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Review Article

Iron Deficiency Anemia: A Review into Newer Insights

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ABSTRACT

Many people globally suffer from iron deficiency. It is the most common cause of iron deficiency anemia IDA that has a devastating effect on infants and their mothers. It occurs when the body's iron storage, iron intake, and iron loss are all out of balance, making it impossible for erythropoiesis to function properly. Microcytic hypochromic anemia is the medical term for this condition. Thalassemia, anemia of chronic disease, and sideroblastic anemias are among the other possible causes of microcytic anemia. Iron parameters such as MCV, MCH and RDW are cost-effective and useful in the diagnosis of iron deficiency. After routine hematological tests like CBC and hemoglobin, serum ferritin is often used as a first diagnostic check. The total iron binding capacity, transferrin saturation, and the serum iron and serum transferrin receptor levels may be beneficial. Stainable iron may be necessary to confirm the diagnosis. High rates of prevalence have negative consequences for both health and the economy. IDA has been known for a while, yet there are still unresolved problems and room for improvement in the way this condition is managed. Every day, new directions in its diagnostic and treatment choices open.

1. INTRODUCTION

Anemia is a major public health problem on a global scale, impacting both industrialized and developing countries. IDA is particularly prevalent in the underdeveloped countries, having reached epidemic proportions on a global scale (1). Worldwide, an estimated 2 billion people suffer from iron deficiency. According to WHO estimates, 39% of children under the age of five, 48% of children between the ages of five and fourteen, 42% of all women, and 52% of pregnant women in developing countries are anemic (2,3). IDA is the most prevalent dietary deficit worldwide and is also the third major cause of disability (4,5,6). In both developing and developed countries, iron deficiency anemia has a significant impact on the lives of premenopausal women and young children. IDA is a global public health issue that is frequently encountered in clinical practice (7). It can impair adults' ability to work and has a detrimental effect on children's motor and mental development (8).

The WHO defines anemia as a decrease in blood hemoglobin concentration to less than 13g/dl in men, 12g/dl in non-pregnant women, and less than 11gm/dl in pregnant women (9,10). Iron deficiency anemia develops when an iron deficiency is severe enough to impair erythropoiesis (9). IDA in newborns continues to be underdiagnosed due to the difficulty of acquiring sufficient blood samples from neonates (11). In older people, iron insufficiency is a relatively common and often diagnosed condition (12).

2. PHYSIOLOGY AND PATHOPHYSIOLOGY

Almost every cell in our body needs iron as a cofactor for basic metabolic functions such as oxygen transport, energy metabolism, and DNA synthesis (13). Iron is found in four broad groups of proteins:
(1) Iron proteins with a single nucleotide
(e.g.,Superoxide dismutase)
(2) Proteins containing diiron-carboxylates
(e.g.,ribonucleotide reductase, ferritin)
(3) Proteins containing iron and sulfur (e.g., aconitase)
(4) Heme proteins (for example, hemoglobin)

Hemoglobin is the iron-binding protein that is most prevalent (13). At least 2.1 grammes of total body iron is found in the hemoglobin of red blood cells and growing erythroid cells, where it aids in oxygen transport (13). The remainder of the body's iron is stored in macrophages (up to 600 mg), muscle myoglobin (300 mg), and liver storage iron (1 gm). Mammalian bodies

lack a controlled system for iron excretion. As a result, balance is maintained through strict monitoring of dietary iron absorption in the duodenum (14). There is no physiological mechanism for iron excretion, and only 1-2mg of iron is lost daily as a result of cells sloughing from the mucosa of the gastrointestinal system, skin, and renal tubules. Normally, a balance is maintained between iron loss and iron absorption on a daily basis. If more iron is lost than is absorbed, the patient's iron stores become depleted, resulting in iron insufficiency. If the patient's condition worsens, he or she develops iron deficiency anemia (15). During gestation, the foetus stores approximately 250mg of iron. Breast milk gives approximately 0.15 mg of absorbed iron per day, while the remaining demand of approximately 0.55 mg/day is met by reserves. Low birth weight infants do not accumulate enough iron throughout fetal life and are at an increased risk of having iron insufficiency while breastfeeding (2).

