritin correlation. Finally, hepcidin may also play a significant role by itself in the pathogenesis of CKD complications associated with disturbed iron metabolism, i.e. unrelated to ESA hyporesponsiveness, such as bacterial infections and atherosclerosis.

Keywords: anemia; cardiovascular disease; hemochromatosis; hepcidin; iron metabolism; infection

Introduction
Iron is critical for living organisms. It is essential for many metabolic processes, including oxygen transport, electron transport and DNA synthesis [1–4]. However, the concentration of free iron must be reduced to a minimum to prevent tissue damage from free radical formation (i.e. hydroxyl radicals) as part of the pathologic consequences of iron overload [5, 6]. Thus, iron balance in the body and in each cell must be tightly regulated.

Hepcidin is a central regulator of body iron metabolism [7]. It limits iron absorption from the intestine and release from macrophages by controlling the synthesis and activity of several iron transport proteins. Therefore, hepcidin levels are tightly regulated by several factors, such as changes in body iron storage, inflammation, erythropoiesis and hypoxia [7, 8].

From a pathophysiological point of view, hepcidin has been shown to play a significant role in the anemia of chronic disease (ACD), which is characterized by decreased serum iron levels and iron-binding capacity (via transferrin), increased serum ferritin and the accumulation of iron in reticuloendothelial cells, mainly macrophages, indicating impaired mobilization of iron from its storage sites [9, 10]. In inflammatory and infectious disorders and neoplastic diseases, hepcidin is ultimately responsible for limiting circulating levels of iron or sequestering it from microorganisms and rapidly growing cancer cells for the purpose of self-defense.

However, in chronic kidney disease (CKD), which is a chronic inflammatory state, hepcidin-induced iron sequestration probably plays a crucial role in the pathogenesis of several complications, such as cardiovascular disease, infections and hyporesponsiveness to erythropoiesis-stimulating agents (ESAs). This review is intended to provide an in-depth analysis of the effects of excessive circulating hepcidin levels on iron maldistribution in the organism and its consequences for patients with CKD.

Hepcidin and iron balance
In healthy individuals, more than two-thirds of the total body iron content is accounted for by hemoglobin in mature erythrocytes and in their precursors. Approximately 20–25 mg of iron is needed every day to sustain the hemoglobinization of new erythrocytes. Most of the iron used for hemoglobin synthesis comes from the recycling of iron from senescent or damaged erythrocytes by macrophages,
while only a small fraction (about 1–2 mg of iron) is provided by intestinal iron absorption [11].

Cellular iron metabolism is coordinately controlled by the regulation of proteins for iron acquisition [transferrin receptor 1 and divalent metal transporter 1 (DMT1)], and for iron export [ferroportin (FPN)]. Hepcidin reduces the protein levels of both DMT1 and FPN. The resulting decrease in plasma iron is due to reduced iron absorption from the intestine, impaired iron recycling from macrophages and decreased mobilization of stored iron from hepatocytes [12, 13]. Thus, the regulation of body iron stores by hepcidin functions as a feedback mechanism that allows sufficient iron to enter the plasma when the demand is high, especially for erythropoiesis, and otherwise to limit iron intake/release when iron stores are adequate.

Transgenic mouse studies have provided further evidence for a major role of hepcidin in the regulation of iron metabolism. Thus, experimental overexpression of hepcidin caused a decrease in body iron levels with severe microcytic hypochromic anemia [14]. In contrast, hepcidin knockout mice developed a massive iron overload [15]. In humans, hepcidin insufficiency can also arise from loss-of-function mutations in the human hepcidin gene, HAMP [16]. However, the majority of patients with the clinical syndrome of genetic hemochromatosis are homozygous for a Cys282Tyr (C282Y) mutation in the human hemochromatosis gene, HFE [17, 18]. Recent studies have suggested that hepcidin is a moderator gene in genetic hemochromatosis. Hepcidin messenger RNA (mRNA) expression is reduced in patients with genetic hemochromatosis and in HFE knockout mice [19, 20]. In addition, constitutive expression of hepcidin has been shown to prevent iron overload in HFE knockout mice [21].

