(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 3, Page No: 363-369
May-June 2021

Role of Serum Ferritin in Diagnosing Iron Deficiency Inflammatory Conditions

Dr. Anil Batta
Professor and Head, Department Of Medical Biochemistry
Govt.Medical College, Amritsar

***Corresponding Author:**
Dr. Anil Batta
Professor and Head, Department of Medical Biochemistry Govt.Medical College, Amritsar

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT

Patients suffering from inflammatory bowel disease (IBD), chronic heart failure (CHF), and chronic kidney disease (CKD), have substantial loss of iron. These patients may have devastating effect with display of harmful clinical features. Under normal conditions, serum ferritin levels act as a specific marker for iron levels. Ferritin is an acute-phase protein that is raised in response to inflammation, vitiating the diagnosis. Cytokines also cause an increase in protein hepcidin expression, which balances absorption of iron in diet. It promotes sequestration of iron by ferritin within storage sites. Patients with inflammatory conditions may thus have rare levels to be provided for erythropoisis and all other cells functioning of hepcidin expression, despite normal or high levels of serum ferritin. Standard threshold for iron deficiency (<30 μg/L) .Consequently it does not apply and transferrin saturation (TSAT), a marker of iron availability, is calculated. A serum ferritin threshold of 125 μg/L or TSAT < 30% can be considered diagnostic for iron deficiency in CHF, CKD, and IBD. If serum ferritin is 100–300 μg/L, TSAT < 20% is required to confirm iron deficiency. Routine estimation of serum ferritin and TSAT in these at-risk groups is ratified so that iron deficiency can be detected and managed.

Keywords: Ferritin, IBD, CKD, Iron Deficiency, Anaemia, TSAT, CHF,

INTRODUCTION

1. IRON DEFICIENCY IN INFLAMMATORY DISEASES

Iron deficiency is a major global health problem, representing one of the leading nonfatal disease conditions throughout [1], and is common in everyday clinical practice [2]. Quick diagnosis and treatment despite is required its prevalence, however, iron deficiency is often overlooked, especially in patients with chronic inflammatory conditions, partly due to the heterogeneity of definitions provided in clinical practice guidelines [3]. Iron deficiency can be defined as “a health-related” condition in which iron availability is inadequate to meet the body’s requirements and which can be present with or without anemia” [4]. Most prevalent are poorly nourished who require high iron demands, such as pregnant women or adolescents, and individuals with chronic blood loss, like, uterine or gastrointestinal bleeding [5]. In addition, growing attention is now laid to the iron level of patients with inflammatory conditions, which predispose them to iron deficiency [4, 6]. The most frequent of these are chronic heart failure (CHF), chronic kidney disease (CKD), and inflammatory bowel disease (IBD). Overall, however, approximately 50% of patients with chronic heart failure, 24–85% of patients with chronic kidney disease, and 45% of patients with irritated bowel syndrome are iron-deficient (Table 1). The cause of iron deficiency is multifold [2, 4, 5]. The reporting patients with long persisting illness may have a poor appetite and inadequate dietary iron intake. This can be exploded by impaired iron absorption from the intestinal lumen caused by medications such as proton pump inhibitors [7], histamine-2 receptor antagonists [7], and calcium-based phosphate binders [8], while antiplatelet treatment can enhance the risk of gross gastrointestinal bleeding [9]. Blood is lost

with repetitive sampling, from gastrointestinal bleeding in IBD, or in CKD patients on prolonged hemodialysis will also contribute. In addition to these patient-specific etiologies, CHF, CKD, and IBD share the common effect of an ongoing inflammatory stimulus. In these chronic conditions, high hepcidin levels can restrict the uptake of dietary iron and, over time, lead to iron deficiency with reduced availability of iron for essential cellular functions [10]. Clinical diagnosis with iron deficiency and iron therapy are expedited when deficiency is so severe to decrease iron stores and stop RBCs synthesis. With lots of biochemical and physiological functions carried out by iron other than blood cell synthesis [11] and lack of iron carries out various adverse effects in addition. As well as being critical for erythropoiesis, iron takes part as isoenzymes of various enzymes in the ETC [12], which may explain subjective feeling of weakness. Iron deficiency weakens immunity also [3]. Proper diagnosis and infusion of iron is mandatory especially in several inflammatory conditions. Normally iron deficiency is calculated by measuring serum ferritin. In the cases of proinflammatory conditions it is difficult. Correlation of serum ferritin and, especially, how levels of serum ferritin are influenced by inflammation leads to correct diagnosis.

