

Research Article

Iron deficiency without anaemia in adults with fatigue and chronic disease

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Abstract: Iron deficiency without anaemia is a common but frequently overlooked clinical state in which iron stores or circulating iron availability are reduced while haemoglobin remains within the reference range. This distinction matters because iron is required not only for erythropoiesis, but also for mitochondrial function, skeletal muscle metabolism, oxygen handling, immune regulation, and neurological processes. Adults with fatigue, women with menstrual blood loss, patients with chronic inflammatory disease, and patients with heart failure may experience symptoms and impaired quality of life before anaemia develops. Diagnosis is often delayed when clinicians rely on haemoglobin alone. Ferritin is the most useful first-line marker of iron stores, but interpretation changes in inflammation because ferritin is an acute-phase reactant. In otherwise healthy adults, ferritin below 30 µg/L is commonly used to support iron deficiency; in chronic inflammatory conditions such as heart failure, chronic kidney disease, and inflammatory bowel disease, ferritin below 100 µg/L or transferrin saturation below 20% may indicate clinically relevant iron deficiency, while ferritin between 100 and 300 µg/L generally requires transferrin saturation below 20% for diagnosis. Evidence from randomized trials and systematic reviews suggests that iron treatment can reduce subjective fatigue in selected non-anaemic iron-deficient adults, especially women with low ferritin, although improvement in objective physical capacity is less consistent. In heart failure, intravenous iron improves symptoms, functional status, and quality of life in several trials, with less certain effects on mortality. The clinical task is to identify iron deficiency early, determine its cause, treat appropriately, and measure response using both biochemical and patient-centred outcomes.

Keywords: Iron deficiency without anaemia, non-anaemic iron deficiency, fatigue, ferritin, transferrin saturation, women's health, inflammatory disease, heart failure, quality of life, intravenous iron

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Introduction

Many patients with iron deficiency are told that their blood count is normal. This may be technically correct and clinically incomplete. Haemoglobin falls late in the process of iron depletion. Before anaemia appears, ferritin may already be low, transferrin saturation may be reduced, and tissues that depend on iron-containing enzymes may be functioning below normal. The patient may describe exhaustion, poor exercise tolerance, reduced concentration, restless legs, hair shedding, palpitations, dizziness, or a general loss of capacity. These symptoms are not specific, but they should not be dismissed simply because haemoglobin remains normal.

Iron deficiency without anaemia is usually defined as evidence of depleted iron stores or reduced iron availability with haemoglobin above the threshold for anaemia. The condition has also been called non-anaemic iron deficiency, latent iron deficiency, iron depletion, or iron deficiency without anaemia. The terminology varies, but the clinical issue is the same: the body has insufficient accessible iron before red cell mass has fallen enough to satisfy the formal definition of anaemia (1-4).

This review examines iron deficiency without anaemia in adults with fatigue and chronic disease. It focuses on diagnostic thresholds, women's health, inflammatory disease, heart

failure, treatment response, and quality of life. The aim is not to label every tired adult as iron deficient. It is to show why haemoglobin alone is an inadequate gatekeeper for iron assessment in selected patients.

Evidence base

This narrative review used PubMed-indexed literature on non-anaemic iron deficiency, iron deficiency without anaemia, ferritin thresholds, transferrin saturation, fatigue, women's health, heavy menstrual bleeding, inflammatory bowel disease, chronic inflammatory disease, chronic kidney disease, heart failure, oral iron, intravenous iron, and quality of life. The included sources comprised reviews, clinical guidance, systematic reviews, randomized controlled trials, consensus recommendations, and disease-specific studies.

The evidence is uneven across patient groups. The strongest direct symptom data for iron deficiency without anaemia come from studies in menstruating or premenopausal women with fatigue and low ferritin (9-11,20,21). Heart failure has a separate evidence base because trials commonly define iron deficiency using ferritin and transferrin saturation, and benefits of intravenous iron are often reported regardless of anaemia status (23-30). In inflammatory bowel disease and other chronic inflammatory disorders, the main challenge is diagnostic interpretation because ferritin rises with inflammation and may conceal iron-restricted states (5,6,31-34).