Dietary iron is composed of heme (derived from animals) and non-heme iron (vegetable source). Heme iron is more bioavailable than non-heme iron. Iron absorption is increased in the presence of iron deficiency and increased erythropoiesis and decreased in the presence of iron replenishment and inflammation. Phytates (found in cereals and legumes), tannins (found in tea), and calcium all impede the absorption of non-heme iron (16). Dietary variables have a negligible effect on heme iron absorption (8). Adults consume 10-15 mg of iron per day on average, with duodenal enterocytes absorbing 1-2 mg. With the help of low stomach PH, ingested iron undergoes enzymatic reduction from ferric ion (Fe3+) to more readily absorbable ferrous ion (Fe2+). When iron is either transmitted across the basolateral membrane to reach plasma bound to transferrin or stored as ferritin and finally excreted as the enterocyte is sloughed, divalent metal transporter 1 (DMT1) on the duodenal epithelium moves it across the apical membrane (17, 18) (Figure 1).

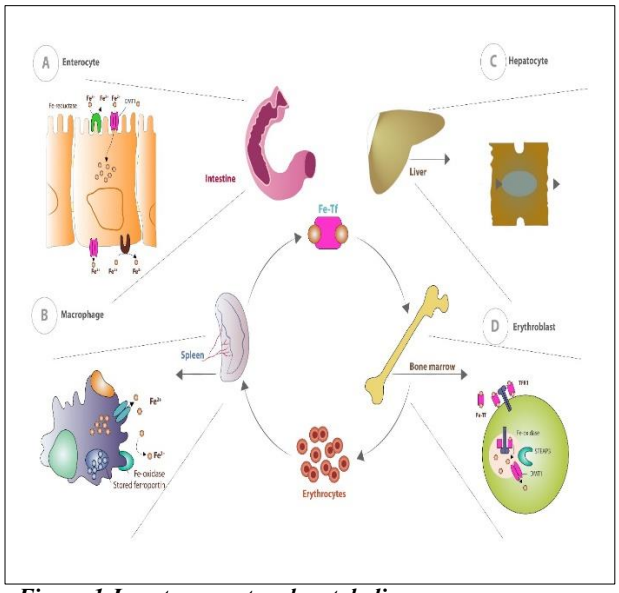

Figure 1:Iron transport and metabolism

Iron deficiency occurs when the body's iron requirements are not met through dietary iron absorption. Thus, patients with iron deficiency who present to primary care may have insufficient dietary intake, impaired absorption, or physiologic losses in females of reproductive age. Additionally, it could be a symptom of occult blood loss (8).

Anemia is caused by poverty, starvation, and hunger. Infancy, rapid growth (adolescence), menstrual blood loss, pregnancy (second and third trimesters), and blood donation are all physiological causes of increased demand for iron. Environmental factors such as insufficient intake due to poverty, hunger, and diet (vegetarian, vegan, or iron-deficient) are also significant contributors in developing nations (7).

3. NEWER INSIGHTS INTO THE IRON REGULATION

Hepcidin is a 25-amino acid peptide hormone generated by the liver that plays a critical role in iron hemostasis (19). Its levels are significantly reduced in IDA. It acts by regulating cellular transport of iron. Ferroportin (FPN) is a protein molecule that is produced in the duodenum, liver, spleen, and placenta. Hepcidin restricts the release of iron from cells by binding to FPN and causing its internalization and destruction. This has a deleterious effect on the absorption of iron from the duodenum and its release from the macrophages of the liver and spleen (20, 21).

