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THE ROLE OF HEPCIDIN IN THE DEVELOPMENT OF IRON DEFICIENCY ANEMIA IN CHRONIC DISEASES

Rahimjanova Maftuna Ayubxon qizi
Impuls Medical Institute
Email: mraximjonova009@gmail.com
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Abstract: Hepcidin is a 25-amino-acid peptide hormone encoded by the HAMP gene and is the central regulator of iron homeostasis in the body. This article provides a comparative analysis of the role of hepcidin in the development of iron deficiency anemia and anemia of inflammation in four major chronic diseases — chronic kidney disease (CKD), rheumatoid arthritis (RA), chronic heart failure (CHF), and oncological diseases — based on real statistical data from published studies (mean values, standard deviations, p-values, correlation coefficients). The results reveal the disease-specific behavior of hepcidin: it increases in conditions where inflammation predominates and decreases in conditions where the erythropoietic drive predominates.

Keywords: hepcidin, ferroportin, iron deficiency anemia, anemia of inflammation, chronic diseases, IL-6, erythroferrone.

Introduction

Anemia is a global public health problem and one of the most common complications in patients with chronic diseases. Anemia of inflammation (AI), also known as anemia of chronic disease (ACD), is the second most common type of anemia in the world after iron deficiency anemia (IDA) and is most frequently observed in hospitalized and chronically ill patients (Weiss G, Ganz T, Goodnough LT. Blood. 2019;133(1):40-50). According to this source, up to 40% of all anemias in the world are anemia of inflammation or combined anemias in which AI plays a significant role, together affecting more than 1 billion people.

The discovery of hepcidin in 2000–2001 radically changed the understanding of iron metabolism. Park and colleagues (Park CH, Valore EV, Waring AJ, Ganz T. J Biol Chem. 2001;276(11):7806-7810) isolated an antimicrobial peptide synthesized in the liver from human urine and named it “hepcidin” (hepar — liver, -cidin — bactericidal activity). Pigeon and colleagues (J Biol Chem. 2001;276(11):7811-7819) identified hepcidin mRNA in mice as a transcript that increased in the liver during iron overload and showed that it also increased during inflammation. In 2004, Nemeth and colleagues (Science. 2004;306(5704):2090-2093) elucidated the mechanism of action of hepcidin: hepcidin binds to ferroportin, the only known cellular iron exporter, and induces its internalization and lysosomal degradation, thereby closing the homeostatic loop of iron homeostasis.

The aim of this article is to provide a comparative analysis of the role of hepcidin in the development of iron deficiency anemia and anemia of inflammation in four major chronic diseases, based on real statistical data from published studies.

Materials and Methods

Study design. This work is an integrative review (narrative review) based on a systematic literature analysis, supplemented with elements of a meta-analytic approach. The study covers peer-reviewed scientific sources published between 2003 and 2025; classic fundamental works (2001–2004) are also included.

Search strategy. The PubMed/MEDLINE, NCBI PMC, Blood (American Society of Hematology), New England Journal of Medicine, Haematologica, European Heart Journal, Kidney International, Nature Genetics, and Annual Review of Medicine databases were searched using the following keywords: “hepcidin”, “ferroportin”, “anemia of chronic disease”, “IL-6”, “BMP/SMAD”, “chronic kidney disease”, “rheumatoid arthritis”, “heart failure”, “cancer-related anemia”, “erythroferrone”.

Inclusion criteria. Studies were included if they: (1) quantitatively measured serum or urinary hepcidin levels; (2) reported the number of patients (n), mean values, standard deviations, or medians; (3) performed statistical analysis (t-test, ANOVA, Mann–Whitney U, Kruskal–Wallis, correlation analysis, multivariate regression, Cox proportional hazards model).

Statistical indicators. For between-group comparisons, p-values, correlation coefficients (Pearson r or Spearman ρ), hazard ratios (HR), odds ratios (OR), and confidence intervals (95% CI) were analyzed. A value of $p < 0.05$ was considered statistically significant. The dependence of hepcidin measurement on assay type (ELISA, LC-MS/MS, WCX-TOF mass spectrometry) was taken into account separately.

Results

1. Molecular biology of hepcidin and its role in iron homeostasis

The mature biologically active hepcidin is a 25-amino-acid peptide encoded by the HAMP gene (chromosome 19q13.1). It is synthesized as an 84-amino-acid preprohepcidin; the signal peptide is cleaved to form the 60-amino-acid prohepcidin, and then, under the action of furin/proprotein convertase, the 25-amino-acid mature hepcidin. Its structure is a β-sheet (hairpin) shape stabilized by 4 disulfide bridges formed by 8 cysteine residues (Hunter HN, et al. J Biol Chem. 2002;277:37597-37603); the N-terminal residues are required for binding to ferroportin.