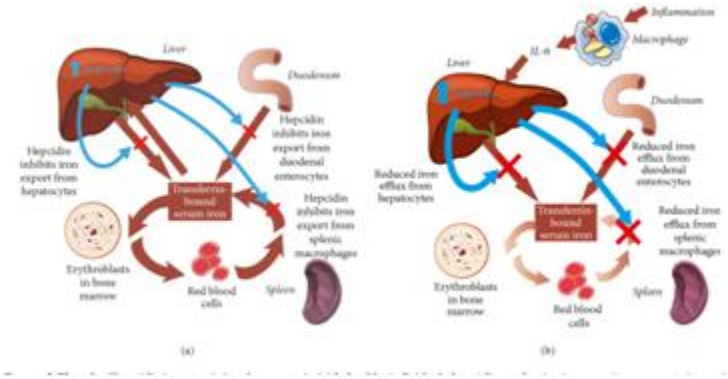

Figure 1: The role of hepcidin in systemic iron homeostasis. (a) In healthy individuals, hepcidin production increases in response to increasing levels of transferrin-bound serum iron and iron stores. Hepcidin internalizes and degrades the iron transporter ferroportin, restricting the export of iron from enterocytes and from iron stores in hepatocytes and macrophages, to restore normal iron levels. (b) In inflammatory conditions, hepcidin production increases in response to inflammatory cytokines such as IL-6, disrupting the usual homeostatic mechanisms. Ferroportin is internalized and degraded, reducing transmembrane export of iron, and the availability of iron to bind to transferrin is restricted.

2. FERRITIN: AN AMAZING IRON STORAGE PROTEIN

Intracellular ferritin is a complex constituted by two types of subunit, H (heavy chain) and L (light chain) [4]. Twenty-four subunits combine to form a shell-like molecule that constitutes a cavity that can store up to approximately 4,500 iron atoms [5, 6]. The H chains of ferritin have ferroxidase activity and convert Fe (II) to Fe (III) as the iron is internalized within the ferritin complex [7]. Fe (III) is concentrated within the core of ferritin in the form of ferric oxyhydroxide phosphate [5]. Concentration of high amounts of iron in this unreactive form within ferritin reduces the concentration of reactive intracellular Fe (II), lowering the potential for generation of oxidant species. The L-subunit promotes formation of the iron core within the ferritin shell [4]. The ratio of H-subunits and L-subunits varies from organ to organ, with L-subunits concentrated in the liver and spleen; on the other hand H-subunits are dominated in the heart and kidney [8]. Secretions from macrophages, or following cell death and lysis also increase ferritin levels [1]. Serum ferritin is iron-poor as compared to intracellular ferritin and formed exclusively of L-subunits [3], while glycosylated subunits, which are similar to the L-chain [3]. Under normal conditions, serum ferritin exhibits correlation with iron stores in liver biopsy samples [4], the "gold standard" for measuring the amount of iron in the body. However,

Volume 4, Issue 3; May-June 2021; Page No 363-369

serum ferritin is affected by the presence of inflammation, since serum ferritin is an "acute-phase protein". The acute-phase response is a major physiological defense reaction, whereby the body aims to restore physiological homeostasis in the face of inflammation [5]. Serum levels of positive acute-phase proteins including ferritin, C-reactive protein (CRP), and alpha-1-acid glycoprotein (AGP) rise dramatically as part of the inflammatory response, mediated by increased expression of cytokines such as IL-6 [5–7]. Increased levels of serum ferritin as part of the acute-phase response mean that serum ferritin levels no longer correlate with iron availability in the presence of inflammation. Assessment of patients' iron status becomes more complex under these conditions and requires wider awareness of iron homeostatic mechanisms.

