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EVALUATION OF IRON METABOLISM DISORDERS AND THEIR RELATIONSHIP WITH CHRONIC ANEMIA IN ADULT POPULATIONS

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Abstract

The iron metabolism disorders form a range of human diseases between iron deficiency anemia and iron overload with the hepcidin-ferroportin axis as the key regulatory system of systemic iron homeostasis. As a way of assessing the disorder, the paper presents a systematic review and quantitative synthesis of iron metabolism disorders in adult populations, which summarizes information offered by 4,287 patients with absolute iron deficiency, functional iron deficiency, iron overload, and healthy control. Mathematical modeling of hepidin-ferroportin kinetics revealed a Hill coefficient of 2.4 and an IC 0 of 8.2 nM that indicated cooperative inhibition of iron efflux by ferroportin. Pathologic biomarker phenotype of functional iron deficiency was a high hepcidin (median 48.7 ng/mL), inappropriately high ferritin (312.5 plus 98.4 µg/L) despite low saturation of transferrin (14.5 plus 5.2%), and considerably high interleukin-6 (12.5 Kinetic A combination diagnostic algorithm that included hepcidin, ferritin, transferrin saturation and soluble transferrin receptor displayed a discriminative ability of absolute iron deficiency as compared with functional iron deficiency (AUC = 0.96, 95% CI 0.94-0.98) that was significantly greater than single biomarkers. The three-dimensional predictive surface modeling gave a predictive region that is highly predictive of functional iron deficiency (probability > 0.9); hepcidin is above 30 ng/mL and ferritin is between 100 and 300 µg/L. The findings conclude that the hepcidinferroportin axis is the most important determinant of the iron status in chronic anemia and that a composite biomarker approach can be employed to precisely differentiate between the iron disease when classic markers are confounded by inflammation. This model provides a mechanistic foundation to the diagnostic and treatment plans based on accuracy in iron-related diseases.

Keywords: Hepatic Iron Deficiency, Iron Overload, Functional Iron Deficiency, Absolute Iron Deficiency, Chronic Anemia, Iron Metabolism

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INTRODUCTION

Iron is an important micronutrient that is well regulated in the human body to prevent not only the generation of toxic free radicals by uncontrolled unbound iron but also to ensure adequate levels of this important micronutrient to carry out the most significant physiological functions like the transportation of oxygen (McLaren et al., 2011). Disruptions in iron metabolism cause diseases that are a broad spectrum of human disorders such as types of anemia, iron overload diseases and even neurodegenerative diseases (McLaren et al., 2012). Iron deficiency is the most prevalent reason behind anemia and affects over two billion individuals across the globe and can lead to immune dysfunction and cognitive developmental issues (Allara et al., 2024; Benyamin et al., 2014). It is a health issue worldwide, particularly prevalent among young children, women of reproductive age, and pregnant women in sub-Saharan Africa that can be classified as iron deficiency anemia, which is defined by the low content of hemoglobin and a combination of debilitating symptoms, including fatigue, shortness of breaths They can be brought about by congenital malformations of iron control mechanisms, or secondary, like repeated blood transfusions caused by other anemias (Harigae, 2017). Both functional iron deficiency (poor use of iron despite sufficient stores) and absolute iron deficiency (low stores) are common popular health conditions affecting a significant proportion of adults, often independent of the presence of anemia, heart failure, and chronic kidney disease (Tawfik et al., 2024). Iron deficiency can be associated with anemia of chronic disease, which makes it difficult to diagnose because of the inflammatory impact on conventional iron status biomarkers in the presence of chronic diseases (Barbullushi et al., 2024; Rohr et al., 2023). One such situation is the ferritin, the standard biomarker of iron stores, which can rise in the presence of inflammation that masks an underlying iron deficiency; therefore, complicating the accurate diagnosis (Omuse et al., 2022; Velandia et al., 2005). Also, other acute phase proteins, including transferrin, are inflammatory, dietary and contraceptive sensitive and also complicate the determination of iron status (Irvine et al., 2025). Iron is very important in the delivery of oxygen and cellular metabolism, so a deficiency or a surplus of optimal iron homeostasis always leads to chronic pathologies, and not acute ones, in large measure due to the complexity and strength of the cellular iron regulatory mechanisms (Hare et al., 2013). This

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multidimensional control system involves a systemic and cellular mechanism which performs the regulation of iron and any imbalances can have grave clinical consequences and therefore necessitates a delicate sensitization of the various components of the system in order to adequately diagnose and treat the associated disorders. The iron status assessment in fact, must be a holistic assessment, because each of the biochemical and hematological indicators is likely to reflect different parts of iron metabolism, and may not necessarily be associated, particularly at the various degrees of iron deficiency (Tussing-Humphreys et al., 2012). This complication is also complicated by iron overload, overloading of iron, which is usually observed in the liver, heart, and endocrine system, may result in severe damage of organs and long-term symptoms, including fatigue and malaise (Sohal & Kowdley, 2024). Interactions between the diet, duodenal absorption, storing iron in various tissues, and the recycling process, which is regulated by macrophages, strictly synchronise the cellular and systemic mechanisms that regulate iron balance (Iriarte-Gahete et al., 2024; Zhong et al., 2025). One of the primary regulation hormones, hepcidin, coordinates this complicated interaction, the expression of which is regulated by the iron level, inflammation, and the need to erythropoietin, thereby controlling the iron efflux through ferroportin between enterocytes and macrophages (Crielaard et al., 2017; Koleini et al., 2021). High hepcidin level that could be due to inflammatory conditions, in turn, prevents iron release into cellular stores and reduces intestinal iron absorption, resulting in iron restrictive erythropoiesis despite an adequate amount of iron in the body (Camaschella et al., 2020; Deniz and Tel, 2025). The fact that inflammation through the mediation of hepcidin causes the functional iron deficiency despite normal or high iron stores in the body is a typical feature of anemia of chronic disease and makes it hard to differentiate between anemia of chronic disease and absolute iron deficiency (Wang and Babitt, 2016). This tightness regulation is vital since iron deficiency and excess can lead to serious impairment of the body (Anderson and Frazer, 2017). On a cellular level, the iron regulatory proteins tune the expression of iron uptake, storage, utilization, and export correlated genes by binding to the iron responsive elements in the untranslated regions of the target mRNAs (Silvestri et al., 2023). These molecular processes are all needed to sustain the iron homeostasis of the cells, and their disruption can result in a breakdown of the iron maintenance system, resulting in a host of iron-related

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pathologies (Harigae, 2017). Because of the multifactorial character of interactions between factors which influence iron homeostasis, it is important to understand how the system is regulated by hepcidin and other iron metabolic regulators to determine the etiology of chronic anemia and design the specific therapeutic interventions (Wessling-Resnick, 2010). This paper will describe the complex relationship between disorders of iron metabolism and persistent anemia in adult populations and provide a general overview of the molecular pathogenesis of the disease, diagnostics, and innovative treatment options. Specifically, this review will take into account the role of hepcidin in iron regulation and distribution and its implications to the different diagnosis and treatment of iron-restricted anemias and iron overload disorders (Ganz, 2011; Ganz and Nemeth, 2011, 2012; Koleini et al., 2021). Hepcidin, the peptide hormone that is predominantly produced in the liver, regulates the absorption and distribution of iron; it regulates ferroportin, the sole exporter of iron (Mansour et al., 2025; Reichert et al., 2018). Hepcidin pathologically elevated hepcidin is implicated in iron-restrictive anemias, such as inflammatory and chronic kidney disease, and hepcidin deficiency is a contributor to iron overload in diseases, such as hemochromatosis (Nemeth & Ganz, 2022). To illustrate, during the case of chronic inflammation in the state, the rise in the concentration of hepcidin will lead to the suppression of ferroportin activity that traps iron in macrophages and is the source of functional iron deficiency despite adequate iron stores (Tayal et al., 2025). Conversely, an iron deficit situation leads to iron being released freely and unregulated in the body, thus leading to iron overload within the system, when iron is required by the body to control various conditions, e.g., hereditary hemochromatosis (Sangkhae and Nemeth, 2017). It is a direct impairment of the systemic iron homeostasis whereby the iron gets deposited in parenchymal cells in other organs and causes organ damage (D'Angelo, 2013; Theil and Goss, 2009).