Hepcidin binds to ferroportin on macrophages, duodenal enterocytes, and hepatocytes, inducing its degradation through JAK2-mediated phosphorylation and ubiquitination; as a result, intestinal iron absorption, recycling of erythrocyte iron from macrophages, and mobilization of iron from liver stores cease.

In healthy adults, the serum hepcidin-25 level is approximately in the range of 1–20 ng/mL. In the largest reference study conducted in the general population by Galesloot and colleagues (Blood. 2011;117(25):e218-e225, n=2998), median values were distributed as follows (Table 1).

Table 1. Reference values of serum hepcidin-25 in the general population (Galesloot 2011, n=2998)

Group	Median hepcidin (nM)	Note
Men	7.8	Stable across age
Premenopausal women	4.1	Lowest value
Postmenopausal women	8.5	Higher than premenopausal

Hepcidin is strongly correlated with ferritin: log-β was 0.78 (95% CI 0.74–0.82) in men and 0.83 (0.78–0.88) in women.

2. Signaling pathways regulating hepcidin synthesis

Hepcidin expression is regulated by three main stimuli.

BMP/SMAD pathway (iron-dependent, positive): Bone morphogenetic protein BMP6 and the co-receptor hemojuvelin (HJV) bind to BMP receptors, inducing phosphorylation of SMAD1/5/8 and formation of a complex with SMAD4; this complex translocates to the nucleus

and activates hepcidin transcription through BMP-response elements in the HAMP promoter. The HFE and TfR2 proteins also modulate this pathway.

IL-6/STAT3 pathway (inflammation-dependent, positive): Nemeth and colleagues (J Clin Invest. 2004;113(9):1271-1276) demonstrated that IL-6 is the cytokine "necessary and sufficient" for hepcidin induction during inflammation. Infusion of IL-6 into healthy volunteers significantly increased urinary hepcidin excretion within 2 hours ($p<0.001$, RM ANOVA) and significantly decreased serum iron and transferrin saturation (both $p<0.001$). After IL-6 binds to its receptor, it acts on the STAT3-response element in the HAMP promoter through JAK1/2 → STAT3 phosphorylation.

Erythroferrone (ERFE) — an erythropoietic regulator (negative): Kautz and colleagues (Nat Genet. 2014;46(7):678-684) found that ERFE, produced by erythroblasts under the action of erythropoietin, suppresses hepcidin. ERFE is produced through an EPO/STAT5-dependent mechanism, acts directly on the liver, and lowers hepcidin by sequestering BMP2, BMP6, and the BMP2/6 heterodimer. This very mechanism explains the decrease in hepcidin when the erythropoietic drive predominates even in the presence of inflammation — this is the molecular basis of the clinical paradoxes.

Hepcidin in chronic kidney disease (CKD)

The prevalence of anemia in CKD increases with disease stage. According to NHANES data (2007–2010), anemia is twice as common in CKD patients compared with the general population (15.4% vs 7.6%), increasing from 8.4% in stage 1 to 53.4% in stage 5 (Stauffer ME, Fan T. PLoS ONE. 2014;9(1):e84943). More than 90% of dialysis patients are anemic. The main statistical results are presented in Table 2.

Table 2. Hepcidin and iron parameters in CKD patients (case-control)

Parameter	CKD (stages 2–4)	Control	p
Hepcidin (pg/mL)	39.8 ± 23.1	13.7 ± 4.8	<0.001
Ferritin (ng/mL)	246 ± 128	160 ± 61	<0.001
Serum iron (μg/dL)	12.38 ± 3.1	118 ± 33.5	<0.001
TIBC (μg/dL)	347 ± 109	385 ± 62	0.004

Additional: in hemodialysis (n=42), hepcidin was 18.2±2.8 vs 8.5±2.3 ng/mL (P=0.000). In non-dialysis CKD (n=505, LC-MS/MS), median hepcidin was 15.4 ng/mL.

In correlation analysis, hepcidin was strongly positively associated with ferritin ($P<0.0001$), with TSAT ($P=0.0217$), and negatively with erythropoietin ($P=0.0258$); no correlation with eGFR was found. In hemodialysis patients with hepcidin-25 ≥131 ng/mL, poorer survival was observed over 24 months of follow-up (Log-rank $P=0.0017$); for each 10 ng/mL increase, the HR for all-cause mortality was 1.225 (95% CI 1.085–1.382, $P<0.001$).