Regulation of hepcidin synthesis

The human hepcidin gene HAMP, which is located on chromosome 19 (19q13), encodes a precursor protein, the 84-amino-acid preprohepcidin. This peptide contains a typical N-terminal 24-amino-acid endoplasmic reticulum-targeting signal sequence and a consensus furin-type propeptide cleavage site. The functional hepcidin molecule is derived from a two-step conversion of preprohepcidin. An N-terminal cleavage of a 24-amino-acid signal peptide yields prohepcidin, which is followed by a second cleavage of a 35-amino-acid peptide to yield the active 25-amino-acid hepcidin [22, 23]. Although a substantial amount of prohepcidin is present in plasma, recent observations have confirmed that prohepcidin lacks biological activity unless it is fully maturated by a furin-dependent process to yield the bioactive 25-amino-acid peptide [24]. In addition, two hepcidin isoforms, hepcidin-20 and -22, have been shown to be present in the serum, but their role in iron homeostasis is unclear [25].

Because hepcidin expression is largely restricted to the liver, the hepatocyte is believed to be the main site of action of the regulatory stimuli. However, it is unclear how hepcidin responds to changes in the body’s iron levels. Furthermore, it is also unclear whether the hepatocyte iron concentration itself plays a primary role in this response or whether an external signal is involved. In addition to being produced by the liver, hepcidin is believed to be produced by macrophages [26], fat cells [27] and the heart [28].

Hepcidin is regulated by a large variety of factors, such as hemojuvelin, bone morphogenetic protein 6, transferrin receptor-2, transferrin, the HFE gene, hypoxia, inflammation and erythroid factors [29]. The mechanisms involved in the regulation of hepcidin expression have been reviewed in recent articles [3, 7, 8, 30]. It is clear that further investigation is needed to fully elucidate the regulation of hepcidin synthesis.

Cellular actions of hepcidin

Hepcidin binds to FPN, the only known cellular iron exporter, which results in the internalization of FPN and its degradation after ubiquitination. This hepcidin binding blocks cellular iron export [13, 31, 32]. The cellular-level response of hepcidin has been elegantly explained by Nemeth et al.: the addition of hepcidin to a stable cell line (HEK293-FPN) expressing mouse FPN with a C-terminal green fluorescent protein (FPN-GFP) alters the distribution of FPN-GFP on the cell surface by moving it to punctate intracellular vesicles. Concentrations of hepcidin as low as 0.1 μM (300 ng/mL) induce FPN internalization within 1 h, whereas concentrations that are 10 times lower require a 3-h time span for FPN internalization [13] (Figure 1A). Similarly, in the human monocytic cell line THP-1, which is a macrophage cell model, hepcidin significantly decreased FPN protein levels with an IC50 (half maximal inhibitor concentration) of 0.1–0.3 μM (300–900 ng/mL) [33]. These values are consistent with estimates of plasma hepcidin concentrations based on urinary hepcidin excretion in conditions of iron loading or inflammation [10, 34] and are comparable to circulating hepcidin levels in humans [35, 36].

Brasse-Lagnet et al. [12] showed that an acute increase in medium hepcidin concentration reduced intestinal iron absorption in vitro through ubiquitin-dependent proteasome degradation of DMT1, without altering FPN protein content, using experimental models of cultured intestinal cells and isolated duodenal segments (Figure 1B). A half-maximum effect of hepcidin-25 on iron transport was observed at 75–100 nM (225–300 ng/mL) [33]. This pathway appears to have a similar sensitivity to changes in hepcidin concentration as the FPN pathway in macrophages.

Recent histological observations may explain why the enterocyte FPN protein is not affected by hepcidin. D’Anna et al. [37] demonstrated that healthy mice had a mainly supranuclear expression of FPN in enterocytes, with weak basolateral expression, whereas in mice with phenylhydrazine (PHZ)-induced anemia, enterocyte FPN expression was detected mainly at the basolateral membrane (Days 4 and 5). In an iron-replete status, FPN proteins mainly exhibited intracellular localization, and FPN-hepcidin binding was prevented. In PHZ-treated anemic mice, hemopoietic activity is enhanced and hepcidin downregulated, which would leave FPN abundance at the basolateral membrane unchanged and consequently facilitate intestinal iron absorption [38].
Hepcidin binding is prevented. In iron-replete condition, FPN protein mainly exhibits intracellular localization, and FPN–DMT1 and thereby limit iron uptake from the intestine. In iron-replete of excessive hepcidin levels would lead to immediate degradation of proteasomal degradation. Even if the iron transport proteins were synthesized in sufficient amounts and present on the cell membrane, the presence of proteasomal degradation. While a high concentration of hepcidin will acutely decrease iron transport proteins, a lower concentration may affect DMT1 and FPN abundance more slowly (Figure 1). Therefore, it is reasonable to assume that even relatively low concentrations of hepcidin may exert a prolonged effect on iron metabolism, with continuous exposure of cells to hepcidin resulting in a consistent downregulation of FPN and DMT1.

