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A Systemic Review of Iron Deficiency Anemia in Adults and the Clinical Management of Diagnosis and Treatment

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Abstract
Iron deficiency is the most frequent cause of anaemia worldwide. It impairs quality of life, increases asthenia and can lead to clinical worsening of patients. In addition, iron deficiency has a complex mechanism whose pathologic pathway is recently becoming better understood. The discovery of hepcidin has allowed a better clarification of iron metabolism regulation. Furthermore, the ratio of concentration of soluble transferrin receptor to the log of the ferritin level, has been developed as a tool to detect iron deficiency in most situations. Therefore, the problem of this research lies in exploring the cause of iron deficiency that always be sought because the underlying condition can be serious. This review will summarize the current knowledge regarding diagnostic algorithms for iron deficiency anemia. The majority of aetiologies occur in the digestive tract, and justify morphological examination of the gut. First line investigations are upper gastrointestinal endoscopy and colonoscopy, and when negative, the small bowel should be explored; newer tools such as video capsule endoscopy have also been developed. The treatment of iron deficiency is aetiological if possible and iron supplementation whether in oral or in parenteral form.

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1.1 Introduction

More than a quarter of the world's population is anemic, with about one-half of the burden from iron deficiency. The prevention and treatment of iron deficiency is a major public health goal, especially in women, children, and individuals in low-income countries. Challenges in the treatment of iron deficiency include finding and addressing the underlying cause and the selection of an iron replacement product that meets the needs of the patient (Schrier, Auerbach & Mentzer, 2013).

Iron deficiency is the most common nutritional disorder worldwide and accounts for approximately one-half of anemia cases. The diagnosis of iron deficiency anemia is confirmed by the findings of low iron stores and a hemoglobin level two standard deviations below normal. Women should be screened during pregnancy, and children screened at one year of age. Supplemental iron may be given initially, followed by further workup if the patient is not responsive to therapy. Men and postmenopausal women should not be screened, but should be evaluated with gastrointestinal endoscopy if diagnosed with iron deficiency anemia (*see figure 1*). The underlying cause should be treated, and oral iron therapy can be initiated to replenish iron stores. Parenteral therapy may be used in patients who cannot tolerate or absorb oral preparations (Short & Domagalski, 2013).

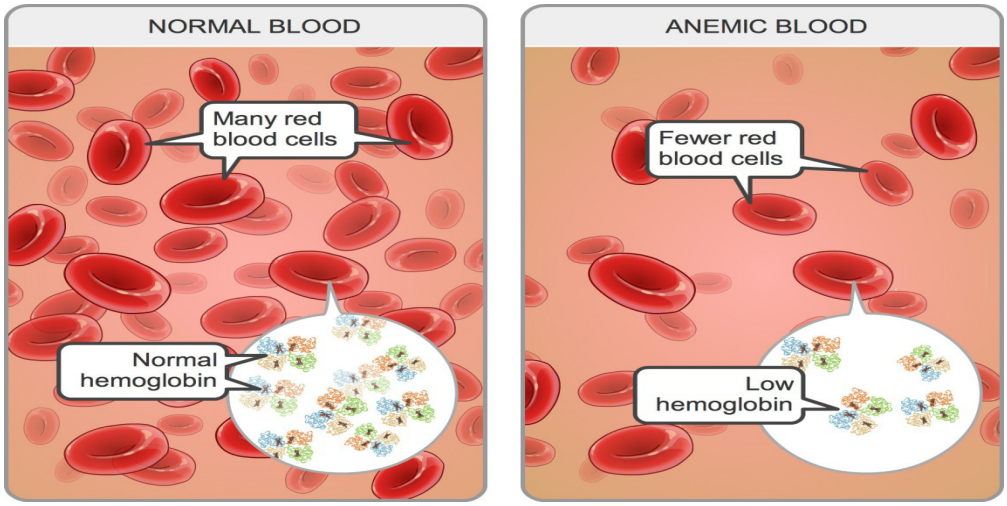

Figure (1): Normal and Anemic blood

Iron deficiency anemia is diminished red blood cell production due to low iron stores in the body. It is the most common nutritional disorder worldwide and accounts for approximately one-half of anemia cases (Johnson-Wimbley & Graham, 2011).

Iron deficiency anemia can result from inadequate iron intake, decreased iron absorption, increased iron demand, and increased iron loss (WHO, 2008).