Hepcidin in rheumatoid arthritis (RA)

The prevalence of mild anemia in RA patients varies from 33% to 60% (Wilson A, et al. Am J Med. 2004). In an Egyptian cohort (n=51), ACD was found in 37.3%, IDA in 11.8%, and combined anemia in 17.6%; hepcidin was higher in ACD ($P\leq0.001$), strongly positively correlated with ferritin ($P<0.001$), and negatively correlated with hemoglobin, serum iron, and TIBC. In a study in The Journal of Rheumatology (n=60), hepcidin was higher in anemic RA patients than in controls ($p<0.001$); 40 of 60 patients (66.6%) were anemic. Treatment effect: in Castleman disease, hepcidin decreased from 52 ng/mL to 7.7 ng/mL over 12 months with tocilizumab ($P<0.01$) (Song SN, et al. Blood. 2010).

Table 3. Major studies on hepcidin and anemia in RA

Study	n	Main finding	Statistics
Egyptian cohort	51	Hepcidin higher in ACD; positive correlation with ferritin	P≤0.001
J Rheumatol	60	Hepcidin higher in anemic RA; 66.6% anemic	p<0.001
Pro-hepcidin	40	237.6±67.9 ng/mL; inverse with iron (r=−0.23)	P=0.04
Castleman (TCZ)	—	Hepcidin 52→7.7 ng/mL, anemia improved	P<0.01

TCZ — tocilizumab (anti-IL-6 receptor antibody). ACD — anemia of chronic disease; IDA — iron deficiency anemia.

Hepcidin in chronic heart failure (CHF) — contradictory findings

Iron deficiency is widespread in CHF. In the international pooled analysis by Klip and colleagues (Am Heart J. 2013;165(4):575-582), iron deficiency was found in 50% (753 of 1506 patients); it was higher in anemic patients (61.2% vs 45.6%, P<0.001). Here, the behavior of hepcidin differs from the classical model.

Jankowska and colleagues (Eur Heart J. 2013;34(11):827-834, n=321 systolic CHF + 66 controls; LVEF 31±9%) found that in early/asymptomatic CHF hepcidin was significantly higher (p<0.001), but as CHF progressed, iron deficiency developed in the advanced NYHA classes and hepcidin decreased (all p<0.001). In longitudinal follow-up, hepcidin declined from 111.3 to 39.5 ng/mL and was negatively associated with an increase in sTfR (r=−0.54, p<0.05). In a multivariate Cox model, LOW hepcidin was independently associated with 3-year mortality (p<0.001) — this differs fundamentally from the classical “high hepcidin = poor” model.

In stable ambulatory CHF patients (n=60), low hepcidin (<31.7 ng/mL) was strongly associated with iron deficiency (OR 16.5, 95% CI 2.2–121.2; p<0.01). These data demonstrate the biphasic nature of hepcidin in CHF (early-high, advanced-low).

Hepcidin in oncological diseases

Macciò and colleagues (Haematologica. 2015;100(1):124-132, n=888 solid tumors) found an anemia prevalence of 63%; hemoglobin was inversely correlated with inflammatory markers, hepcidin, ferritin, and erythropoietin. In multiple myeloma (Maes K, et al. Clin Cancer Res. 2008), urinary hepcidin in stage III patients (n=44) was 3-fold higher than in controls; in the subgroup without renal failure, hepcidin was inversely correlated with hemoglobin (P=0.014). In another study, serum hepcidin was 99.4±10.5 vs 19.9±2.8 μg/L (p<0.001); it was negatively correlated with IL-6 (r=−0.894) and CRP (r=−0.916; p<0.001).

Cross-disease comparative summary

Across the four chronic diseases, the direction of hepcidin depends on the relative predominance of inflammation and the erythropoietic drive (Table 4).

Table 4. Comparative analysis of the direction of hepcidin in chronic diseases

Disease	Hepcidin	Main mechanism	Anemia prev.
CKD (dialysis)	↑ High	Inflammation + ↓ renal clearance	>90%
Rheumatoid arthritis	↑ High	IL-6 / STAT3	33–60%

Disease	Hepcidin	Main mechanism	Anemia prev.
Heart failure (advanced)	↓ Low	ERFE / erythropoietic drive	~50% ID
Oncological diseases	↑ High	IL-6 + tumor effect	~63%

ID — iron deficiency. ERFE — erythroferrone. In CHF, "low hepcidin" indicates a poor prognosis.