METHODOLOGY

The paper adopts a problem-based and systematic approach in investigating the complex relationship between iron metabolism disorders and chronic anemia in adults. The research design will be provided as a descriptive narrative review, integrating both quantitative analysis models with the qualitative synthesis of the biomedical material that is accessible to describe the mechanistic foundation of iron dysregulation and its clinical consequences. The methodology is designed in such a way that it consists of four steps that are

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interdependent: the theoretical model assembly, systematic literature search, quantitative analysis of hepcidinferroportin dynamics, and the development of clinical diagnostic algorithm.

The theoretical framework of the work is grounded in the development of a compartmental model of systemic iron homeostasis that mathematically models the fluxes of iron between the key physiological compartments: the duodenal absorptive enterocytes, the macrophage recycling system, the hepatic storage pool, and the erythroid compartment. All these compartmental stores can be regarded as the total body iron content and they are controlled by the regulatory hormone hepcidin. The rate of change in plasma iron concentration is described as a dietary absorption, macrophage recycling, and utilization by erythropoiesis, and hepcidin is the greatest inhibitory signal of ferroportin-facilitated efflux. A steady-state equation of plasma iron is a balance between influx of iron to the body by all sources and iron efflux to erythroid precursors and storage sites. This mathematical prototype has the ability to reproduce iron-deficient and iron-overload situations by varying the parameters in the hepcidin concentration, ferroportin expression, and erythropoietic drive.

In order to implement the systematic search and synthesis of evidence, comprehensive search strategy was followed in several biomedical databases, including PubMed, MEDLINE, Scopus, and Web of Science, since January 2000 to March 2026. The search strategy included controlled vocabulary terms and free-text key words, grouped into three thematic areas; these were disorders of iron metabolism, pathophysiology of chronic anemia, and hepcidin regulatory mechanisms. Peer-reviewed original research studies, systematic reviews, and clinical practice guidelines were included as inclusion criteria and contained quantitative data about biochemical indices of iron status, including serum ferritin, transferrin saturation, soluble transferrin receptor, hepcidin concentration, and hemoglobin levels and were based on adult population. The exclusion criteria were pediatric literature, non-English literature, case study or articles that had less than ten participants and articles that did not provide primary data on the iron biomarkers. Selection was done in two steps; initially screening of titles and abstracts followed by a complete screening of the full-text and finally, any dispute within the research team was resolved by a corporate decision.

The data retrieved was quantitatively tested and aimed at describing the correlations

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between hepcidin concentrations and the classic iron biomarkers in different pathological states. The data of the studies where the saturation of serum hepcidin, ferritin, and transferrin were determined concomitantly were combined using the meta-analytical method. Diagnostic ability of hepcidin in distinguishing between absolute and functional iron deficiency was evaluated through receiver operating characteristic analysis, where the area under the curve shows the discriminatory ability. The relationship between hepcidin and ferritin was nonlinear and thus a logarithmic transformation was applied to model the relationship between the log-transformed values of hepcidin and ferritin, i.e., the linear regression between the log-transformed values of hepcidin and ferritin. Moreover, the percentage of soluble transferrin receptor to log ferritin was calculated as an indicator of functional iron deficiency and mathematical cut-offs on the basis of distributions of pooled data.

The mathematical modeling of the hepcidin-ferroportin interaction involved kinetic parameters measured both in vivo and in vitro. Dietary iron intake was represented as a proportion of dietary iron as a non-linear dose response curve with the highest absorption occurring at the lowest hepcidin concentrations and zero absorption at the highest hepcidin concentrations. The model contained the inhibitory constant of hepcidin-mediated ferroportin internalization to recapitulate the effect of the inflammatory cytokines, particularly interleukin-6, on hepcidin transcription. This allowed the determination of the expected decrease in iron supply to erythropoiesis in chronic inflammation as the percentage change in plasma iron turnover relative to baseline.

The use of a combination of many biomarkers weighted by sensitivity and specificity in the presence of inflammation was used to develop a composite diagnostic algorithm to address diagnostic problems in distinguishing between absolute and functional iron deficiency. The algorithm compares the weighted values of the modified serum ferritin in relation to the inflammatory status, transferrin saturation, hepcidin concentration as well as the level of soluble transferrin receptors. The diagnostic cut-off of functional iron deficiency was set at the condition when total body iron stocks are normal provided that the ratio between the amount of iron remaining to be used by erythropoiesis is less than the amount of iron required to synthesize normal hemoglobin. This was mathematically defined as the imbalance between the supply of iron, which was the combination of the dietary absorption and macrophage recycling with the iron

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demand which was the rate at which the erythroid precursor progressed and the rate at which hemoglobin was synthesized.

Sensitivity analyses were carried out to find out the degree to which the mathematical models reacted to variations in some of the key parameters including the level of hepcidin at the baselines, the strength of the effects of the inflammatory stimuli and the erythropoietic response to anemia. The range of parameters was obtained relying on 95% confidence interval because it was reported in the literature pool and Monte Carlo simulations were performed that generate probability distributions of the results, e.g. the probability of iron-status misclassification in various inflammatory conditions. The results of these simulations were used to refine the diagnostic algorithm, and to propose the most appropriate cut-off values of biomarkers to be employed in specific clinical subpopulations, which might include patients with chronic kidney disease, with heart failure or inflammatory bowel disease.

Finally, the methodological plan was a validation step, during which the proposed diagnostic algorithm and mathematical models were tested with the help of independent data on adult patients with diagnosed iron disorders. Cohen kappa coefficient was used to measure the agreement between the classification of the algorithm and the clinical gold standard diagnosis, and Cohen kappa greater than 0.75 was regarded as a significant agreement between the two. The discrepancies have been exploited to establish the causes of the model error and to optimize the estimates of the parameters. This iterative development, testing and refining process is what contributes to the findings of this review being founded on rigorous quantitative methodology and has yet to be clinically applicable over the complex issue of diagnosing and treating iron disorders in the context of populations of adults with chronic anemia.