Hepcidin is thought to play a key role in inflammatory anemia. Hepcidin levels have been reported to be higher in disorders including rheumatoid arthritis and sepsis, which are characterized by overt inflammation (19, 22). There is currently no reliable test for hepcidin levels (7). Low or nonexistent hepcidin levels have been linked to simple iron insufficiency in studies (16, 14). When distinguishing between IDA (low hepcidin levels) and anemia of inflammation (high hepcidin levels), hepcidin levels have the ability to increase accuracy (19, 23). Hepcidin assays have made little progress in clinical treatment due to interlaboratory variation and a lack of suitable standards (14).

There is a condition known as functional iron deficit, in which iron cannot be recruited for erythropoiesis despite adequate reserves. Hepcidin has a role in this process. The percentage of hypochromic red cells and the quantity of reticulate hemoglobin have been used to assess iron status in patients receiving erythropoietin stimulating medications, and may be a good indicator of functional iron shortage (16).

As the main regulator of systemic iron levels, hepcidin is a prospective pharmaceutical target for the treatment of iron-related diseases. Deregulated iron metabolism can be addressed in several organs, including the liver (synthesis of hepcidin), kidneys (production of erythropoietin), and bone marrow (erythropoiesis).

Multiple diseases, including anemia, cardiovascular disorders, neurodegenerative diseases, inflammation, and cancer, may be treatable by targeting iron metabolism. While conventional treatments target systemic iron depletion or replacement, new pharmaceutical strategies target intracellular iron regulatory mechanisms (24).

Numerous studies have established the importance of a formula known as Mentzer's index, which is calculated as MCV/RBC and is greater than 13 in IDA and less than 13 in thalassemia. The Mentzer index is used to distinguish IDA from thalassemia trait. MCV is decreased in both IDA and thalassemia trait, while RBC count is decreased in IDA but elevated in thalassemia trait (5) Unfortunately, sTFRC and hepcidin measurements are not widely available, remain costly, and are almost solely employed for research purposes nowadays (20).

4. CLINICAL FINDINGS

Iron deficiency symptoms vary according on the degree and duration of the anemia, in addition to the standard anemic symptoms such as weariness, pallor, and decreased activity ability (25). Because iron deficiency anemia is a manifestation of a disease, patients may experience irritability, palpitation, dizziness, shortness of breath, headache, and fatigue (26). Physical examination may indicate tachycardia, generalized and conjunctival pallor, koilonychia, glossitis, and stomatitis, as well as other signs and symptoms of heart failure. Pica and restless leg syndrome (RLS) may also be present. Patients with gastrointestinal causes of IDA may occasionally present with "alarm" symptoms such as altered stool caliber, epigastric discomfort, altered bowel habits, weight loss, early satiety, and low appetite. Plummer-Vinson syndrome is characterized by esophageal webs linked with IDA (27). Children with IDA may exhibit motor and cognitive impairment, as well as mental issues (5). Children who are anemic have impaired growth and intellectual development and are more prone to sickness as a result of their immunological deficit (28). Pregnant women frequently exhibit widespread oedema, weakness, and dyspnea (3). Table 1 lists the clinical presentations due to iron deficiency and iron deficiency anemia (5, 12, 29, 30, 20, 31).

Table 1: Clinical presentation in Iron deficiency Anemia

Nutritional
Pica, pagophagia
Neurocognitive
Reduced mental and motor function
Poorer outcomes in executive function and recognition memory
Visual and auditory systems' functioning
Central Nervous System
Irritability-malaise
Fainting
Papilledema
Pseudotumor cerebri
6th nerve palsy
Restless leg syndrome
Breath holding spell
Sleep disturbance
Attention deficit
Learning difficulty
Behavioral disorder
Decrease in perception functions
Retardation in motor and mental developmental tests
Cardiac
Impaired myocyte function
Increased cardiac output
Tachycardia
Cardiomegaly
Heart failure
Immunologic
Impaired resistance to bacterial infection
T lymphocyte and polymorphonuclear leukocyte dysfunction
Gastrointestinal
Epithelial tissue injury (glossitis; angular stomatitis)
Esophageal web or stricture, gastric atrophy
Microvillus damage; protein-losing enteropathy
Loss of appetite
Dysphagia
Gluten sensitive enteropathy
Plummer-Vinson syndrome
Hematologic
Anemia (fatigue; diminished exercise tolerance and productivity)
Others
Impairment of muscle function and muscle strength
Increased absorption of heavy metals: Lead intoxication