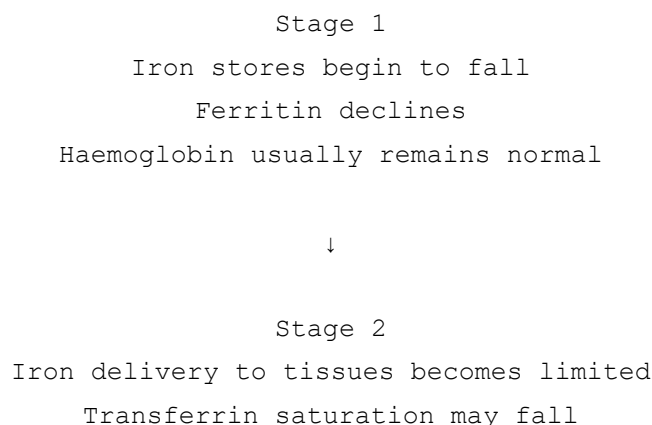
Why iron deficiency can cause symptoms before anaemia

Iron is best known for its role in haemoglobin, but that is not its only function. Iron is part of myoglobin, cytochromes, mitochondrial enzymes, ribonucleotide reductase, and many proteins involved in energy production and cellular metabolism. A fall in haemoglobin reduces oxygen-carrying capacity. A fall in available iron may impair tissue function before haemoglobin declines (1,2).

This explains why fatigue can appear early. Fatigue in iron deficiency is likely multifactorial. Reduced mitochondrial energy production, altered muscle oxygen use, impaired myoglobin function, changes in neurotransmitter metabolism, sleep disruption from restless legs, and the inflammatory state that caused or accompanied the deficiency may all contribute. In chronic disease, the problem can be more complex because symptoms may be caused by the underlying illness, iron deficiency, medications, poor sleep, deconditioning, depression, pain, or all of these together.

Iron biology also changes during inflammation. Interleukin-6 and other inflammatory signals increase hepatic hepcidin production. Hepcidin degrades ferroportin, the iron export channel on enterocytes and macrophages. As a result, oral iron absorption falls and iron becomes trapped in storage sites. A patient can therefore have adequate or even increased measured ferritin but poor circulating iron availability. This is often called functional iron deficiency (5,6).

Figure 1 How iron deficiency can exist before anaemia



Fatigue, restless legs, reduced endurance, poor concentration may appear

↓

Stage 3

Iron-restricted erythropoiesis develops
Reticulocyte haemoglobin may fall
Mean corpuscular volume may still be normal

↓

Stage 4

Iron-deficiency anaemia appears
Haemoglobin falls
Microcytosis and hypochromia may develop later

The figure shows a typical sequence. In inflammatory disease, the pattern can be less clear because ferritin may be normal or raised despite restricted iron availability.

Diagnostic thresholds and the problem with ferritin

Ferritin is the most useful first-line test for iron stores in adults without major inflammation. A very low ferritin is highly specific for iron deficiency. The difficulty is deciding where “low” begins. Traditional cut-offs such as 12 or 15 µg/L are specific but may miss many symptomatic adults with depleted or insufficient stores. Many clinical reviews and recent recommendations support ferritin below 30 µg/L as a practical adult threshold for iron deficiency in the absence of inflammation (1,4,8).

In fatigue trials involving non-anaemic women, higher entry thresholds were often used. Verdon et al. studied non-anaemic women with unexplained fatigue and found benefit from oral iron, especially when ferritin was low or borderline (9). Vaucher et al. enrolled menstruating non-anaemic women with fatigue and ferritin below 50 µg/L and found improvement in fatigue after oral iron therapy (10). These trials do not prove that every patient with ferritin below 50 µg/L needs iron. They do show that symptoms may improve in selected patients even when haemoglobin is normal.

Inflammation changes interpretation. Ferritin is an acute-phase reactant. In heart failure, chronic kidney disease, and inflammatory bowel disease, a ferritin of 80 or 150 µg/L may not mean iron sufficiency if transferrin saturation is low. Dignass et al. noted that ferritin below 100 µg/L or transferrin saturation below 20% can be considered diagnostic for iron deficiency in chronic heart failure, chronic kidney disease, and inflammatory bowel disease; if ferritin is 100-300 µg/L, transferrin saturation below 20% is generally needed to confirm iron deficiency (5). Similar principles appear in expert recommendations across inflammatory conditions (6).

Serum iron alone is a poor diagnostic test. It fluctuates with time of day, diet, inflammation, and recent iron intake. It should be interpreted as part of an iron panel rather than alone. Transferrin saturation is more informative because it estimates the proportion of transferrin binding sites occupied by iron. C-reactive protein can help interpret ferritin when inflammation is suspected.