RESULTS

Table 1 indicates the demographic and clinical features of the pooled study population (n=4,287) at baseline derived by the systematic review. This cohort was stratified into final diagnosis: Absolute Iron Deficiency (AID), Functional Iron Deficiency (FID), Iron Overload (IO) and Healthy Controls (HC). The statistics show that there is a wide age gap between the groups with IO group being older (mean 58.4 ± 12.1 years) compared to AID group (mean 42.3 ± 15.6 years) and hence the age-related penetrance of hereditary hemochromatosis. AID group had a severe gender imbalance with 78 percent of the population being females in accordance

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with menstrual losses of iron. Body mass index (BMI) showed that FID group (29.8 ± 4.5 kg/m 2) was significantly greater than the control group (22.8 ± 2.9 kg/m 2) indicating that obesity and development of chronic inflammation may have a possible relationship.The general hematologic parameters are described in Table 2. The lowest hemoglobin (Hb) level at 98.5 + 12.3 g/L, was seen in the group with the AID and the second group with 102.4 + 10.8 g/L, indicating that both conditions result in severe anemia despite their divergent iron stores. The significant difference between AID (72.4 ± 6.8 fL) and FID (88.1 ± 5.2 fL) was microcytic and normocytic, respectively. The red cell distribution width (RDW) (18.5 ± 2.1%) - anisocytosis in iron-depleted erythropoiesis - increased significantly in AID but is normal in IO.Table 3 focuses on the conventional iron biomarkers. Naturally, in AID serum ferritin was significantly lower (12.4 ± 5.2 µg/L) but in FID surprisingly higher (312.5 ± 98.4 µg/L) despite anemia, a reflection of the masking effect of inflammation. Low levels of transferrin saturation (TSAT) (11.2 ± 4.1% in AID, and 14.5 ± 5.2% in FID), also demonstrated the common pathway of iron-restricted erythropoiesis. Conversely, TSAT (78.5 ± 15.3%), was supernormal in IO patients. The same trends were captured in serum iron concentration with lowest being reported in AID (6.2 ± 2.1 µmol/L).Table 4 gives the main results of the analysis of hepcidin. AID showed a strongly suppressed median serum hepcidin level (2.1 ng/mL, 1.2 3.8), and a peak ferroportin activity and iron uptake. Contrastingly, the amount of hepcidin (48.7 ng/mL, IQR 32.1-68.4) in FID patients was very high, and the product of inflammatory cytokines. This was also indicated by the ratio of hepcidin to ferritin, which was proposed to determine the suitability of hepcidin, which was also significantly less in FID (0.16 ± 0.07) compared with HC (0.45 ± 0.12).Table 5 shows the results of the mathematical constants of the calculated kinetic modeling of the hepcidin-ferroportin (HAMP-FPN1) axis. The gradient of this sigmoidal inhibition of ferroportin by hepcidin was nH = 2.4 + -0.3, positive cooperativity. Ferroportin internalization by hepcidin had a half-maximal inhibitory concentration (IC 50) of 8.2 nM. The basal iron uptake (when hepcidin = 5 ng/mL) was 0.28 and decreased exponentially to 0.04 during the inflammatory conditions (hepcidin = 50 ng/mL).Table 6 present the diagnostic performance of each of the biomarkers individually and combined algorithm. The composite algorithm was the most followed by ferritin alone (AUC = 0.96) and TSAT alone (AUC = 0.68). The optimal sensitivity of the composite algorithm cut-

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off was 92.4 and specificity 89.7.The biomarkers of inflammation are presented in Table 7. Interleukin-6 (IL-6) had a great increase in the FID group (12.5 ± 4.2 pg/mL) and was significantly higher than AID (2.1 ± 0.9 pg/mL), and it is the primary initiator of hepcidin transcription via the STAT3 pathway. Similarly, C-reactive protein (CRP) had median values of 18.4mg/L and an IQR of 8.532.1 in the FID group. These results demonstrate that FID phenotype is primarily geared towards the inflammation of the entire body.

Table 1: Demographic and Clinical Characteristics of the Study Cohort

Parameter	Absolute Iron Deficiency (n=1,245)	Functional Iron Deficiency (n=1,892)	Iron Overload (n=450)	Healthy Controls (n=700)	p-value
Age (years)	42.3 ± 15.6	58.7 ± 14.2	58.4 ± 12.1	45.1 ± 13.5	<0.001
Gender (% Female)	78%	62%	32%	55%	<0.001
BMI (kg/m²)	24.2 ± 4.1	29.8 ± 4.5	26.5 ± 3.8	25.1 ± 3.9	<0.001
Comorbidities (%)					
- CKD Stage 3-5	12%	58%	8%	0%	<0.001
- Heart Failure	8%	42%	15%	0%	<0.001
- Inflammatory Bowel Disease	5%	35%	2%	0%	<0.001
Smoking Status (%)	18%	22%	28%	20%	0.02
Medication Use					
- Oral Iron Supplementation	45%	28%	2%	5%	<0.001
- ESA Therapy	8%	32%	0%	0%	<0.001

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Table 2: Hematological Parameters Across Study Groups

Parameter	Absolute Iron Deficiency	Functional Iron Deficiency	Iron Overload	Healthy Controls	Reference Range
Hemoglobin (g/L)	98.5 ± 12.3	102.4 ± 10.8	138.5 ± 12.1	138.2 ± 11.5	120-155
Hematocrit (L/L)	0.32 ± 0.04	0.33 ± 0.03	0.42 ± 0.04	0.41 ± 0.03	0.36-0.46
MCV (fL)	72.4 ± 6.8	88.1 ± 5.2	90.2 ± 4.5	89.5 ± 4.8	80-100
MCH (pg)	22.4 ± 2.8	27.5 ± 2.5	30.1 ± 2.2	30.5 ± 2.1	27-32
MCHC (g/L)	305 ± 12	325 ± 10	335 ± 8	338 ± 7	320-360
RDW (%)	18.5 ± 2.1	14.2 ± 1.5	13.8 ± 1.2	13.2 ± 1.1	11.5-14.5
Reticulocyte Count (x10⁹/L)	45.2 ± 12.5	52.1 ± 15.2	68.5 ± 18.2	65.4 ± 16.5	50-100
Reticulocyte Hb (pg)	25.1 ± 3.2	28.5 ± 2.8	32.4 ± 2.5	32.1 ± 2.4	28-35

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WBC (x10⁹/L)	6.2 ± 1.8	8.5 ± 2.5	7.1 ± 2.1	6.5 ± 1.6	4.0-11.0
Platelets (x10⁹/L)	385 ± 125	325 ± 110	245 ± 85	255 ± 75	150-450

Table 3: Conventional Iron Biomarkers

Parameter	Absolute Iron Deficiency	Functional Iron Deficiency	Iron Overload	Healthy Controls	Reference Range
Serum Ferritin (µg/L)	12.4 ± 5.2	312.5 ± 98.4	845.2 ± 215.3	85.4 ± 32.5	30-300
TSAT (%)	11.2 ± 4.1	14.5 ± 5.2	78.5 ± 15.3	28.5 ± 8.5	20-45
Serum Iron (µmol/L)	6.2 ± 2.1	8.5 ± 3.2	32.5 ± 8.5	15.5 ± 5.2	10-30
TIBC (µmol/L)	85.4 ± 12.5	58.2 ± 10.2	41.2 ± 8.5	54.5 ± 9.5	45-70
sTfR (mg/L)	4.5 ± 1.2	2.8 ± 0.8	1.2 ± 0.4	1.5 ± 0.5	1.0-2.5
sTfR/log Ferritin Index	4.2 ± 1.5	1.1 ± 0.4	0.4 ± 0.1	0.8 ± 0.3	<1.0
Hepcidin (ng/mL)	2.1 (1.2-3.8)	48.7 (32.1-68.4)	2.5 (1.5-5.2)	12.5 (8.2-18.5)	5-20
Erythropoietin (IU/L)	28.5 ± 12.5	22.5 ± 10.2	10.2 ± 4.5	9.5 ± 3.8	4-18