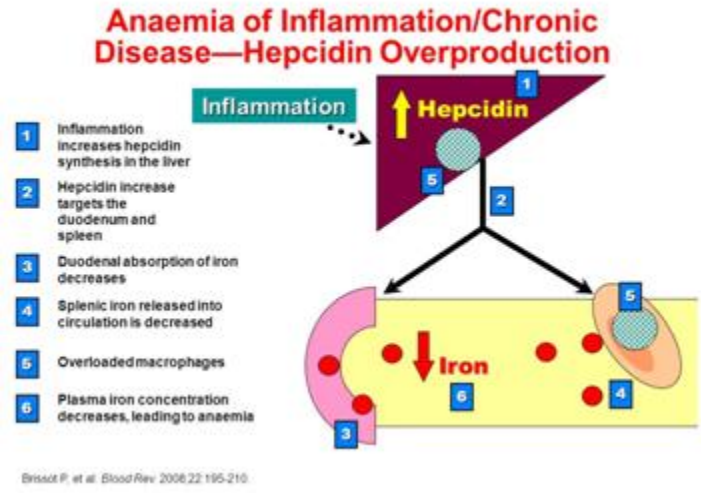

Fig:2

3. FERRITIN AS A COMPONENT OF THE IRON REGULATORY SYSTEM IN HEALTHY INDIVIDUALS

The uptake, transport, and storage of iron are regulated in the body, while ferritin playing an important role. Dietary iron in the form of inorganic Fe (III) is absorbed from the intestinal lumen across the brush border of duodenal enterocytes via active uptake mechanisms that reduce Fe (III) to Fe (II). This uptake of iron from the lumen occurs via the divalent metal transporter-1 (DMT1), which is expressed on the apical membrane of the duodenal enterocytes and is closely associated with the membrane ferrireductase DCYT-B that is responsible for the reduction of Fe (III) [5]. Once within the enterocyte, Fe (II) is then exported across the basolateral membrane by the Fe (II) transporter ferroportin [9]. After export, it is deoxidized from Fe (II) to Fe (III) by the membrane-bound ferroxidase hephaestin and possibly by intestinal ceruloplasmin [8]. Fe (III) is then released into the circulation, where it binds to the iron transport glycoprotein transferrin. Transferrin has two high-affinity binding sites for Fe (III) which maintains the iron in a redox-inert state [9]. Iron is delivered by transferrin to cells by binding to transferrin receptor 1, which is expressed on the cell surface as a response to low intracellular iron levels. Circulating iron-laden transferrin binds to transferrin receptor 1, triggering endocytosis and uptake of the iron cargo. Once internalized, the iron may be transported to mitochondria for the synthesis of heme or of iron-sulfur clusters, which are essential cofactors of various enzymes or are used to synthesize other iron-containing enzymes that are important for fundamental cellular functions such as DNA synthesis or repair [9]. If not required immediately, the iron is instead safely stored within the cell in the form of ferritin [7]. The main intracellular storage compartment, where most ferritin is located, is the cytosol. In response to the cell's need, ferritin is targeted towards lysosomes for degradation by a specific cargo molecule (NCOA4) via a process called ferritinophagy [4]. The iron is then in the so-

Volume 4, Issue 3; May-June 2021; Page No 363-369

called labile iron pool, a form of readily available cytosolic iron, and can be used for cellular functions.