Hepcidin as a diagnostic biomarker — limitations

1. Absence of an FDA-approved commercial assay; because of the low specificity of ELISA for the hepcidin-25 isoform, it overestimates hepcidin compared with mass spectrometry.
2. Circadian variability and high inter-individual variability; uncertainty between serum and urinary measurements.
3. Discrimination limitation: in the most complex cases (low TSAT + high ferritin), hepcidin moves in the same direction as ferritin and cannot distinguish ACD from IDA.
4. In combined ACD+IDA cases, hepcidin has an intermediate value, so a single cut-off value is diagnostically useless.

Therapeutic strategies

1. Anti-hepcidin agents: LY2787106 (a hepcidin monoclonal antibody) temporarily increased serum iron and TSAT in cancer anemia but did not correct hemoglobin (Vadhan-Raj S, et al. J Hematol Oncol. 2017).
2. HIF-PHI (roxadustat): suppresses hepcidin and increases iron mobilization; in NDD-CKD it significantly increased hemoglobin (1.9±1.2 vs placebo 0.4±0.8 g/dL), although its cardiovascular safety is debated.
3. Anti-IL-6 (tocilizumab): confirming the IL-6→hepcidin axis, it lowers hepcidin and improves anemia in RA and Castleman disease.

Discussion

This analysis demonstrates the central but disease-specific role of hepcidin in the pathogenesis of anemia in chronic diseases. The classical pathophysiological model — "chronic disease → inflammation → IL-6 → high hepcidin → ferroportin degradation → functional iron deficiency → iron-restricted erythropoiesis" — is well confirmed in pure anemia of inflammation (RA, Castleman disease, many oncological diseases, and dialysis CKD). In these conditions, hepcidin is high and positively correlated with ferritin and IL-6 and negatively correlated with hemoglobin.

However, the most important nuance is that this model breaks down in conditions where the erythropoietic drive predominates over inflammation. In advanced heart failure, hepcidin is low, and it is precisely low hepcidin that predicts mortality (Jankowska 2013; Cox, $p<0.001$). The molecular basis of this paradox is erythroferrone (ERFE), which is produced by erythroblasts under the action of EPO and, by sequestering BMP2/6, suppresses hepcidin downward even in the presence of inflammation. Thus, in each chronic disease the relative predominance of inflammation and the erythropoietic drive determines the direction of hepcidin.

The diagnostic limitations of hepcidin (lack of assay standardization, isoform cross-reactivity) and the inconclusive results of direct anti-hepcidin therapies are slowing its entry into clinical practice. At the same time, indirect approaches — suppression of inflammation (anti-IL-6) and activation of the HIF pathway (roxadustat) — show promise.

Limitations. This review is integrative (not meta-analytic), so direct comparison of hepcidin values from studies using different assays is limited. Some of the cited cohorts are small. Data on the cardiovascular safety of roxadustat remain conflicting.

Conclusion

1. Hepcidin is the central regulator of iron homeostasis and the development of anemia in chronic diseases, controlled by inflammation (IL-6/STAT3), iron status (BMP/SMAD/HJV/HFE/TfR2), as well as the erythropoietic drive (EPO→ERFE).
2. In pure anemia of inflammation (RA, oncological diseases, dialysis CKD), hepcidin is high and causes functional iron deficiency and iron-restricted erythropoiesis; correlational and therapeutic data support a causal relationship.
3. In heart failure, hepcidin is biphasic — high early, low in the advanced stage — and it is precisely low hepcidin that indicates a poor prognosis; this is explained by ERFE-mediated erythropoietic suppression.
4. Hepcidin is promising as a biomarker, but because of problems with assay standardization and its poor discrimination in mixed anemia conditions, it has not yet entered routine practice.

Recommendations

1. In clinical practice, interpret hepcidin not in isolation but as a complex panel together with ferritin, TSAT, sTfR, and inflammatory markers (CRP/IL-6).
2. To distinguish ACD from IDA, use the sTfR-ferritin index (cut-off ~1.5) and the log[hepcidin]:log[ferritin] index; do not use hepcidin as a marker of absolute iron deficiency in CKD stage 3 and above.
3. In therapy: (a) anti-IL-6/tocilizumab in RA; (b) HIF-PHI (roxadustat) in renal anemia of CKD — with monitoring of cardiovascular risk; (c) in heart failure, since low hepcidin indicates iron deficiency, intravenous iron therapy.
4. For future research: international standardization of hepcidin assays; study of the ERFE-hepcidin axis in combined ACD+IDA conditions; conduct therapeutic trials stratifying patients based on hepcidin/ERFE.

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