Identifying the underlying etiology and administering the appropriate therapy are keys to the evaluation and management of this condition.

A complete blood count can be helpful to determine the mean corpuscular volume or red blood cell size. Although iron deficiency is the most common cause of microcytic anemia, up to 40 percent of patients with iron deficiency anemia will have normocytic erythrocytes. As such, iron deficiency should still be considered in all cases of anemia unless the mean corpuscular volume is greater than 95 μm^3 (95 fL), because this cutoff has a sensitivity of 97.6 percent.[6] Other causes of microcytosis include chronic inflammatory states, lead poisoning, thalassemia, and sideroblastic anemia.

1.2 Terminology

1.2.1 Anemia

The World Health Organization defines anemia as a haemoglobin (Hb) concentration below 13 g/dl in men over 15 years of age, below 12 g/dl in non-pregnant women over 15 years of age, and below 11 g/dl in pregnant women (World Health Organisation, 2008).

The diagnostic criteria for anaemia in IDA vary between published studies. The normal range for Hb also varies between different populations in the world. Therefore it is reasonable to use the lower limit of the normal range for the laboratory performing the test to define anemia (Goddard, James, McIntyre & Scott, 2011).

1.2.2 Iron deficiency

Modern automated cell counters provide measurements of the changes in red cells that accompany iron deficiency: reduced mean cell Hb (MCH) hypochromiadand increased percentage of hypochromic red cells and reduced mean cell volume (MCV) microcytosis (Lewis, Bain, Bates, Dacie & Lewis, 2001).

The MCH is probably the more reliable because it is less influenced by the counting machine used and by storage. Both microcytosis and hypochromia are sensitive indicators of iron deficiency in the absence of chronic disease or coexistent vitamin B12 or folate deficiency (Jolobe, 2000).

1.2.3 Functional iron deficiency

Functional iron deficiency' occurs where there is an inadequate iron supply to the bone marrow in the presence of storage iron in cells of the monocyte macrophage system. Perhaps the most important clinical setting for this is in patients with renal failure who require parenteral iron therapy to respond to administered erythropoietin to correct anaemia. Functional iron deficiency also occurs in many chronic inflammatory diseases (eg, rheumatoid arthritis and inflammatory bowel disease) the anemia of chronic disease.

1.3 Iron metabolism

Iron in the diet exists in ferrous or ferric form (*see figure 2*). Ferrous iron (Fe2+) can cross the apical brush border of enterocytes through the ferrous iron (Fe2+) transporter Divalent Metal ion Transporter 1 (DMT1). Ferric iron, that is the most important iron in diet, needs to be reduced in ferrous iron with the action of the iron reductase before absorption. The newly absorbed iron (1–2 mg per day) enters the intracellular iron pool of enterocyte. If the body does not require the iron, it is loaded onto the iron storage protein ferritin. Iron required

by the body is transferred across the basolateral membrane of enterocyte by ferroportin (FPN).

Hephaestin (or Ceruleoplasmin) converts ferric iron to ferrous iron, which can be bound to transferrin and transported in the plasma. The major source of iron is provided by the macrophages that recycle iron from senescent red blood cells. Iron bound to transferrin enters in the hepatocytes by endocytose of the transferrin–transferrin receptor complex. Iron loss is from desquamation, menstruation and other blood loss (1–2 mg per day) (Zhu, Kaneshiro & Kaunitz, 2010).