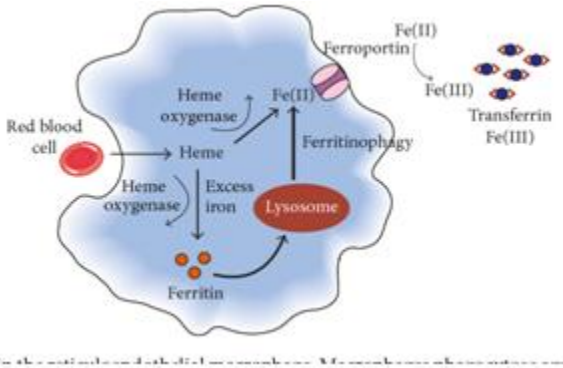

Figure 3: Normal iron homeostasis in the reticuloendothelial macrophage. Macrophages phagocytose aged or damaged red blood cells, using heme oxygenase 1 to release iron from heme, a recycling process that accounts for… Expand

The body's stores of ferritin dominate in hepatocytes and in the macrophages of the RE system. Macrophages phagocytose aged or damaged erythrocytes, recycle the iron deposited in heme using heme with the help of oxygenase 1 to release the iron [9] (Figure 1). This recycling bears 90% of the body's iron needs in a day, with only ~10% intestinal absorption [9]. Iron comes out from these storage sites as Fe (II) via ferroportin in the cell membrane. The export process is coupled to reoxidation of Fe (II) to Fe (III) by the ferroxidase enzyme ceruloplasmin and is followed by loading of Fe (III) onto transferrin for systemic distribution to other sites [6]. Transferrin saturation (TSAT) is a marker for the amount of iron helps in red cell synthesis or other cellular needs. Systemic iron homeostasis is usually maintained in the face of varied dietary intake and varying levels of demand by regulatory mechanisms coordinated by the hepatic hormone hepcidin. Hepcidin binds to and leads to internalization and degradation of the iron exporter ferroportin. This reduces the mobilization of iron into the circulation from enterocytes and from iron stores in hepatocytes and macrophages (Figure 2(a)) [4]. In healthy individuals, increasing levels of transferrin-bound iron and elevated iron stores stimulate hepcidin upregulation, which suppresses iron export and thus lowers circulating levels of iron [4]. Hepcidin production is inhibited in the presence of decreasing levels of iron in the blood circulation and in tissues or due to stimuli such as hypoxia and intensified erythropoiesis after blood loss [9]. In this situation, reduced hepcidin levels stimulate increased iron acquisition and release by the enterocytes in the duodenum and efflux of ferritin-bound iron from storage sites to normalize iron availability and meet increased erythroid needs.