Table 1 Practical interpretation of iron tests in adults without anaemia

Clinical context	Ferritin pattern	Transferrin saturation pattern	Likely interpretation
Otherwise healthy adult with fatigue	<30 µg/L	Often <20% but may be normal	Iron deficiency likely
Menstruating woman with unexplained fatigue	<50 µg/L in several fatigue trials	May be low or borderline	Iron deficiency may be clinically relevant
Inflammatory bowel disease in remission	<30 µg/L	Often low	Absolute iron deficiency likely
Active inflammatory disease	<100 µg/L or ferritin 100-300 µg/L with TSAT <20%	<20% supports restricted availability	Iron deficiency or functional iron deficiency likely
Heart failure	<100 µg/L or 100-299 µg/L with TSAT <20%	<20% important for diagnosis	Clinically relevant iron deficiency
Chronic kidney disease	Ferritin may be misleadingly normal or high	TSAT often central to interpretation	Functional iron deficiency should be considered
Normal ferritin with high CRP	May be falsely reassuring	TSAT and other markers may be needed	Iron deficiency cannot be excluded confidently

Women's health and the missed burden of iron depletion

Women of reproductive age carry a high burden of iron deficiency because of menstruation, pregnancy, childbirth, postpartum blood loss, and in some patients heavy menstrual bleeding. A primary care study found a high prevalence of iron deficiency without anaemia among women aged 18-50 years when ferritin below 30 ng/mL was used, and only a minority progressed to anaemia over five years (13). This finding supports an important point: waiting for anaemia means waiting until a later stage of disease.

Heavy menstrual bleeding is one of the most common and most correctable causes. A review of guidelines on heavy menstrual bleeding found that recommendations vary in how consistently they advise screening for iron deficiency and iron-deficiency anaemia, despite the clear connection between menstrual blood loss and reduced iron stores (14). Munro et al. also described heavy menstrual bleeding as a major contributor to iron deficiency and iron-deficiency anaemia in girls and women of reproductive age (15).

Women may present with fatigue, poor concentration, reduced work capacity, headache, dizziness, restless legs, hair shedding, or exercise intolerance. These symptoms overlap with thyroid disease, mood disorders, sleep disturbance, chronic infection, autoimmune disease, pregnancy, and perimenopause. Iron deficiency is not the only explanation. It is, however, one of the explanations that can be tested and treated.

The clinical history should include menstrual pattern, clotting, flooding, duration of bleeding, intermenstrual bleeding, pregnancies, postpartum status, diet, blood donation, gastrointestinal symptoms, use of antiplatelet or anticoagulant therapy, non-steroidal anti-inflammatory drugs, bariatric surgery, and family history of bleeding disorders. Treating iron deficiency without addressing heavy menstrual bleeding may produce temporary improvement followed by recurrence.

Fatigue and treatment response in non-anaemic adults

The strongest direct evidence for symptom improvement comes from randomized trials in women with fatigue and low ferritin. In the BMJ trial by Verdon et al., non-anaemic women with unexplained fatigue were treated with oral iron or placebo; fatigue improved more with iron, and benefit appeared greater in those with low or borderline ferritin (9). Vaucher et al. later showed that oral iron improved fatigue in non-anaemic menstruating women with ferritin below 50 µg/L, and suggested reassessment after six weeks (10).

The evidence is positive but not uniform. Waldvogel et al. studied non-anaemic but iron-deficient female blood donors after donation and found biochemical improvement with oral iron but no significant clinical improvement in fatigue over four weeks (20). This suggests that context matters. Fatigue after blood donation may differ from chronic unexplained fatigue. Duration of deficiency, baseline symptom severity, ferritin level, follow-up period, and the reason for iron depletion may influence response.

Systematic review evidence supports a modest effect on subjective fatigue. Houston et al. concluded that iron supplementation in iron-deficient non-anaemic adults was associated with reduced subjective fatigue, but not with clear objective improvement in physical capacity (11). A systematic review and meta-analysis of intravenous iron in non-anaemic iron-deficient adults found reduced fatigue scores and improved physical function, but the certainty of evidence was limited for many outcomes (19).

The practical lesson is balanced. A therapeutic trial of iron is reasonable when a patient has fatigue plus documented iron deficiency, especially if ferritin is clearly low. However, fatigue should be reassessed rather than assumed to be solved. If ferritin rises but symptoms do not improve, clinicians should look for other causes. If symptoms improve but ferritin falls again, the source of iron loss or impaired absorption must be revisited.