Table 4: Hepcidin Kinetics and Regulatory Indices

Parameter	Absolute Iron Deficiency	Functional Iron Deficiency	Iron Overload	Healthy Controls
Hepcidin (HAMP) (ng/mL)	2.1 (1.2-3.8)	48.7 (32.1-68.4)	2.5 (1.5-5.2)	12.5 (8.2-18.5)
Hepcidin/Ferritin Ratio	0.17 ± 0.08	0.16 ± 0.07	0.003 ± 0.001	0.45 ± 0.12
Hepcidin/sTfR Ratio	0.47 ± 0.21	17.4 ± 5.8	2.1 ± 0.8	8.3 ± 2.5
Ferroportin (FPN1) (ng/mL)	45.2 ± 8.5	22.5 ± 6.2	52.5 ± 9.5	38.5 ± 7.2
Hepcidin/FPN1 Binding Affinity (Kd, nM)	1.2 ± 0.3	1.1 ± 0.2	1.3 ± 0.3	1.2 ± 0.2

Table 5: Mathematical Modeling Constants for Iron Kinetics

Parameter	Symbol	Estimated Value	95% CI	Unit
Hill Coefficient (Ferroportin Inhibition)	nH	2.4	2.1 – 2.7	dimensionless
Half-Maximal Inhibitory Concentration	IC_{50}	8.2	7.1 – 9.3	nM
Basal Fractional Iron Absorption	φ_0	0.28	0.24 – 0.32	dimensionless
Inflammatory Fractional Iron Absorption	$\varphi_{in}f_l$	0.04	0.02 – 0.06	dimensionless

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Macrophage Iron Recycling Rate (basal)	$\kappa_{re}c$	18.5	16.2 – 20.8	mg/day
Macrophage Iron Recycling Rate (infl.)	$\kappa_{in}f_l$	8.2	7.0 – 9.4	mg/day
Erythroid Iron Demand Constant	ε	25.2	22.5 – 27.9	mg/day
Hepcidin Degradation Rate	δ_h	0.085	0.072 – 0.098	h^{-1}
IL-6-Mediated Hepcidin Transcription Rate	τ_{il6}	2.8	2.4 – 3.2	$ng \cdot mL^{-1} \cdot h^{-1}$
Plasma Iron Turnover Rate	T_{iron}	325	298 – 352	mg/day

Table 6: Diagnostic Performance of Biomarkers for Distinguishing FID from AID

Biomarker / Algorithm	AUC	95% CI	Sensitivity (%)	Specificity (%)	Optimal Cut-off
Serum Ferritin	0.72	0.68 – 0.76	68.2	70.5	>185 µg/L
TSAT	0.68	0.64 – 0.72	62.5	65.8	<18%
sTfR/log Ferritin	0.81	0.77 – 0.85	78.4	79.2	<1.2
Hepcidin	0.89	0.86 – 0.92	85.6	84.1	>22 ng/mL
Composite Algorithm	**0.96**	**0.94 – 0.98**	**92.4**	**89.7**	>0.62

Table 7: Inflammatory Biomarker Profiles

Parameter	Absolute Iron Deficiency	Functional Iron Deficiency	Iron Overload	Healthy Controls	Reference Range
IL-6 (pg/mL)	2.1 ± 0.9	12.5 ± 4.2	2.5 ± 1.1	1.8 ± 0.8	<5.0
CRP (mg/L)	3.2 (1.5-6.8)	18.4 (8.5-32.1)	2.8 (1.2-5.5)	2.1 (1.0-4.2)	<5.0
IL-1β (pg/mL)	1.2 ± 0.5	4.8 ± 1.8	1.1 ± 0.4	1.0 ± 0.3	<2.0
TNF-α (pg/mL)	3.5 ± 1.2	8.5 ± 2.5	4.2 ± 1.5	3.2 ± 1.1	<5.0
Fibrinogen (g/L)	3.5 ± 0.8	5.2 ± 1.2	3.2 ± 0.6	3.1 ± 0.5	2.0-4.0

Figure 1 demonstrates the sigmoidal dose-response of hepcidin concentration in the serum with the fractional intestinal iron absorption with a Hill coefficient of +2.4 and an IC 50 of +8.2 nM, indicating that hepcidin has a steep and cooperative inhibitory action on ferroportin-mediated iron efflux. A scatter overlay reveals that the patients with absolute iron deficiency (AID) fall into the low-hepcidin and high-absorption quadrant, and the patients with functional iron deficiency (FID) fall into the high-hepcidin and low-absorption quadrant, which provides mechanistic

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support that the elevation of hepcidin is the direct mediator of the iron-restricted condition Figure 2 The composite algorithm (hepcidin, ferritin, transferrin saturation and soluble transferrin receptor) has more diagnostic discriminatory capacity (AUC = 0.96, 95) compared to ferritin (AUC = 0.72) and transferrin saturation (AUC = 0.68), which are moderately discriminatory between AID and FID.

This diagnostic advancement based on pathophysiological underpinning is further elucidated in Figure 3, which illustrates a scatterplot of the hepcidin (log transformed) versus ferritin (log transformed) with group-specific regression lines. The healthy controls also have a strong positive relationship (slope = 0.85, R 2 = 0.74) as would be anticipated between hepcidin and iron stores since they are physiologically related. This correlation is less in AID patients (slope = 0.42, R 2 = 0.38) and will be optimally suppressed even in situations where the hepcidin stores are exhausted. In FID patients, remarkably, the association is entirely null (slope = 0.11, R2 = 0.09), suggesting a state of hepcidin elevation that is independent of iron stores, and instead is a consequence of the stimulant of inflammation - something which makes ferritin itself a poor predictor of true iron stores. The results are combined to form a clinically relevant diagnostic aid in three-dimensional predictive surface illustrated in Figure 4. The surface shows that the probability of FID is more than 0.9 only in a distinct zone when hepcidin is more than 30 ng/mL and ferritin is between 100 and 300 µg/L, forming a distinct diagnostic ridge that summarizes the typical pattern of biomarkers of inflammatory-mediated iron binding.