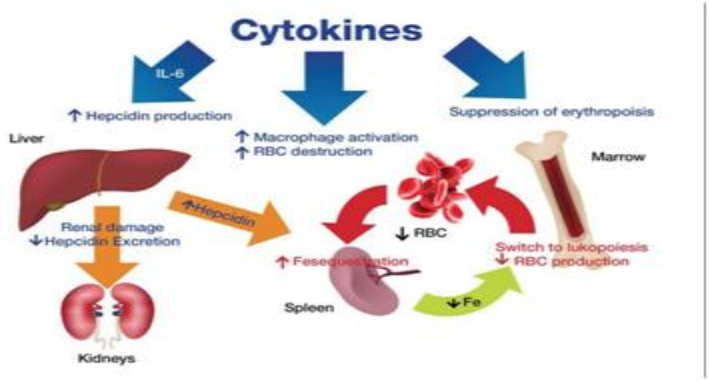

Fig:4

Volume 4, Issue 3; May-June 2021; Page No 363-369

9. Special Situations Affecting Serum Ferritin Levels

Some of these (particularly obesity and old age) are frequent in patients with inflammatory conditions such as CHF. Obese patients are known to have an increased risk for iron deficiency [12]. Patients with high body mass index have increased levels of hepcidin [83], likely due to adiposity-related inflammation [84], resulting in restricted dietary iron absorption [13] and reduced TSAT levels [2]. As in other inflammatory conditions, serum ferritin levels are higher than in nonobese individuals [86]. Older patients are also prone to absolute iron deficiency due to factors such as an iron-poor diet and medications that inhibit dietary iron absorption [8]. Low-grade inflammation [8] is often present in older people [8–9], with the potential for functional iron deficiency. Inadequate iron for erythropoiesis, as determined by bone marrow aspirates, is frequently found even in elderly patients with serum ferritin levels up to 75 μg/L[9]. Concomitant diseases can also complicate the interpretation of serum ferritin concentrations. Ferritin levels are elevated in the serum of many patients with cancer, particularly in the presence of more aggressive disease [2], due to chronic inflammatory effects as indicated by upregulation of IL-6, CRP, and hepcidin [3–5]. Patients with liver disease exhibit complex iron homeostasis disturbances [9] that become more pronounced with greater severity of disease [7]. Reduced expression of ferroportin and the consequent inhibition of iron export from hepatocytes [9] can lead to iron deposits in the liver [9], stimulating increased hepcidin production [7]. Hepatitis promotes an increase in serum ferritin in response to the inflammatory stimulus [9], such that functional iron deficiency can develop. In nonalcoholic liver disease, for example, approximately one-third of patients have elevated serum ferritin levels [9, 10]. Careful interpretation of serum ferritin levels in the obese and elderly and in patients with liver disease is required, and TSAT measurement should be performed before ruling out a diagnosis of iron deficiency.

MECHANISMS CONTRIBUTING TO ID IN CICS

Condition	Reduced iron absorption	Increased iron loss
CKD	Anorexia/GI tract edema; frequent use of proton pump inhibitors; use of phosphate chelators; high hepcidin with blockade of duodenal absorption	Uremic platelet dysfunction; antiplatelet therapy and anticoagulation; blood loss from hemodialysis
HF	Anorexia/GI tract edema; high hepcidin with blockade of duodenal absorption	Antiplatelet therapy and anticoagulation
IBDs	High hepcidin with blockade of duodenal absorption; small bowel resection	Chronic diarrhea with high epithelial turnover; GI tract bleeding; use of corticosteroids
Obesity	High hepcidin due to adipose tissue inflammation;	Increased uterine bleeding (when associated with

Volume 4, Issue 3; May-June 2021; Page No 363-369

Condition		Reduced iron absorption	Increased iron loss	
		bariatric surgery	polycystic ovarian syndrome)	
Liver disease		Anorexia/GI tract edema; diarrhea caused by laxatives	Variceal bleeding; thrombocytopenia; coagulopathy	
Rheumatologic disorders		High hepcidin with blockade of duodenal absorption	Use of corticosteroids and NSAIDs	
Chuang *et al.*	Functional (30% ↓ in EPO dose after intravenous iron 2200 mg over 24 wk)	Serum ferritin < 300 ng/ml	CHr 78%serum ferritin 83%	CHr 87%serum ferritin 57%

10. Conclusions

Iron deficiency often remains undiagnosed and untreated in the context of inflammatory conditions [10]. It may not be suspected because the typical symptoms, such as fatigue, can be similar to those of the underlying disease. Even in the absence of anemia, however, iron deficiency can negatively affect patients' quality of life, and expert guidelines in CHF, CKD, and IBD recognize that iron deficiency should be detected and managed [6]. Routine laboratory testing is advisable, with reassessment every 3 to 12 months or in the event of disease progression [4]. Measurement of both serum ferritin and TSAT offers a straightforward means to identify the presence of iron deficiency in these at-risk groups [4]. A diagnosis of iron deficiency can be made in these conditions, regardless of whether anemia is present, if serum ferritin is <100 μg/L or TSAT is <20%, using TSAT to confirm iron deficiency if serum ferritin is between 100 and 300 μg/L [4, 5]. This approach improves diagnostic sensitivity and allows prompt initiation of treatment. Iron replenishment can be achieved despite the presence of inflammation by use of intravenous iron therapies, as per expert guidelines [3, 4, 5]. The intravenous route bypasses the hepcidin-induced blockade of oral iron uptake and release and avoids the problem of intolerance to oral iron [6, 10]. Clinical trials have shown intravenous iron to achieve iron repletion more rapidly and efficiently than oral iron, including studies in patients with inflammatory conditions [10]. Intravenous iron should be avoided in case of potential infections. With effective therapy available, surveillance of serum ferritin and TSAT levels in these at-risk groups is prudent so that iron deficiency can be treated before progression to symptomatic anemia or other complications. At the same time, iron overload should be avoided, and markers to be followed need to be established.