FPN was originally isolated from the duodenal mucosa, where it has a high expression. Another site of high FPN expression is the macrophage, particularly those that reside in the red pulp of the spleen, the liver (Kupffer cells) and the placenta. Moderate FPN expression is found in the kidney, lung and brain, where FPN proteins have been located in neurons and oligodendrocytes of the white matter. In fact, FPN is expressed in most cells. The relationship between FPN and hepcidin may inform as to whether hepcidin causes iron accumulation in such cells. Further investigation is needed to clarify this claim, in particular in iron-overloaded cells jeopardized by oxidative stress.

Measurement of hepcidin

An accurate assessment of hepcidin concentrations in serum should improve our understanding of iron metabolism disorders and allow hepcidin to become a useful tool in the differential diagnosis and clinical management of these disorders.

Despite growing interest in the regulation of iron metabolism by hepcidin, few investigative tools are currently available. The assays for hepcidin-25 can be principally divided into radioimmunoassays, enzyme-linked immunosorbent assays (ELISAs) and mass spectrometry methods. Immunoassays detect more than the biologically active hepcidin-25, namely also hepcidin-20 and -22, whereas mass spectrometric assays are specific for hepcidin-25 but are labor intensive and require costly and sophisticated instrumentation. Thus, although mass spectrometry is more accurate, it is currently less practical for routine clinical use than immunoassays for the determination of circulating hepcidin-25 concentrations.

Determinants of hepcidin levels in CKD

Regarding the determinants of serum hepcidin concentration in the circulation, it appears that serum ferritin has the highest predictive value, as compared to other serum parameters. Several recent observations, including a recent

These tissue-specific differences are compatible with specific interactions between hepcidin and iron transport proteins in each cell type involved in iron homeostasis, in particular macrophages and duodenal enterocytes, in line with previous studies. By investigating the in vitro effect of hepcidin on the THP-1 monocyte/macrophage cell line and the intestinal epithelial Caco-2 cell line as well as its in vivo effects on mice, different modes of action have been demonstrated in macrophages and enterocytes. In response to a hepcidin challenge in vitro, the FPN expression of macrophages was reduced acutely, while it remained unaltered in intestinal epithelial cells over the same time scale. When hepcidin was injected into mice in vivo, the rapid effects of hepcidin were again absent at the level of the duodenum, but present at the level of the recycling macrophage, with resulting downregulation of FPN protein levels and possible hypoferremia.

A prolonged decrease in serum iron levels in response to human synthetic hepcidin was demonstrated in the mouse in vivo, due to the long half-life of circulating hepcidin. Hepcidin reduced the abundance of iron transport proteins by proteasomal degradation in a dose-dependent manner. The protein abundance corresponds to a balance between synthesis and degradation. While a high concentration of hepcidin will acutely decrease iron transport proteins, a lower concentration may affect DMT1 and FPN abundance more slowly (Figure 1). Therefore, it is reasonable to assume that even relatively low concentrations of hepcidin may exert a prolonged effect on iron metabolism, with continuous exposure of cells to hepcidin resulting in a consistent downregulation of FPN and DMT1.
The relationship between serum hepcidin and inflammatory markers observed in general population is less clear in patients with CKD. Although hepcidin expression was initially found to be induced by IL-6 in inflammatory conditions [34] and some studies reported a relationship between hepcidin and C-reactive protein (CRP) in patients on maintenance hemodialysis (MHD) [47, 48], no association with CRP and IL-6 was observed in other studies in patients with CKD [46, 49, 50]. In a personal study in patients on MHD, we examined a possible relationship between serum hepcidin-25 levels and IL-6 after separation of the patients by high sensitivity C-reactive protein (hs-CRP) levels into two groups [35]. In the patients with hs-CRP levels <0.3 mg/dL, serum IL-6 and tumor necrosis factor (TNF)-α levels were significantly higher than in healthy volunteers, but the values were not correlated with hepcidin. However, both IL-6 and ferritin were selected as significant determinants of hepcidin by multivariate analysis in the group of patients with higher hs-CRP levels (≥0.3 mg/dL). We therefore assume that the expression of hepcidin-25 is associated with serum IL-6 only in the presence of significant inflammation. This hypothesis is supported by data from Tomosugi et al. [51], who demonstrated an association between serum IL-6 and hepcidin-25 concentrations in patients with high-grade inflammatory diseases but not in stable subjects on MHD.