Chart 1 Expected response after iron treatment in non-anaemic iron deficiency

Response domain	Usual timing	Clinical interpretation
Reticulocyte indices availability if measured	1-2 weeks	Early marrow iron
Ferritin and TSAT treatment failure	4-8 weeks	Biochemical repletion or
Fatigue symptoms patients	4-12 weeks	May improve in selected
Exercise tolerance subjective fatigue	6-12 weeks or longer	Less consistent than
Quality of life disease and symptom burden	4-24 weeks	Depends on baseline
Recurrence after stopping iron loss or malabsorption	Months	Suggests ongoing blood

Chronic inflammatory disease

In chronic inflammatory disease, iron deficiency is often both real and hidden. The patient may have rheumatoid arthritis, inflammatory bowel disease, chronic infection, chronic

kidney disease, heart failure, obesity-associated inflammation, cancer, or another inflammatory disorder. In these settings, ferritin may rise because of inflammation while tissue iron availability falls. The clinician may see a ferritin in the “normal” range and falsely conclude that iron status is adequate.

The hepcidin-ferroportin pathway explains much of this problem. Inflammation increases hepcidin, reducing intestinal absorption and limiting iron release from macrophages. Transferrin saturation falls because less iron is available in circulation. Ferritin may remain normal or high because iron is retained in storage sites and because ferritin itself rises as an acute-phase reactant (5,6).

Inflammatory bowel disease is a useful model because all mechanisms may coexist: chronic intestinal blood loss, reduced intake during flares, malabsorption, inflammation-driven hepcidin elevation, and intolerance of oral iron. ECCO consensus guidance recommends regular monitoring using haemoglobin, ferritin, transferrin saturation, and C-reactive protein, especially after correction because recurrence is common (31). A prospective study in patients with inflammatory bowel disease found that iron deficiency was associated with disease activity and anaemia risk, and emphasized early detection and management (33).

Iron deficiency without anaemia can affect patients with inflammatory bowel disease even during remission. Herrera-deGuise et al. reported that iron deficiency in the absence of anaemia impaired perceived health-related quality of life in patients with inflammatory bowel disease (32). This matters because fatigue in inflammatory bowel disease is often attributed only to intestinal inflammation, mood, sleep, or medication. Iron status may be one modifiable contributor.

Heart failure and iron deficiency without anaemia

Heart failure has changed the way clinicians think about iron deficiency. In heart failure, iron deficiency predicts worse symptoms, lower exercise capacity, poorer quality of life, and increased clinical risk, even when anaemia is absent. The widely used heart failure definition is ferritin below 100 µg/L, or ferritin 100-299 µg/L with transferrin saturation below 20% (5,23-30).

The FAIR-HF trial showed that intravenous ferric carboxymaltose improved symptoms, functional capacity, and quality of life in patients with chronic heart failure and iron deficiency, with or without anaemia (23). CONFIRM-HF found sustained improvement in functional capacity, symptoms, and quality of life over one year in symptomatic iron-deficient heart failure patients treated with ferric carboxymaltose (24). AFFIRM-AHF studied patients after acute heart failure and found that ferric carboxymaltose reduced heart failure hospitalisations, although the composite primary outcome narrowly missed conventional statistical significance (25). IRONMAN tested ferric derisomaltose and showed a numerically lower rate of recurrent heart failure hospitalisation and cardiovascular death, with interpretation affected by the COVID-19 pandemic and trial conduct issues (26).

The HEART-FID trial did not meet its primary hierarchical composite endpoint in ambulatory patients with heart failure and iron deficiency (27). This does not erase earlier findings, but it does make the field more nuanced. Meta-analyses suggest that intravenous iron reduces heart failure hospitalisation, while effects on cardiovascular and all-cause mortality remain uncertain (29,30). Oral iron has been less convincing. The IRONOUT HF trial found that high-dose oral iron did not improve exercise capacity over 16 weeks in patients with heart failure with reduced ejection fraction and iron deficiency (28).

Heart failure therefore illustrates two principles relevant to the wider review. First, iron deficiency can be clinically important without anaemia. Second, route of treatment matters. In inflammatory or hepcidin-mediated states, oral iron may not provide enough usable iron, while intravenous iron can bypass intestinal absorption.