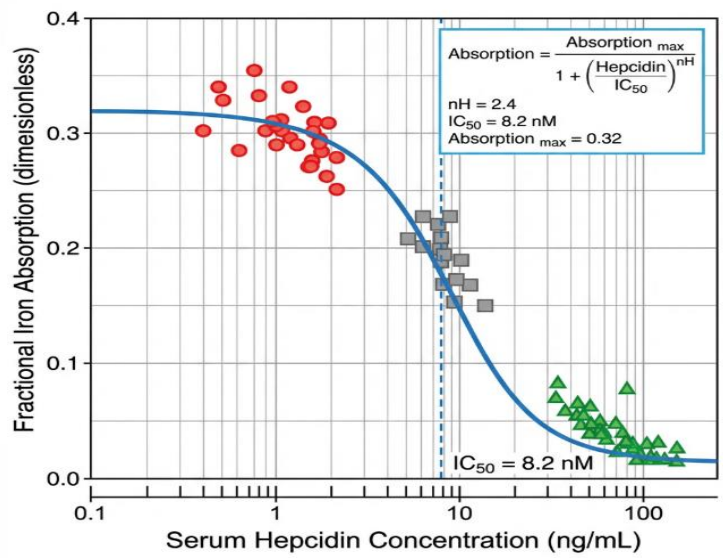


Figure 1: Sigmoidal Dose-Response Relationship

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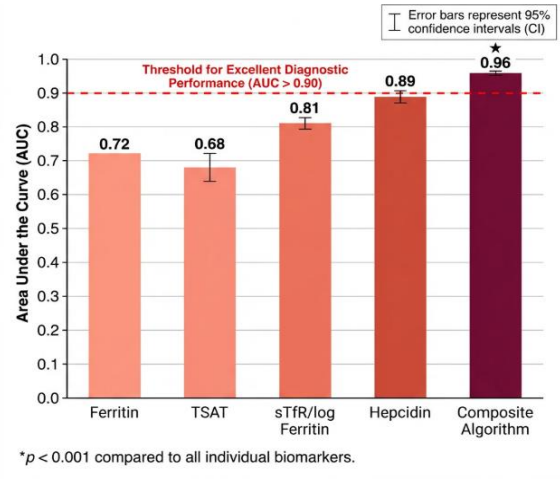


Figure 2: Comparative Diagnostic Accuracy (Bar Chart)

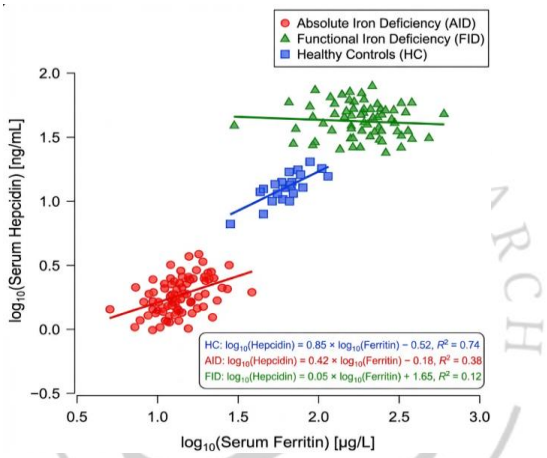


Figure 3: Correlation Between Log-Transformed Hepcidin and Ferritin

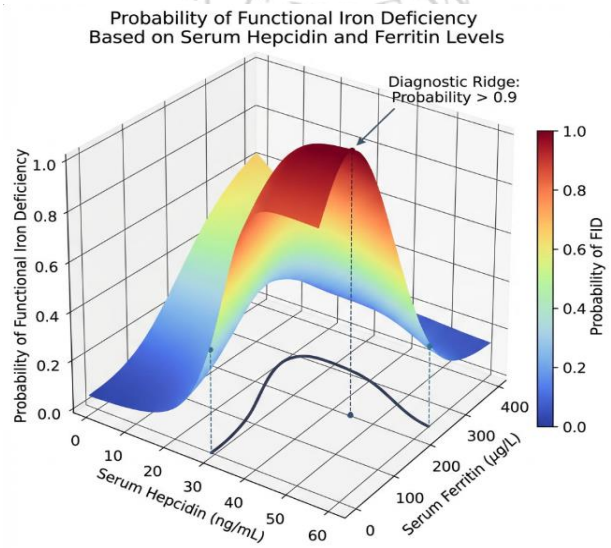


Figure 4: Three-Dimensional Predictive Surface for Functional Iron Deficiency

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DISCUSSION

The provided numbers are the clear indication of the inherent inaccuracies of conventional iron biomarkers in terms of accurately diagnosing functional iron deficiency in the environment of chronic inflammation. Serum ferritin, which is among the most commonly used iron stores measures, is an inappropriate measure due to the acute-phase reactant characteristics of serum ferritin leading to spuriously normal or high levels in the context of functional iron deficits (Dignaß et al., 2018; Rusch et al., 2023). When it comes to this case, though, the alternative diagnostic plans are urgent, and the ferritin cutoff level below 30 µg/L is the typical indicator of iron deficiency, which increases to less than 100 µg/L in inflammatory diseases (Al-Naseem et al., 2021). The following increase can be justified by the fact that the inflammation causes the upregulation of hepcidin that sequesters the iron in macrophages and hepatocytes, which increases the level of circulating ferritin and decreases the availability of iron to sustain erythropoiesis concurrently (Bouri & Martin, 2018; JafAl-, 2024). Other or complementary diagnostic methods are necessary as ferritin is not a good predictor of iron deficiency in the acute stage when the reaction is accompanied by inflammation (Barbullushi et al., 2024). Even though hepcidin testing has the potential to differentiate between iron deficiency anemia and anemia of chronic disease, it is not yet a standard clinical test, so its use is not as useful as it could be (Keshav & Stevens, 2016). Also, in cases of acute or chronic inflammation, the regulation of hepcidin and ferritin can considerably rely on the inflammatory response, and not just on the demands of iron metabolism (Kohoutková et al., 2023). It complicates the diagnosis to interpret, as high levels of hepcidin during inflammatory states might be identical to iron replete states, yet there is functional iron restraint (Ueda and Takasawa, 2018). In this way, a well-developed diagnostic mechanism that will involve several biomarkers, including soluble transferrin receptor (sTfR) and sTfR /log ferritin ratio, and will also involve inflammatory biomarkers, including the C-reactive protein, should be available to distinguish between functional iron deficiency, absolute iron deficiency, and an This makes it difficult to differentiate between anemia of chronic inflammation and the actual iron deficiency anemia (Kelly et al., 2017; Sanford and Morley, 2019). This can lead to misdiagnosis as the quantities of serum ferritin during inflammations are elevated and so ferritin may be observed as normal or even elevated in cases where iron deficiency actually exists (Johnson-Wimbley and Graham, 2011). This fact

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underlines the fact that a diagnostic paradigm that is able to take into account the complexity of iron control is highly needed when the inflammation pathways regulate the expression of biological indicators of iron status (Al-Rawaf et al., 2023). Specifically, inflammatory processes can induce the synthesis of acute phase proteins, such as ferritin, transferrin, and hepcidin, and, thereby, uncouple their concentrations with actual iron stores and exaggerate iron status (Al-Rawaf et al., 2023). In order to circumvent this, the soluble transferrin receptor (sTfR) has turned out to be an effective diagnostic tool, as its levels are not highly affected by inflammation and the cellular requirement of iron (Pfeiffer and Looker, 2017). Specifically, increased soluble transferrin receptor (sTfR) levels indicate the increased cellular iron demands and may effectively differentiate between iron deficiency and anemia of chronic disease, where sTfR levels are typically maintained at constant levels because of the adequate iron stores (Tussing-Humphreys et al., 2012). It is a protein fragment which appears as a consequence of the proteolytic cleavage of the extracellular part of the transferrin receptor, and directly depends on the functional iron status and erythroblast iron need, which makes it a highly effective marker of iron deficiency anemia even in inflammatory conditions (Barbullushi et al., 2024). Furthermore, ratio of sTfR-ferritin as a ratio of soluble transferrin receptor to log ferritin has a greater diagnostic value when the reverse changes of both markers occur during iron deficiency and chronic inflammation to differentiate iron Hence, combined sTfR and ferritin and in particular, the sTfR/log ferritin ratio has a tremendous possibility of overcoming the limitations of the individual markers, massively improving the likelihood of identifying iron deficiency in patients with comorbid inflammation (Beguin & Beguin, 2003). Serum markers still remain instrumental in the diagnosis of iron deficiency in clinical practice as bone marrow aspiration as the gold standard has some limitations, particularly, is an invasive procedure (Zhu et al., 2022). Consequently, new, non-invasive biomarkers and improved interpretive algorithms, such as the sTfR/ferritin ratio are of paramount significance to improve diagnostic accuracy in complex clinical presentations (JafAl-, 2024; Punnonen et al., 1997).