**Hepcidin and intestinal iron absorption**

The link between iron absorption and hepcidin in humans was examined in healthy non-pregnant women using radio-labeled iron. Concomitantly, serum hepcidin was measured by ELISA, ranging from 1.5 to 248.5 ng/mL. Intestinal iron absorption from supplemental and food-based non-heme iron sources was inversely associated with serum hepcidin levels in these iron-replete healthy women [52].

Previously, several groups had studied the relationship between iron metabolism and intestinal iron absorption in normal volunteers. A highly significant inverse correlation between iron stores as reflected by serum ferritin and the absorption of non-heme iron was found consistently [35, 54]. Geometric mean non-heme iron absorption was 1.9% in healthy subjects with serum ferritin values >100 ng/mL [53]. With a serum ferritin down to 10 ng/mL in the presence of iron deficiency, a 10-fold rise in non-heme iron absorption occurred. Hallberg et al. also demonstrated that, in normal subjects with a serum ferritin concentration >60 ng/mL, iron absorption was within the range needed to meet basal requirements. This means that excessive iron accumulation in body stores would not occur via the absorption of non-heme iron from the diet [55]. A similar relationship was also found in patients with MHD and in healthy subjects [54, 56, 57]. (Figure 2).

In normal subjects, high serum ferritin values observed in iron-replete men, above the critical range of 60 ng/mL, were not due to absorption of non-heme iron but probably absorption of heme iron [55]. Despite the sharp decrease in the assimilation of non-heme iron with storage iron repletion, heme iron absorption appears to be relatively independent of body iron stores [53]. In patients with ACD or CKD, high serum ferritin values can also be linked to acute hemolysis, inflammation, hepatic dysfunction and intravenous iron administration.

From the relationship between serum ferritin, percentage of non-heme iron absorption, and serum hepcidin level, we estimated the range of serum hepcidin-25 level that could block intestinal iron absorption (Figure 2). Thus, serum ferritin levels of 40–130 ng/mL, at which the intestinal absorption of non-heme iron will be less than 2–5%, and will not increase body iron stores, may correspond to hepcidin-25 levels of 10–25 ng/mL [35]. Of note, the range of serum hepcidin-25 levels able to affect iron metabolism in terms of effective downregulation of non-heme iron absorption appears to be similar to the levels at which hepcidin-25 induces intestinal DMT1 and macrophage FPN degradation after a long-term exposure.

**Hepcidin and infection**

Hepcidin was first isolated as a peptide and named LEAP-1 (liver-expressed antimicrobial peptide, from human blood) [58], whereas the same peptide was isolated from human urine as hepcidin (hepatic bactericidal protein) [22]. The synthesis of hepcidin is induced by inflammation [10].

Hepcidin is active against Gram-negative (e.g. *Bacillus subtilis*) and Gram-positive (e.g. *Neisseria cinerea*) bacteria
and yeasts (e.g. *Saccharomyces cerevisiae*) [58]. While its antibacterial and antifungal activities are in the concentration range of 10–30 µM, its urinary and plasma concentration is in the 3–30 nM range. Thus, it is doubtful that hepcidin can exert antimicrobial activity in urine or plasma [59].

However, a major function of hepcidin, which is the downregulation of FPN, the only known cellular iron exporter, could be to potentiate the growth of intracellular pathogens or invading organisms. In an investigation of the influence of macrophage FPN and its ligand hepcidin on intracellular *Salmonella* growth, elevated FPN expression inhibited bacterial multiplication, whereas hepcidin-induced FPN degradation enhanced it [60]. These findings indicate an important role for FPN in controlling the growth of *Salmonella* inside cells and suggest that diminished FPN expression and possibly iron overload states in general may explain the susceptibility of phagocytosed cells to intracellular pathogens [60–62].