Table 2 Clinical settings where iron deficiency without anaemia should be actively considered

Setting	Why haemoglobin alone is insufficient	Key tests
Menstruating women with fatigue	Iron stores may be depleted before anaemia develops	CBC, ferritin, TSAT, menstrual history
Heavy menstrual bleeding	Chronic loss can be substantial and recurrent	CBC, ferritin, TSAT, pregnancy test when relevant, gynaecological assessment
Inflammatory bowel disease	Blood loss, malabsorption, and inflammation may coexist	CBC, ferritin, TSAT, CRP, disease activity assessment
Heart failure	Iron deficiency worsens symptoms and function even without anaemia	CBC, ferritin, TSAT, renal function
Chronic kidney disease	Functional iron deficiency may occur with normal or high ferritin	CBC, ferritin, TSAT, renal profile, inflammatory markers
Blood donors	Repeated donation can reduce stores while haemoglobin screening remains acceptable	Ferritin in frequent donors where available
Post-bariatric surgery	Reduced intake and absorption can cause recurrent deficiency	CBC, ferritin, TSAT, B12, folate
Older adults with new iron deficiency	Occult gastrointestinal blood loss must be considered	CBC, ferritin, TSAT, stool or endoscopic evaluation based on risk

Choosing oral or intravenous iron

Oral iron remains appropriate for many adults with iron deficiency without anaemia. It is inexpensive, accessible, and effective when absorption is intact and losses are not excessive. Gastrointestinal adverse effects are common and include nausea, constipation, abdominal discomfort, diarrhoea, and dark stools. Poor tolerance is a major reason for non-adherence.

Traditional high-dose daily regimens are being reconsidered. Oral iron increases hepcidin, and increased hepcidin can reduce absorption from subsequent doses. Studies in iron-depleted women showed that daily or divided dosing can increase hepcidin and reduce fractional iron absorption, while alternate-day dosing may improve absorption and tolerability in some settings (35-37). In practice, lower-dose or alternate-day dosing can be useful when patients cannot tolerate daily therapy, although the optimal regimen depends on severity, urgency, and the patient's baseline status.

Intravenous iron should be considered when oral iron is not tolerated, ineffective, poorly absorbed, or unlikely to work because of active inflammation or heart failure. It may also be useful when rapid repletion is clinically important or when recurrent blood loss outpaces oral replacement. In non-anaemic fatigued women with low ferritin, intravenous iron studies such as the trial by Kravenbuehl et al. and the PREFER study showed improvement in fatigue in selected groups, especially with lower baseline ferritin, although adverse events and cost must be considered (21,22). In heart failure, the intravenous route has the strongest trial evidence (23-30).

Intramuscular iron is generally not favoured because of pain, staining, unpredictable absorption, and safer intravenous alternatives.

Table 3 Treatment approach according to clinical context

Patient context	Initial treatment approach	When to escalate or change
Fatigue with ferritin <30 µg/L and no inflammation	Oral iron plus search for cause	If intolerance, poor response, malabsorption, or ongoing loss
Menstruating woman with ferritin <50 µg/L and unexplained fatigue	Oral iron is reasonable; treat menstrual cause if heavy bleeding	Consider IV iron if severe symptoms, intolerance, poor absorption, or poor response
Inflammatory bowel disease in remission with mild deficiency	Oral or IV depending on severity, prior tolerance, and disease status	IV iron if active disease, intolerance, significant deficiency, or rapid repletion needed
Active inflammatory bowel disease	IV iron often preferred	Reassess inflammation and recurrence risk
Heart failure with iron deficiency	IV iron has the strongest evidence base	Repeat ferritin and TSAT; monitor symptoms and HF events
Chronic kidney disease without anaemia	Individualised; evidence base is less direct	Consider specialist input when ferritin and TSAT conflict or ESA therapy is planned
Post-bariatric surgery	Oral iron may fail because of absorption limits	IV iron if recurrent or refractory deficiency
Older adult or male with unexplained iron deficiency	Treat iron deficiency but investigate cause	Gastrointestinal evaluation is often required depending on clinical context

Measuring response

Response should not be judged by haemoglobin alone because haemoglobin may be normal at baseline. A better approach is to measure both laboratory and patient-centred outcomes.

Laboratory response includes rising ferritin and transferrin saturation. The timing varies by dose, route, adherence, inflammation, and ongoing losses. For oral iron, reassessment after six to twelve weeks is common. For intravenous iron, reassessment depends on formulation and local practice, but testing too early can be misleading because ferritin may rise sharply after infusion.