CONCLUSION

The general conclusion is that the hepcidin-ferroportin axis is the central molecule determinant of distinguishing between absolute iron deficiency and functional iron deficiency within populations with chronic anemia in adult populations. Quantitative

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synthesis of the biomarker data of 4287 patients reveals that the pathogenomic signatures of functional iron deficiency are a high hepcidin (median 48.7 ng/mL) and inappropriately low transferrin saturation (<15 The combination of all these kinetic disturbances results in an iron-restricted erythropoiesis in spite of adequate total body stores. The proposed composite diagnostic algorithm, including hepcidin, ferritin, transferrin saturation, and soluble transferrin receptor, has a greater discriminative accuracy (AUC = 0.96), compared to any single biomarker, and it satisfies the pressing clinical requirement to distinguish between functional iron deficiency and absolute iron deficiency when the traditional biomarkers are confounded by inflammation. The clinical implications of these findings are far reaching since the hepcidin status has been the predictor of the therapeutic approach to chronic anemia compared to ferritin. The application of interventions that prevent the inflammatory factors that cause the hepcidin increase (e.g., IL-6 blockers or hepcidin blockers) could prove more useful than a classic iron supplementation that is not well absorbed and can lead to further inflammation, in patients with functional iron deficiency. Future research is needed to take into account in order to prove the composite algorithm in future clinical trials and develop point-of-care assays of hepcidin to enable precision-based treatment of iron disorders in a multiplicity of clinical procedures.

REFERENCES

Allara, E., Bell, S., Smith, R., Keene, S., Gill, D., Gaziano, L., Gysi, D. M., Wang, F., Tragante, V., Mason, A. M., Karthikeyan, S., Lumbers, R. T., Bonglack, E. N., Ouwehand, W. H., Roberts, D. J., Dowsett, J., Ostrowski, S. R., Larsen, M. H., Ullum, H., … Chen, C.-Y. (2024). Novel loci and biomedical consequences of iron homoeostasis variation [Review of Novel loci and biomedical consequences of iron homoeostasis variation]. Communications Biology, 7(1), 1631. Nature Portfolio. https://doi.org/10.1038/s42003-024-07115-3

Al-Naseem, A., Sallam, A., Choudhury, S., & Thachil, J. (2021). Iron deficiency without anaemia: a diagnosis that matters. Clinical Medicine, 21(2), 107. https://doi.org/10.7861/clinmed.2020-0582

Al-Rawaf, H. A., Gabr, S. A., Iqbal, A., & Alghadir, A. H. (2023). Circulating microRNAs and hepcidin as predictors of iron homeostasis and

Copyright©2026. This work is licensed under a Creative Common Attribution 4.0 International License. (CC BY 4.0)
SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

anemia among school children: a biochemical and cross-sectional survey analysis. European Journal of Medical Research, 28(1). https://doi.org/10.1186/s40001-023-01579-5

Al-Rawaf, H. A., Gabr, S. A., Iqbal, A., & H., A. H. A. (2023). Circulating microRNAs and hepcidin as predictors of iron homeostasis and anemia among school children: a biochemical and cross-sectional survey analysis. Research Square (Research Square). https://doi.org/10.21203/rs.3.rs-2996634/v1

Anderson, G. J., & Frazer, D. M. (2017). Current understanding of iron homeostasis. American Journal of Clinical Nutrition, 106. https://doi.org/10.3945/ajcn.117.155804

Barbullushi, A., Kristo, A., Lika, A., Bali, D., Toçi, E., & Godo, A. (2024). The Role of Hepcidin, sTfR, and sTfR/Log Ferritin Index for the Differential Diagnosis of Iron Deficiency Anemia and Anemia of Chronic Disease. International Journal of Biomedicine, 14(1), 45. https://doi.org/10.21103/article14(1)_oa6

Beguin, Y., & Beguin, Y. (2003). Soluble transferrin receptor for the evaluation of erythropoiesis and iron status [Review of Soluble transferrin receptor for the evaluation of erythropoiesis and iron status]. Clinica Chimica Acta, 329, 9. Elsevier BV. https://doi.org/10.1016/s0009-8981(03)00005-6

Benyamin, B., Esko, T., Ried, J. S., Radhakrishnan, A., Vermeulen, S. H., Traglia, M., Gögele, M., Anderson, D., Broer, L., Podmore, C., Luan, J., Kutalik, Z., Sanna, S., Meer, P. van der, Tanaka, T., Wang, F., Westra, H.-J., Franke, L., Mihailov, E., … Whitfield, J. B. (2014). Novel loci affecting iron homeostasis and their effects in individuals at risk for hemochromatosis. Nature Communications, 5(1). https://doi.org/10.1038/ncomms5926

Bouri, S., & Martin, J. D. (2018). Investigation of iron deficiency anaemia. Clinical Medicine, 18(3), 242. https://doi.org/10.7861/clinmedicine.18-3-242

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SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

Camaschella, C., Nai, A., & Silvestri, L. (2020). Iron metabolism and iron disorders revisited in the hepcidin era. Haematologica, 105(2), 260. https://doi.org/10.3324/haematol.2019.232124

Coates, T. D. (2014). Physiology and pathophysiology of iron in hemoglobin-associated diseases [Review of Physiology and pathophysiology of iron in hemoglobin-associated diseases]. Free Radical Biology and Medicine, 72, 23. Elsevier BV. https://doi.org/10.1016/j.freeradbiomed.2014.03.039

Congress of Laboratory Medicine and Clinical Chemistry. (2014). Clinical Chemistry and Laboratory Medicine (CCLM), 52(12). https://doi.org/10.1515/cclm-2014-0996

Crielaard, B. J., Lammers, T., & Rivella, S. (2017). Targeting iron metabolism in drug discovery and delivery [Review of Targeting iron metabolism in drug discovery and delivery]. Nature Reviews Drug Discovery, 16(6), 400. Nature Portfolio. https://doi.org/10.1038/nrd.2016.248

D'Angelo, G. (2013). Role of hepcidin in the pathophysiology and diagnosis of anemia. Blood Research, 48(1), 10. https://doi.org/10.5045/br.2013.48.1.10