Similarly, Paradkar et al. demonstrated that macrophages that were isolated from flatiron mice, a strain heterozygous for a loss-of-function FPN mutation with impaired FPN activity, exhibited increased susceptibility to intracellular bacterial growth. The addition of hepcidin to infected macrophages (with full function) from wild-type mice also enhanced the intracellular growth of these pathogens. In contrast, macrophages that expressed FPN on their cell surface were able to limit intracellular growth of these bacteria [63].

The upregulation of hepcidin expression in response to inflammation and infections is associated with several advantages but also negative effects. The upregulation is beneficial for an organism during the course of an infection because the sequestration of iron in cellular stores makes iron less accessible for invading microorganisms in the extracellular space to use. However, this also has a deleterious effect on intracellular pathogens residing in the macrophages. In addition, iron sequestration could contribute to the development of ACD. This pathological situation may occur in CKD patients with infections and renal anemia, when receiving massive iron supplementation.

From these results, a normal expression of the mammalian iron exporter FPN can be assumed to limit the growth of intracellular bacteria by depleting cytosolic iron. Although the upregulation of hepcidin in response to infection has been generally considered to be protective, the above observations suggest that the opposite may be true for the growth of intracellular pathogens (Figure 3A).

The risk of potentiating bacterial growth by increasing the amount of unbound iron in the body or macrophages by highly expressed hepcidin has not been shown to adversely affect patient outcomes: however, existing data regarding the exacerbation of infection after the administration of intravenous iron is concerning. Further investigation should be necessary for clarifying the relation between hepcidin-25 and the risk of bacteremia.

**Hepcidin and cardiovascular disease**

The experimental observation that iron increases hydroxyl radical formation and oxidative stress led to the hypothesis that iron accumulation in vascular cells or in macrophages in the vascular wall might contribute to endothelial dysfunction and atherosclerosis [64, 65]. Several reports have demonstrated high iron content in atherosclerotic lesions [66, 67]. However, the relationship between iron content and the progression of atherosclerotic diseases remains controversial. Several large epidemiological studies that were designed to evaluate this association yielded conflicting results [68–74].

Studies examined arterial alterations in hemochromatosis as a human model of the effect of marked iron overload on cardiovascular diseases and atherosclerosis [75]. Hereditary hemochromatosis is a genetic disorder that leads to excessive iron accumulation in various body tissues. In 1996, Feder et al. discovered that homozygosity for a C282Y mutation in the *HFE* gene was the principal cause of hereditary hemochromatosis in individuals of northern European descent [18]. An association between iron storage estimated by serum ferritin levels and cardiovascular
disease was not apparent in these patients. Coronary artery disease, stroke and peripheral artery disease were not increased in hemochromatosis, and they even appeared to have a lower probability of occurring than in control populations, as assessed by epidemiologic studies and autopsy studies [76–79]. However, in most of these studies, the exact mutation that caused hemochromatosis was not examined in each patient, with some of the studies being completed before the HFE mutation was identified.

The Atherosclerosis Risk in Communities (ARIC) study, which is a population-based cohort that found a rate of 0.42% C282Y homozygosity, demonstrated that similar rates of all-cause mortality, cardiovascular disease and diabetes across HFE genotypes [78]. In patients with clinical and ultrasonographic evidence of non-alcoholic fatty liver disease (NAFLD), vascular damage was analyzed using common carotid artery intima-media thickness measurements [80]. These patients were stratified by serum ferritin levels and HFE mutations. The prevalence of carotid plaque was significantly higher in patients with hyperferritinemia and normal HFE than in all the other groups. Thus, HFE mutations have not been convincingly associated with vascular damage and might attenuate atherosclerosis or carotid plaques even in the presence of hyperferritinemia [80].