5. LAB DIAGNOSIS OF IRON DEFICIENCY ANEMIA

5.1 Routine Laboratory tests

Routine laboratory testing is frequently used to diagnose IDA. A complete blood count (CBC), a peripheral smear examination, serum ferritin, serum iron, total iron binding capacity (TIBC), and other novel tests. Low MCV, low MCH, low MCHC, and elevated RDW-CV are common hematological findings in IDA, along with low hemoglobin. The erythrocytes on the smear are microcytic and hypochromic. Increased RDW-CV with low MCV is indicative of iron deficiency anemia, however it is not always diagnostic. It's estimated that up to 40% of 'pure' IDA patients are normocytic. As a result, a normal MCV does not rule out iron deficiency as the cause of anemia. Microcytosis is not always indicative of iron deficiency and can be caused by various anemias such as chronic illness anemia, sideroblastic anemia, and thalassemia (9).

Iron deficiency anemia is diagnosed in children with an RDW >15 percent and hemoglobin 10 gm/dl without the use of iron status indicators (32). Increased red cell

distribution width (RDW), decreased red blood cell (RBC) count, decreased RBC hemoglobin, and decreased mean cell volume (MCV) are almost all diagnostic for IDA. Typical variations in blood parameters for iron control, storage, transit, and use are shown by laboratory analysis (14).

The red cell indices gradually deteriorate as the ID becomes microcytic and hypochromic. These are rather late alterations in comparison to serum and storage iron levels. Modern cell analyzers quantify and express reticulocyte count as a percentage of total red cells, preferably in absolute counts per microliter of whole blood. It can be used to determine the effective marrow production rate in comparison to normal (33). Indices of reticulocyte immaturity are increased in the presence of iron deficit, indicating a deficiency in the raw material required to synthesize hemoglobin and thus serving as possible early markers of iron deficiency and anemia (34).

In thalassemia carrier state, rather than iron insufficiency, a normal RDW and a low MCV are observed. In iron deficiency anemia, the RDW is the first variable to change in the CBC. Simultaneously, the first IDA finding on peripheral smear is anisocytosis (5). However, RDW, which quantifies the degree of red cell anisocytosis, is not regarded a sensitive or specific diagnostic for iron deficiency (16, 9).

The diagnosis of IDA is made by interpreting iron studies. Using simple laboratory markers, such as serum ferritin and transferrin saturation (TSAT), iron reserves can be evaluated (35) IDA is characterized by low serum ferritin levels, low transferrin saturation, and elevated TIBC. Serum ferritin is by far the most sensitive biochemical marker of iron reserves and has supplanted the more intrusive bone marrow iron levels as the gold standard for diagnosing IDA. It is believed to be the most sensitive and specific test available for detecting iron deficiency, which is defined as a level of 30 g per liter. However, ferritin is an acute phase reactant, and it is worth noting that it can be raised during infection and inflammation (5, 6, 27,36, 37). Serum ferritin is a measure of the body's iron reserves under normal conditions. Ferritin levels are difficult to interpret in the presence of inflammation and hepatocellular damage. If inflammation is ruled out, the ferritin level serves as a useful indicator of iron storage. A low TSAT value in conjunction with a low blood ferritin concentration (15-25ng/ml) supports the diagnosis of iron insufficiency (27). Serum ferritin reveals total body iron deposition in the absence of inflammation (often characterized as a normal C reactive protein level). However, because serum ferritin is an acute phase reactant, the presence of normal or even increased ferritinemia does not rule out the possibility of iron shortage. ID is possible even at ferritin concentrations of up to 100ng/ml. (16, 9). Ferritin levels more than 400 g/L are frequently reported in patients with chronic renal failure in the absence of large marrow iron reserves (14). According to some research, iron status can be accurately determined by plasma ferritin concentrations alone, provided that another biomarker such as CRP is concurrently assessed to rule out artificially high plasma ferritin due to concurrent inflammation. It is challenging to diagnose anemia caused by multiple factors using a few selected determinations. Such a scenario exists in the case of mixed anemia found in inflammatory gastrointestinal disease or malignancy. (5).