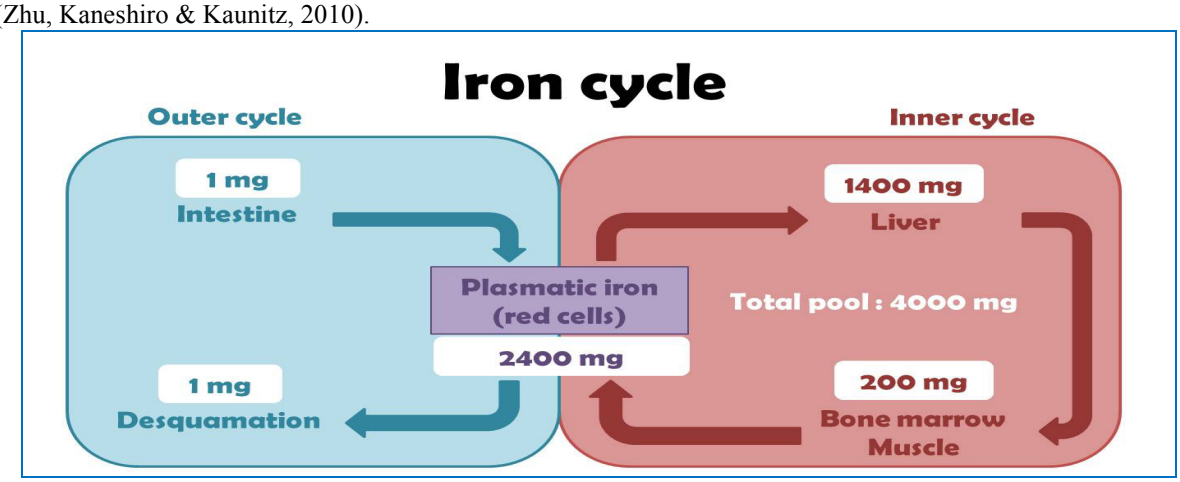

Figure (2): Iron Cycle

1.4 Mechanism of adaptation to iron deficiency

Iron deficiency anemia usually develops slowly. As iron levels decline in the stores (iron deficiency) and in the circulation (iron restricted erythropoiesis) becoming insufficient for the full hemoglobinization of mature erythroblasts (iron deficiency anemia), the liver peptide hormone hepcidin is transcriptionally suppressed. Indeed serum hepcidin levels are significantly lower in young women with a negative iron balance compared with males and postmenopausal women, and are even undetectable in serum of individuals with iron deficiency anemia. The decrease of hepcidin enhances iron release into plasma through ferroportin from both enterocytes and macrophages in the attempt of maintaining normal transferrin (Galesloot, Vermeulen & Geurts-Moespot, 2011).

1.5 Traditional and emerging causes of iron deficiency

Groups of individuals at risk and traditional causes of iron deficiency and iron deficiency anemia are well known, summarized in *table (1)* and will not be extensively discussed here. For thorough coverage the readers are referred to a recent review (Kassebaum, Jasrasaria & Naghavi, 2014).

Table (1): Causes of iron deficiency anemia

Digestive disorders
Increased losses of iron
Cancer/polyp: colon, stomach, esophagus, small bowel
Peptic ulcer, esophagitis
NSAID use
Inflammatory bowel disease: ulcerative colitis, Crohn's disease
Intestinal parasites
Vascular lesions: angiodysplasia, watermelon stomach
Meckel's diverticulum
Reduced iron absorption
Celiac disease
Bacterial overgrowth
Whipple's disease
Lymphangiectasia
Gastrectomy (partial and total) and gastric atrophy
Gut resection or bypass
Urological and gynecological disorders
Intravascular hemolysis
Deficient iron intake

Reduced iron absorption is the second category of ID causes of digestive origin, and can be caused by celiac disease, atrophic gastritis, and postsurgical status (gastrectomy, intestinal resection) among others. Celiac disease

is very relevant and specific evaluation to exclude it must be performed. In a study on patients referred to a specialized gastroenterological consultation because of ID or IDA, celiac disease was finally the diagnosis in 10% of cases; other authors described that at least 2%-3% of patients with IDA are finally diagnosed as celiac disease (Yates, Logan & Stewart, 2004).

Impaired iron absorption may result from surgical and medical conditions. Bariatric surgery, increasingly performed to control caloric intake or diabetes, is emerging as a potential cause of iron deficiency. Post-operative iron deficiency is influenced by preoperative iron status, which is often low in obese patients, and is found more commonly in females (Khanbhai, Dubb, Patel, Ahmed & Richards, 2015).

1.6 Laboratory diagnosis of iron deficiency anemia

The World Health Organization defines anemia as blood hemoglobin values of less than 7.7 mmol/l (13 g/dl) in men and 7.4 mmol/l (12 g/dl) in women. Typically, the evaluation of the cause of anemia includes a complete blood cell count, peripheral smear, reticulocyte count, and serum iron indices. The severity of anemia is based on the patient's hemoglobin/hematocrit level. Iron deficiency anemia is characterized by microcytic, hypochromic erythrocytes and low iron stores. The mean corpuscular volume is the measure of the average red blood cell volume and mean corpuscular hemoglobin concentration is the measure of the concentration of hemoglobin in a given volume of packed red blood cells. The normal reference ranges for mean corpuscular volume is 80–100 fL and mean corpuscular hemoglobin concentration is 320–360 g/l. The patient's cells are said to be microcytic and hypochromic, respectively, when these values are less than the normal reference range. Of note, up to 40% of patients with true iron deficiency anemia will have normocytic erthrocytes (i.e. a normal mean corpuscular volume does not rule out iron deficiency anemia) (Bermejo & Garcia-Lopez, 2009).