Recently, the association between the HFE mutation and a lower hepcidin expression has been clarified. In patients with adult-onset HFE-related diseases, both hepatic expression and serum levels of hepcidin were low [19, 81], indicating that reduced hepcidin expression might be a central pathogenic factor in classic hemochromatosis. Because the disease is associated with increased transferrin saturation, hepatic iron loading and reticuloendothelial iron sparing (i.e. within Kupffer cells and macrophages), it is reasonable to assume that macrophages in atherosclerotic lesions are also exempt from the hepcidin-induced iron sequestration process under the condition of low serum hepcidin levels [81]. The same could be true for vascular endothelium since we have previously demonstrated that FPN is also expressed in human umbilical vein endothelial cells [82]. Therefore, regarding arterial disease, the reduction of hepcidin in HFE mutants may cause a decreased retention of iron by macrophages and vascular cells or else a more rapid clearance of iron from arterial lesions in patients with an HFE mutation.

In the NAFLD studies described above, the authors demonstrated that hepcidin-25 levels were higher only in patients with hyperferritinemia and normal HFE levels compared to all other groups, and hepcidin-25 was demonstrated to be independently associated with carotid plaques by multivariate analysis [80]. Thus, these data support the controversial hypothesis that decreased hepcidin favors atherosclerosis by preventing iron accumulation in macrophages or vascular cells in the arterial wall [83]. (Figure 3B).

We also recently demonstrated that serum levels of both hepcidin and TNF-α were independently associated with brachial-ankle pulse wave velocity, a surrogate for arterial disease and arterial stiffness in MHD patients. These data suggested that microinflammation and iron metabolism might synergistically affect the structural integrity of the arterial wall and induce a decrease in arterial compliance [84].

**Hepcidin and anemia management**

Several in vivo and in vitro studies have defined the effects of erythropoiesis and erythropoietin, respectively, on hepcidin expression [85–87]. In mice treated with phlebotomy, anemia or epoetin-induced suppression of hepcidin also required an increase in erythropoiesis [85]. However, in the clinical situation of CKD patients, the place of hepcidin regulation with respect to anemia management remains controversial.

Hepcidin has been suspected of contributing to ESA resistance through iron metabolism and of having a direct inhibitory effect on erythroid progenitor proliferation and survival [88]. However, the relationship between hepcidin-25 and ESA dose or resistance index may seem paradoxical. In a study done in MHD patients, high hepcidin levels were related to low ESA dose, suggesting that erythropoietin suppresses hepcidin levels [50]. An inverse correlation has also been reported between hepcidin levels and darbepoetin resistance [36]. These inverse correlations could reflect the link between iron stores and ESA response because of the strong hepcidin–ferritin relationship since Kalantar-Zadeh et al. [89] demonstrated that higher iron stores or availability were associated with improved ESA responsiveness. These data are also consistent with the conclusion drawn from the Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) I study that patients who received IV iron had a greater increase in their hemoglobin and response to ESA than patients who did not receive iron supplementation [90].

**Strategies for controlling serum hepcidin levels**

Controlling hepcidin levels might be able to overcome ACD during inflammatory conditions and attenuate several serious complications of CKD. Recently, preliminary experience with anti-hepcidin therapy was reported. Hepcidin mRNA suppression or antibody-mediated neutralization was able to overcome ACD and increase serum iron and hemoglobin levels in a mouse model of ACD [91]. Thus, a therapeutic decrease in hepcidin synthesis, as exemplified by the use of anti-hepcidin antibody, may be capable of redistributing iron from its storage sites, correcting impaired intestinal iron absorption and increasing iron availability for erythropoiesis, which may attenuate the iron-sequestration related complications.

**Conclusion**

The association of serum hepcidin with complications of CKD such as infections and atherosclerosis confers this recently discovered hormone a major role in the regulation of iron metabolism. In states of hyperferritinemia, there is a linear relationship between serum ferritin and hepcidin.
The improved ESA response after iron repletion in patients with CKD leads to accelerated erythropoiesis and anemia correction. However, the concomitant increase in serum hepcidin levels could be responsible for a higher frequency in comorbid events. The diverse iron regulatory functions of the acute phase protein hepcidin and its possible role in the disturbances of iron metabolism in CKD patients have led to the hypothesis that hepcidin is a key to understanding the complex relationship of renal anemia and its correction with cardiovascular disease. Further investigation into the role of hepcidin in the cellular handling of iron and its maldistribution across the organism in a wide array of diseases should help to define more precisely the place of this hormone in the initiation or aggravation of several comorbidities observed in patients with CKD.

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