It is critical to analyze the entire picture when establishing iron status rather than depending on a single test result. Iron deficiency anemia cannot be diagnosed with a single test in the presence of inflammation (7). When assessing iron factors, caution should be exercised. The serum iron content is determined by the amount of iron bound to the transport protein transferrin and is dependent on the efficient recycling of iron by tissue macrophages from senescent erythrocytes and/or iron received from the diet. Serum iron concentrations are also affected by natural diurnal fluctuation and inflammatory situations. As a result, blood iron levels are not always indicative of iron insufficiency (33). Plasma iron levels are inconclusive in differentiating IDA from chronic illness anemia because they are also decreased in chronic disease anemia (5). As blood iron levels decline, total iron birding capacity (TIBC) increases. Transferrin saturation (TSAT), a functional indicator of transferrin levels in circulation, is calculated by dividing serum iron by TIBC and is decreased in iron insufficiency. Additionally, iron and TIBC are acute phase reactants that are elevated during inflammation and infection (5). TSAT values less than 20% indicate an insufficient iron supply for hemoglobin synthesis and red cell formation. A very low TSAT (usually less than 15%) is indicative of iron insufficiency but is not diagnostic in and of itself (33).

Although some writers continue to regard bone marrow iron stores as the gold standard, they have been largely supplanted by serum ferritin assays and are no longer routinely utilized (7). When everything else fails and it is critical to determine the presence of iron insufficiency, demonstrating the lack of stainable iron via a bone marrow biopsy remains the gold standard for diagnosis (15). The test's high interobserver variability and invasive nature makes it less desirable. Although bone marrow examination is normally unnecessary, it should be considered if the diagnosis of iron insufficiency remains questionable following biochemical examinations (18). Guyatt et al assessment's of 55 studies established the superiority of serum ferritin over other iron deficiency markers, including serum transferrin, MCV, and erythrocyte zinc protoporphyrin (38).

5.2 Newer laboratory tests to assess iron deficiency

Several new tests have been developed to aid in the definitive identification of anemia due to iron deficiency. These include the measurement of the soluble transferrin receptor, the concentration of reticulocyte hemoglobin, the proportion of hypochromic red cells, and even hepcidin (9). In IDA, there is an increase in the serum transferrin receptor. Zinc Protoporphyrin is formed when iron is deficient and zinc is replaced for iron in IDA. In

some instances, a conclusive diagnosis can be made only through the combination of many tests (5).

A study concluded that assessing sTfRs levels is no more accurate than serum ferritin (23). While several studies have demonstrated that sTfR measurements are beneficial for diagnosing iron shortage and differentiating between different kinds of anemia, the combination of sTfR and ferritin tests had the highest sensitivity and specificity (39). The amount of soluble transferrin receptors is a relatively underutilized scientific test. Erythroid cells increase the number of surface TfR in the absence of iron, which is reflected in plasma TfR levels. It's worth noting that sTfR levels do not increase in response to inflammation or iron-restricted erythropoiesis, making sTfR measures valuable for differentiating between real iron deficiency and inflammatory diseases associated with low serum iron and low TSAT (anemia of inflammation) (33). Iron shortage increases the expression of the transferrin membrane receptor, which in turn influences the serum soluble receptor concentration (sTFRC). The concentration of sTFRC is unaffected by inflammatory or infectious processes, making it a valuable diagnostic tool. The ratio of sTFRC to ferritin, which is low in iron deficiency anemia and high in chronic illness anemia, is useful for distinguishing between the two disorders (20).