Symptom response should be specific. The patient should be asked about fatigue severity, exercise tolerance, sleep, restless legs, concentration, work capacity, palpitations, breathlessness, and dizziness. A simple 0-10 fatigue score can be useful. In heart failure, functional class, six-minute walk distance, health-related quality of life instruments, and hospitalisations may be relevant. In inflammatory bowel disease, fatigue scores and disease activity should be interpreted together.

Failure to respond has several explanations. The diagnosis may be wrong. The patient may not have taken oral iron because of adverse effects. Iron may not have been absorbed because of inflammation, proton pump inhibitor use, coeliac disease, atrophic gastritis, bariatric surgery, or ongoing intestinal disease. Blood loss may be continuing. Another diagnosis

such as hypothyroidism, depression, sleep apnoea, malignancy, chronic infection, autoimmune disease, chronic kidney disease, vitamin B12 deficiency, or medication adverse effects may be responsible for symptoms.

Quality of life

Quality of life is often where iron deficiency without anaemia becomes clinically visible. The complaint is not always dramatic. Patients may say they are “not themselves,” cannot complete usual work, need to rest after minor exertion, lose concentration in the afternoon, avoid exercise, or feel mentally slower. These symptoms are easy to minimise because they are common and non-specific.

The trial evidence supports the relevance of quality of life in selected settings. The PRE-FER study reported improvement in mental quality-of-life and cognitive function scores after ferric carboxymaltose in fatigued iron-deficient women with normal or borderline haemoglobin (22). In inflammatory bowel disease, iron deficiency without anaemia has been associated with impaired perceived health-related quality of life (32). In heart failure, trials of intravenous ferric carboxymaltose reported improvements in symptoms, functional capacity, and quality-of-life measures, with benefits not limited to patients with anaemia (23,24).

Quality-of-life outcomes should be interpreted cautiously. Fatigue and poor function are influenced by many variables. The presence of iron deficiency does not prove causality. However, when iron deficiency is documented and clinically plausible, treatment is reasonable, especially when the risks of replacement are low and the cause is being addressed.

Diagnostic pathway

A structured pathway prevents both underdiagnosis and overdiagnosis. The starting point is the clinical situation, not a random ferritin result. Testing is most useful when there is fatigue, restless legs, exercise intolerance, heavy menstrual bleeding, pregnancy or postpartum status, blood donation, inflammatory disease, heart failure, chronic kidney disease, gastrointestinal symptoms, post-bariatric surgery, or unexplained symptoms compatible with iron deficiency.

Initial tests should include a complete blood count, ferritin, transferrin saturation, and C-reactive protein where inflammation is possible. Mean corpuscular volume and mean corpuscular haemoglobin may be normal in early deficiency. Red cell distribution width may rise, but it is not enough to exclude or confirm iron deficiency. Reticulocyte haemoglobin content and soluble transferrin receptor can help in selected cases, especially when inflammation complicates interpretation, but availability varies.

The clinician should then ask why iron is low. In a menstruating woman with heavy bleeding, the cause may be clear, though still requiring treatment. In a postmenopausal woman or adult man, unexplained iron deficiency should raise concern for gastrointestinal blood loss until reasonably excluded. In inflammatory bowel disease, both disease activity and iron indices need monitoring. In heart failure, iron deficiency may be part of the syndrome itself and should be managed within heart failure care.

Figure 2 A practical diagnostic pathway for adults with fatigue and normal haemoglobin

Adult with fatigue or reduced exercise tolerance



— Check for common non-iron causes

sleep, thyroid disease, mood disorder, infection, inflammatory disease,
medication effects, pregnancy, renal disease, cardiopulmonary disease



CBC ferritin transferrin saturation ± CRP

- |
 - |— Ferritin <30 µg/L
 - | Iron deficiency likely
 - | Treat and identify cause
- |
 - |— Ferritin 30-50 µg/L with symptoms or menstrual loss
 - | Possible clinically relevant deficiency
 - | Consider trial of iron and reassess
- |
 - |— Ferritin <100 µg/L in inflammatory disease or heart failure
 - | Iron deficiency likely in context
 - | Consider disease-specific pathway
- |
 - |— Ferritin 100-300 µg/L with TSAT <20%
 - | Functional or inflammatory iron deficiency likely
 - | Consider IV iron in selected settings
- |
 - |— Ferritin normal with normal TSAT and low clinical suspicion
 - | Look for other causes of fatigue

Discussion

Iron deficiency without anaemia occupies an awkward place in clinical medicine. It is common enough to matter, but non-specific enough to invite overdiagnosis. The answer is not to test everyone with tiredness, nor to ignore iron status until anaemia appears. The answer is targeted testing in patients whose history or chronic disease context makes iron deficiency plausible.