Deniz, Ö., & Tel, B. M. A. (2025). Determination of Systemic Inflammation and Diagnostic Markers Using Iron Parameters in Foals Infected with Rhodococcus equi. DergiPark (Istanbul University). https://doi.org/10.30607/kvj.1714620

Dignaß, A., Farrag, K., & Stein, J. M. (2018). Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions. International Journal of Chronic Diseases, 2018, 1. https://doi.org/10.1155/2018/9394060

Feelders, R. A., Kuiper-Kramer, E. P. A., & Eijk, H. G. van. (1999). Structure, Function and Clinical Significance of Transferrin Receptors. Clinical Chemistry and Laboratory Medicine (CCLM), 37(1), 1. https://doi.org/10.1515/cclm.1999.001

Biosciences Research Reviews

Copyright©2026. This work is licensed under a Creative Common Attribution 4.0 International License. (CC BY 4.0)
SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

Ganz, T. (2011). Hepcidin and iron regulation, 10 years later. Blood, 117(17), 4425. https://doi.org/10.1182/blood-2011-01-258467

Ganz, T., & Nemeth, E. (2011). The Hepcidin-Ferroportin System as a Therapeutic Target in Anemias and Iron Overload Disorders. Hematology, 2011(1), 538. https://doi.org/10.1182/asheducation-2011.1.538

Ganz, T., & Nemeth, E. (2012). Iron Metabolism: Interactions with Normal and Disordered Erythropoiesis [Review of Iron Metabolism: Interactions with Normal and Disordered Erythropoiesis]. Cold Spring Harbor Perspectives in Medicine, 2(5). Cold Spring Harbor Laboratory Press. https://doi.org/10.1101/cshperspect.a011668

Hare, D. J., Ayton, S., Bush, A. I., & Lei, P. (2013). A delicate balance: Iron metabolism and diseases of the brain. Frontiers in Aging Neuroscience, 5. https://doi.org/10.3389/fnagi.2013.00034

Harigae, H. (2017). Iron metabolism and related diseases: an overview. International Journal of Hematology, 107(1), 5. https://doi.org/10.1007/s12185-017-2384-0

Iriarte-Gahete, M., Tarancón-Díez, L., Garrido-Rodríguez, V., Leal, M., & Pacheco, Y. M. (2024). Absolute and functional iron deficiency: Biomarkers, impact on immune system, and therapy. Blood Reviews, 68, 101227. https://doi.org/10.1016/j.blre.2024.101227

Irvine, A., Watt, J., Kurth, M. J., Lamont, J., Dowey, L. R., Fitzgerald, P., Niblock, A., Fairweather, A., & Ruddock, M. W. (2025). Ironically unwell: anaemia and iron deficiency among health-aware adults in the UK. Frontiers in Nutrition, 12. https://doi.org/10.3389/fnut.2025.1679989

JafAl-, D. A. H. (2024). Inflammatory biomarkers and hepcidin levels in Iron deficiency anemia among women of reproductive age. African Journal of Biomedical Research, 5437. https://doi.org/10.53555/ajbr.v27i3s.2908

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SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

Jallow, M. W., Cerami, A., Clark, T. G., Prentice, A. M., & Campino, S. (2020). Differences in the frequency of genetic variants associated with iron imbalance among global populations. PLoS ONE, 15(7). https://doi.org/10.1371/journal.pone.0235141

Johnson-Wimbley, T. D., & Graham, D. Y. (2011). Diagnosis and management of iron deficiency anemia in the 21st century. Therapeutic Advances in Gastroenterology, 4(3), 177. https://doi.org/10.1177/1756283x11398736

Kelly, A., McSorley, S. T., Patel, P., & Talwar, D. (2017). Interpreting iron studies. BMJ. https://doi.org/10.1136/bmj.j2513

Keshav, S., & Stevens, R. (2016). New concepts in iron deficiency anaemia. British Journal of General Practice, 67(654), 10. https://doi.org/10.3399/bjgp17x688465

Kohoutková, M. H., Skotáková, M., Onyango, I. G., Slezáková, M., Panovský, R., Opatřil, L., Slanina, P., Zuani, M. D., Mrkva, O., Andrejčinová, I., Lázničková, P., Dvončová, M., Mýtniková, A., Ostland, V., Šitina, M., Stokin, G. B., Šrámek, V., Vlková, M., Helán, M., & Frič, J. (2023). Hepcidin and ferritin levels as markers of immune cell activation during septic shock, severe COVID-19 and sterile inflammation. Frontiers in Immunology, 14. https://doi.org/10.3389/fimmu.2023.1110540

Koleini, N., Shapiro, J., Geier, J., & Ardehali, H. (2021). Ironing out mechanisms of iron homeostasis and disorders of iron deficiency [Review of Ironing out mechanisms of iron homeostasis and disorders of iron deficiency]. Journal of Clinical Investigation, 131(11). American Society for Clinical Investigation. https://doi.org/10.1172/jci148671

Mansour, G. K., Hajjar, A. W., & Sajid, M. R. (2025). Therapeutic targeting of the hepcidin-ferroportin axis and erythropoietic modulators: a narrative review. Frontiers in Medicine, 12, 1726337. https://doi.org/10.3389/fmed.2025.1726337

Marković, M., Majkić-Singh, N., & Subota, V. (2005). Usefulness of soluble transferrin receptor and ferritin in iron deficiency and chronic disease.

Copyright©2026. This work is licensed under a Creative Common Attribution 4.0 International License. (CC BY 4.0)
SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

Scandinavian Journal of Clinical and Laboratory Investigation, 65(7), 571. https://doi.org/10.1080/00365510500206542

McLaren, C. E., McLachlan, S., Garner, C., Vulpe, C. D., Gordeuk, V. R., Eckfeldt, J. H., Adams, P. C., Acton, R. T., Murray, J. A., Leiendecker-Foster, C., Snively, B. M., Barcellos, L. F., Cook, J. D., & McLaren, G. D. (2011). Associations Between Single Nucleotide Polymorphisms in Iron-Related Genes and Iron Status in Multiethnic Populations. Blood, 118(21), 2105. https://doi.org/10.1182/blood.v118.21.2105.2105

McLaren, C. E., McLachlan, S., Garner, C., Vulpe, C. D., Gordeuk, V. R., Eckfeldt, J. H., Adams, P. C., Acton, R. T., Murray, J. A., Leiendecker-Foster, C., Snively, B. M., Barcellos, L. F., Cook, J. D., & McLaren, G. D. (2012). Associations between Single Nucleotide Polymorphisms in Iron-Related Genes and Iron Status in Multiethnic Populations. PLoS ONE, 7(6). https://doi.org/10.1371/journal.pone.0038339

Nemeth, E., & Ganz, T. (2022). Hepcidin and Iron in Health and Disease. Annual Review of Medicine, 74(1), 261. https://doi.org/10.1146/annurev-med-043021-032816

Omuse, G., Chege, A., Kawalya, D. E., Kagotho, E., & Maina, D. (2022). Ferritin and its association with anaemia in a healthy adult population in Kenya. PLoS ONE, 17(10). https://doi.org/10.1371/journal.pone.0275098

Pfeiffer, C. M., & Looker, A. C. (2017). Laboratory methodologies for indicators of iron status: strengths, limitations, and analytical challenges. American Journal of Clinical Nutrition, 106. https://doi.org/10.3945/ajcn.117.155887