The novel erythrocyte and reticulocyte parameters offer an economical alternative to conventional red cell indices and biochemical iron analyses. A study demonstrated that patients with iron deficit (ID) had significantly reduced reticulocyte hemoglobin (Ret-He) and significantly greater percentages of microcytic RBC (% Micro-R) and hypochromic red cells (% Hypo-He) than those without iron deficiency. In conjunction with prior research, it is clear that these measurements properly reflect the severity of ID and anemia. Few studies have examined the novel reticulocyte and erythrocyte parameters as iron status indicators in pregnancy. In a study of 114 pregnant individuals, the Ret-He and zinc protoporphyrin measurements successfully separated IDA from anemia caused by hemodilution. Ret-He and Ret-He/RBC-He ratio increased significantly, demonstrating that these markers are also excellent monitoring techniques in pregnancy (40).

In a patient population with minimal resources, the Ret-He, % Hypo-He, and percentage microcytic RBC (% Micro-R) as single parameters or in combination are particularly useful in an outpatient situation. There are some limits to the normal use of these tests. Their limited availability is their primary limitation. In addition, the Ret-He is computed using forward scattered light, a metric of cell size. It is therefore essential to interpret the Ret-He in light of the patient's RBC indices, vitamin B12, red cell folate levels, and Hb electrophoresis results. Another consideration for outpatient testing is that the % Hypo-He and % Micro-R are stable for fewer than 12 hours following collection (40).

The amount of hemoglobin in reticulocytes is measured by their hemoglobin content (CHr). For confirming the diagnosis of iron deficiency disorders, blood CHr has been demonstrated to be equivalent to classic iron deficiency criteria such as serum iron, serum ferritin, and hemoglobin (23, 28). Reticulocyte hemoglobin content was found to be the most sensitive variable in the diagnosis of IDA in some investigations, but it has a drawback in that it is also reduced in thalassemia trait (34). Low reticulocyte hemoglobin may be useful for screening in newborns and children; however thalassemia mutations can make reticulocyte hemoglobin quantification difficult to interpret. During erythroblast maturation, iron deprivation causes increased formation of zinc protoporphyrin and decreased heme production. An iron deficiency is indicated by a ratio of more than 40 moles of zinc protoporphyrin per mole of heme, but the presence of recent illness may impair the sensitivity of this test (23, 14). Studies on the evaluation of iron status in hemodialysis patients, the diagnosis of iron deficiency in children, and the diagnosis and treatment of numerous hematologic illnesses all point to the value of this indicator in monitoring erythropoietic function. (41). Due to its unpredictable outcomes in the presence of inflammation and in patients receiving enthropoietic stimulating medications, reticulocyte haemoglobin concentration (CHr) has not been frequently used and adopted as part of the work up of suspected ID (33).

Iron deficiency and anemia remain major global health problems despite the significant progress made in understanding iron metabolism in recent years. New formulations, particularly for intravenous administration, have been created, but controlled clinical trials are still required. In addition, inhibiting hepcidin to target iron metabolism has significant potential. To transfer the promising preclinical results into practical use, more advanced clinical trials are required.

6. CONCLUSION

Anemia caused by iron deficiency is rarely fatal, although it has a substantial influence on human health. Even though much has been learnt, new frontiers in diagnosis and therapy emerge daily. The identification and characterization of the hepcidin molecule may aid in better defining sideropenia and monitoring treatment response in the presence of certain etiopathogenetic moments, such as concurrent infection, anemia related to inflammation, and genetic iron deficiency anemia refractory to oral treatment (IRIDA) Iron deficiency anemia has been reviewed in light of current breakthroughs in understanding iron metabolism and its homeostasis, and the etiology, clinical symptoms, and laboratory diagnosis of this condition. It is possible to make a correct diagnosis of IDA in the majority of patients, if not all. Understanding the biology and physiology of iron will aid in the development of techniques to eliminate it.

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