The most important diagnostic correction is to stop treating haemoglobin as a screening test for iron stores. Haemoglobin answers a different question. It tells whether anaemia is present. It does not tell whether iron stores are adequate, whether tissue iron delivery is impaired, or whether ferritin is being distorted by inflammation.

Thresholds should be contextual. In otherwise healthy adults, ferritin below 30 µg/L is a practical marker of iron deficiency. In symptomatic menstruating women, fatigue trials suggest that ferritin below 50 µg/L may identify a group in whom iron treatment can help. In inflammatory disease and heart failure, ferritin must be interpreted with transferrin saturation and inflammatory markers. A ferritin value that would look adequate in a healthy adult may be inadequate in chronic inflammation.

The treatment evidence is strongest for subjective fatigue in selected non-anaemic iron-deficient women and for functional outcomes in heart failure. Objective performance outcomes are less consistent. This distinction should be discussed honestly with patients. Iron may improve fatigue, but it is not a universal treatment for tiredness. Clinical response should be measured, and failure to improve should trigger reassessment.

Women's health deserves particular attention because iron depletion is often normalised. Heavy menstrual bleeding is common, but patients may not volunteer it unless asked specifically. A woman may have years of fatigue, normal haemoglobin, and ferritin below 20 µg/L, yet no one has connected the symptoms to menstrual iron loss. Treating such a patient with iron without addressing bleeding is incomplete care.

Chronic disease adds another layer. Inflammatory bowel disease, chronic kidney disease, and heart failure can all produce iron deficiency through blood loss, malabsorption, inflammation, hepcidin elevation, or reduced iron mobilisation. These patients need disease-specific thresholds and follow-up. In heart failure, intravenous iron has become part of evidence-based supportive care for iron-deficient patients, mainly improving symptoms, functional status, quality of life, and heart failure hospitalisation risk, while mortality effects remain uncertain.

The article also highlights a broader issue in laboratory medicine. Reference ranges are not the same as clinical adequacy. A ferritin value can be “within range” and still be too low for a symptomatic patient with ongoing losses. Conversely, a ferritin value can look adequate but be misleading in inflammation. The clinician must interpret results in context.

Conclusion

Iron deficiency without anaemia is a clinically important and treatable condition in selected adults. It should be considered in patients with unexplained fatigue, reduced exercise tolerance, restless legs, heavy menstrual bleeding, pregnancy or postpartum iron loss, inflammatory bowel disease, chronic kidney disease, heart failure, recurrent blood donation, malabsorption, or post-bariatric surgery.

Diagnosis requires more than a complete blood count. Ferritin and transferrin saturation should be assessed, with C-reactive protein or other markers of inflammation when relevant. In otherwise healthy adults, ferritin below 30 µg/L strongly supports iron deficiency. In symptomatic menstruating women, ferritin below 50 µg/L may be clinically relevant. In inflammatory disease and heart failure, ferritin below 100 µg/L or ferritin between 100 and 300 µg/L with transferrin saturation below 20% should raise concern for iron deficiency or restricted iron availability.

Treatment should be individualized. Oral iron is suitable for many patients, especially when deficiency is mild, absorption is intact, and rapid repletion is not required. Lower-dose or alternate-day regimens may improve tolerability. Intravenous iron is appropriate when oral iron is ineffective, not tolerated, poorly absorbed, or unsuitable because of inflammatory disease, heart failure, or the need for rapid repletion.

The cause of iron deficiency should always be sought. In menstruating women, heavy menstrual bleeding must be addressed. In adult men and postmenopausal women, unexplained iron deficiency requires careful evaluation for gastrointestinal blood loss or other pathology. In chronic inflammatory disease, iron status should be monitored rather than checked once.

A normal haemoglobin should not end the assessment when the clinical picture suggests iron deficiency. For many patients, recognising iron deficiency before anaemia develops can improve fatigue, function, and quality of life, while also preventing progression to overt anaemia.

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