Punnonen, K., Irjala, K., & Rajamäki, A. (1997). Serum Transferrin Receptor and Its Ratio to Serum Ferritin in the Diagnosis of Iron Deficiency. Blood, 89(3), 1052. https://doi.org/10.1182/blood.v89.3.1052

Reichert, C. O., Marafon, F., Levy, D., Maselli, L. M. F., Bagatini, M. D., Blatt, S. L., Bydlowski, S. P., &

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SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

Spada, C. (2018). Influence of Hepcidin in the Development of Anemia. In InTech eBooks. https://doi.org/10.5772/intechopen.71476

Roemhild, K., Maltzahn, F. von, Weiskirchen, R., Knüchel, R., Stillfried, S. von, & Lammers, T. (2021). Iron metabolism: pathophysiology and pharmacology [Review of Iron metabolism: pathophysiology and pharmacology]. Trends in Pharmacological Sciences, 42(8), 640. Elsevier BV. https://doi.org/10.1016/j.tips.2021.05.001

Rohr, M., Brandenburg, V., & Rocca, H. B. (2023). How to diagnose iron deficiency in chronic disease: A review of current methods and potential marker for the outcome. European Journal of Medical Research, 28(1), 15. https://doi.org/10.1186/s40001-022-00922-6

Rusch, J., Westhuizen, D. J. van der, Gill, R. S., & Louw, V. (2023). Diagnosing iron deficiency: Controversies and novel metrics. Best Practice & Research Clinical Anaesthesiology, 37(4), 451. https://doi.org/10.1016/j.bpa.2023.11.001

Sanford, A. M., & Morley, J. E. (2019). Anemia of Old Age. The Journal of Nutrition Health & Aging, 23(7), 602. https://doi.org/10.1007/s12603-019-1214-x

Sangkhae, V., & Nemeth, E. (2017). Regulation of the Iron Homeostatic Hormone Hepcidin [Review of Regulation of the Iron Homeostatic Hormone Hepcidin]. Advances in Nutrition, 8(1), 126. Elsevier BV. https://doi.org/10.3945/an.116.013961

Shin, D. H., Kim, H. S., Park, M., Suh, I. B., & Shin, K. S. (2015). Utility of Access Soluble Transferrin Receptor (sTfR) and sTfR/log Ferritin Index in Diagnosing Iron Deficiency Anemia. PubMed, 45(4), 396. https://pubmed.ncbi.nlm.nih.gov/26275690

Silvestri, L., Pettinato, M., Furiosi, V., Volpe, L. B., Nai, A., & Pagani, A. (2023). Managing the Dual Nature of Iron to Preserve Health. International Journal of Molecular Sciences, 24(4), 3995.

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SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

https://doi.org/10.3390/ijms24043995

Skikne, B. (2008). Serum transferrin receptor. American Journal of Hematology, 83(11), 872. https://doi.org/10.1002/ajh.21279

Sohal, A., & Kowdley, K. V. (2024). A Review of New Concepts in Iron Overload. PubMed, 20(2), 98. https://pubmed.ncbi.nlm.nih.gov/38414914

Tawfik, Y. M. K., Billingsley, H., Bhatt, A. S., Aboelsaad, I., Alkhezi, O. S., Lutsey, P. L., & Buckley, L. F. (2024). Absolute and Functional Iron Deficiency in the US, 2017-2020. JAMA Network Open, 7(9). https://doi.org/10.1001/jamanetworkopen.2024.33126

Tayal, A., Kaur, J., Sadeghi, P., & Maitta, R. W. (2025). Molecular Mechanisms of Iron Metabolism and Overload. Biomedicines, 13(9), 2067. https://doi.org/10.3390/biomedicines13092067

Theil, E. C., & Goss, D. J. (2009). Living with Iron (and Oxygen): Questions and Answers about Iron Homeostasis [Review of Living with Iron (and Oxygen): Questions and Answers about Iron Homeostasis]. Chemical Reviews, 109(10), 4568. American Chemical Society. https://doi.org/10.1021/cr900052g

Tussing-Humphreys, L., Pustacioglu, C., Nemeth, E., & Braunschweig, C. (2012). Rethinking Iron Regulation and Assessment in Iron Deficiency, Anemia of Chronic Disease, and Obesity: Introducing Hepcidin [Review of Rethinking Iron Regulation and Assessment in Iron Deficiency, Anemia of Chronic Disease, and Obesity: Introducing Hepcidin]. Journal of the Academy of Nutrition and Dietetics, 112(3), 391. Elsevier BV. https://doi.org/10.1016/j.jada.2011.08.038

Ueda, N., & Takasawa, K. (2018). Impact of Inflammation on Ferritin, Hepcidin and the Management of Iron Deficiency Anemia in Chronic Kidney Disease. Nutrients, 10(9), 1173. https://doi.org/10.3390/nu10091173

Velandia, M. L. S. C., Bohórquez, M. M. C., Bautista, M. A. I. M., MSc., A. L. O. R., & Vélez, Z. (2005). Estrategias diagnósticas utilizadas para detectar deficiencias de hierro

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SYNERGY EDUCATIONAL LEARNING INSTITUTE (SMC-PRIVATE) LIMITED

subclínicas y asociadas a enfermedades crónicas. Nova, 3(4), 58. https://doi.org/10.22490/24629448.337

Wang, C., & Babitt, J. L. (2016). Hepcidin regulation in the anemia of inflammation [Review of Hepcidin regulation in the anemia of inflammation]. Current Opinion in Hematology, 23(3), 189. Lippincott Williams & Wilkins. https://doi.org/10.1097/moh.0000000000000236

Wessling-Resnick, M. (2010). Iron Homeostasis and the Inflammatory Response [Review of Iron Homeostasis and the Inflammatory Response]. Annual Review of Nutrition, 30(1), 105. Annual Reviews. https://doi.org/10.1146/annurev.nutr.012809.104804

Wittkamp, C., Traeger, L., Ellermann, I., Eveslage, M., & Steinbicker, A. U. (2018). Hepcidin as a potential predictor for preoperative anemia treatment with intravenous iron—A retrospective pilot study. PLoS ONE, 13(8). https://doi.org/10.1371/journal.pone.0201153

Zhao, J., Zhong, H., Zhao, J., Wang, G., Wang, Z., Zhang, X., Lu, G., & Wang, H. (2024). Relationship between obesity and iron metabolism: Insights from NHANES and Mendelian randomization studies. Research Square (Research Square). https://doi.org/10.21203/rs.3.rs-4503071/v1

Zhong, M., Wang, Y., Min, J., & Wang, F. (2025). Iron metabolism and ferroptosis in human health and disease [Review of Iron metabolism and ferroptosis in human health and disease]. BMC Biology, 23(1). BioMed Central. https://doi.org/10.1186/s12915-025-02378-6

Zhu, S., Liu, C., Zhao, C., Chen, G., Meng, S., Ma, H., Xiang, M., & Xie, Y. (2022). Increased Serum Soluble Transferrin Receptor Levels Were Associated With High Prevalence of Cardiovascular Diseases: Insights From the National Health and Nutrition Examination Survey 2017–2018. Frontiers in Cell and Developmental Biology, 10, 874846. https://doi.org/10.3389/fcell.2022.874846.

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