REFERENCES

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, "Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of disease Study 2016," *The Lancet*, vol. 390, no. 10100, pp. 1211–1226, 2017.
2. C. Camaschella, "Iron-deficiency anemia," *The New England Journal of Medicine*, vol. 372, no. 19, pp. 1832–1843, 2015.

Volume 4, Issue 3; May-June 2021; Page No 363-369

3. L. Peyrin-Biroulet, N. Williet, and P. Cacoub, "Guidelines on the diagnosis and treatment of iron deficiency across indications: A systematic review," *American Journal of Clinical Nutrition*, vol. 102, no. 6, pp. 1585–1594, 2015.
4. M. D. Cappellini, J. Comin-Colet, A. de Francisco et al., "Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management," *American Journal of Hematology*, vol. 92, no. 10, pp. 1068–1078, 2017.
5. C. Camaschella, "New insights into iron deficiency and iron deficiency anemia," *Blood Reviews*, vol. 31, no. 4, pp. 225–233, 2017.
6. L. De Franceschi, A. Iolascon, A. Taher, and M. D. Cappellini, "Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment," *European Journal of Internal Medicine*, vol. 42, pp. 16–23, 2017.
7. J. R. Lam, J. L. Schneider, C. P. Quesenberry, and D. A. Corley, "Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency," *Gastroenterology*, vol. 152, no. 4, pp. 821–829, 2017.
8. T. McDonagh and I. C. Macdougall, "Iron therapy for the treatment of iron deficiency in chronic heart failure: Intravenous or oral?" *European Journal of Heart Failure*, vol. 17, no. 3, pp. 248–262, 2015.
9. K. Barada, H. Abdul-Baki, I. I. El Hajj, J. G. Hashash, and P. H. Green, "Gastrointestinal bleeding in the setting of anticoagulation and antiplatelet therapy," *Journal of Clinical Gastroenterology*, vol. 43, no. 1, pp. 5–12, 2009.
10. M. Wessling-Resnick, "Iron homeostasis and the inflammatory response," *Annual Review of Nutrition*, vol. 30, pp. 105–122, 2010.
11. E. A. Jankowska, P. Rozentryt, A. Witkowska et al., "Iron deficiency: An ominous sign in patients with systolic chronic heart failure," *European Heart Journal*, vol. 31, no. 15, pp. 1872–1880, 2010.
12. I. T. Klip, J. Comin-Colet, A. A. Voors et al., "Iron deficiency in chronic heart failure: An international pooled analysis," *American Heart Journal*, vol. 165, no. 4, pp. 575–e3, 2013.
13. C. Enjuanes, I. T. Klip, J. Bruguera et al., "Iron deficiency and health-related quality of life in chronic heart failure: Results from a multicenter European study," *International Journal of Cardiology*, vol. 174, no. 2, pp. 268–275, 2014.
14. J. Comín-Colet, C. Enjuanes, G. González et al., "Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status," *European Journal of Heart Failure*, vol. 15, no. 10, pp. 1164–1172, 2013.
15. C.-Y. Hsu, C. E. McCulloch, and G. C. Curhan, "Iron status and hemoglobin level in chronic renal insufficiency," *Journal of the American Society of Nephrology*, vol. 13, no. 11, pp. 2783–2786, 2002.
16. S. Fishbane, S. Pollack, H. I. Feldman, and M. M. Joffe, "Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988-2004," *Clinical Journal of the American Society of Nephrology*, vol. 4, no. 1, pp. 57–61, 2009.
17. W. McClellan, S. L. Aronoff, W. K. Bolton et al., "The prevalence of anemia in patients with chronic kidney disease," *Current Medical Research and Opinion*, vol. 20, no. 9, pp. 1501–1510, 2004.

Volume 4, Issue 3; May-June 2021; Page No 363-369