The red cell distribution width is a measure of the variation of red blood cell width and is used in combination with the mean corpuscular volume to distinguish an anemia of mixed cause from that of a single cause. The normal reference range is 11–14%; an elevated red cell distribution width value signifies a variation in red cell size, which is known as anisocytosis. The red cell distribution width may be elevated in the early stages of iron deficiency anemia or when a patient has both iron deficiency anemia and folate with or without vitamin B12 deficiencies, which both produce macrocytic anemia. It is not uncommon for the platelet count to be greater than 450,000/µl in the presence of iron deficiency anemia. Upon examination of a patient's peripheral smear with chronic iron deficiency anemia one will typically see hypochromic, microcytic erythrocytes; thrombocytosis may also be apparent. It is important to note that microcytosis visible on the peripheral smear may be seen prior to abnormalities on the complete blood cell count. If the patient has coexistent folate or vitamin B12 deficiency, the peripheral smear will be a mixture of macrocytic and microcytic hypochromic erythrocytes, along with normalization of the mean corpuscular volume.

In the presence of an underlying infection or inflammation other iron markers may be useful including the reticulocyte hemoglobin content which, because reticulocytes are only 1–2 days old, is reflective of the iron available in the bone marrow for erythropoiesis. The alternative, which is likely to be more readily available, is the measurement of soluble transferrin receptor. In the setting of iron deficiency with increased erythroid activity (e.g. following administration of exogenous erythropoiesis stimulating agents), there is increased expression of membrane transferrin receptors in the bone marrow and some of these receptors are detectable in the serum. The limitations are that it is not as reliable as ferritin, it is not yet widely available, and the clinician must exclude other causes of elevated erythroid activity.

1.7 Oral iron therapy and its limitations

Traditionally hemodynamically stable patients with iron deficiency anemia resultant from chronic blood loss from the gut are prescribed oral iron therapy. The two categories of iron supplements are those containing the ferrous form of iron and those containing the ferric form of iron. The most widely used iron supplements are those that contain the ferrous form of iron given that it is the better absorbed of the two. The three commonly administered types of ferrous iron supplements: ferrous fumarate, ferrous sulfate, and ferrous gluconate, which differ in the amount of elemental iron (the form of iron in the supplement that is available for absorption by the body), and contain 33%, 20%, and 12% iron, respectively (NIH, 2010). Recent studies have suggested that these iron preparations are essentially equivalent in terms of bioavailability.

The recommended daily dose of treatment by the Centers for Disease Control and Prevention (CDC) ranges from 150 mg/day to 180 mg/day of elemental iron administered in divided doses two to three times a day [CDC, 1998]. The reticulocyte count begins to increase within the first week of iron therapy, whereas the hemoglobin usually trails by 1–2 weeks (National Institutes of Health, 2010).

Oral iron supplements are desirable as first-line therapy as they are safe, cheap, and effective in restoring iron balance in the average chronic gastrointestinal bleeder.

Therapy with iron supplements may be limited by gastrointestinal side effects, such as abdominal discomfort, nausea, vomiting, constipation, and dark colored stools. Enteric-coated and delayed-release iron

supplements have been developed to increase compliance as they are associated with fewer side effects; however, they are not as well absorbed as the no enteric-coated preparations.

Physicians are often faced with the challenge of managing iron deficiency anemia with oral iron when a patient's iron losses exceed the maximum amount of iron that the gut is able to absorb. It is this group of patients that generally requires repeated transfusions and suffers end-organ damage as the patients are not able to replenish their iron stores with oral supplementation alone. One of the most challenging groups of patients is those patients that suffer from chronic gastrointestinal bleeding secondary to vascular angiodysplasia. These patients typically have multiple lesions that occur in clusters and/or scattered throughout the gastrointestinal tract, and frequently rebleed resulting in chronic iron deficiency anemia. When the patient's gastrointestinal blood loss results in more iron loss than that which they are able to absorb from the gut, these patients develop anemia that is clinically refractory to oral iron therapy.

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