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Iron Deficiency Anemia in Adults and its Diagnosis and Treatment: A Systemic Review

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Abstract
The aim of this study is to explore the clinical management in diagnosis and treatment of the iron deficiency anemia in adults with a systematic review methodology, as the iron deficiency is the most frequent cause of anemia worldwide. And 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. This review summarizes 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.

Acknowledgment
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Introduction

As a common human pathologic conditions, comes the disorders of iron metabolism. Iron deficiency, defined as low body iron with or without anemia, is estimated to affect more than two billion people around the world. Iron deficiency anemia is the most prevalent anemia (*see figure 1*) worldwide roughly affecting 1 of 8 persons, with the highest prevalence in developing countries. Still iron deficiency anemia often remains undiagnosed and untreated (Kassebaum, Jasrasaria & Naghavi, 2014).

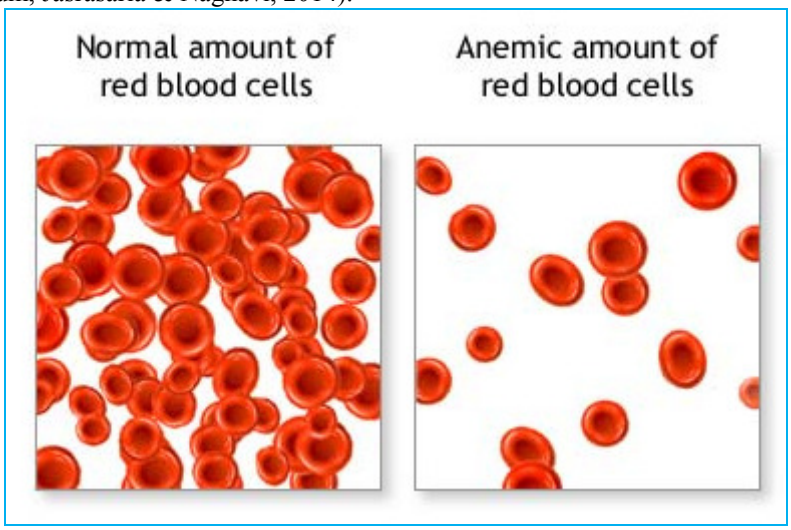

Figure (1): Normal and Anemia affected blood

Iron (*see figure 2*) is tightly regulated at both the cellular and systemic level. Systemic iron homeostasis is under the control of hepcidin and is dominated by the erythropoietic needs for hemoglobin synthesis in the blood (Hentze, Muckenthaler, Galy & Camaschella, 2010).

Thus, individuals at increased risk of developing iron deficiency are young children and adolescents, because of expanding erythropoiesis during rapid growth, and postpartum women. Also regular blood donors may develop iron deficiency and anemia after multiple donations (Cable, Glynn & Kiss, 2011).

Insufficient iron intake, diets containing poorly bioavailable sources of iron, and parasitic infections account for most cases in low-income countries. In high-income countries, iron deficiency anemia, usually with the

exception of groups with increased iron needs, may point to pathologic conditions associated with poor iron absorption and/or chronic blood loss.

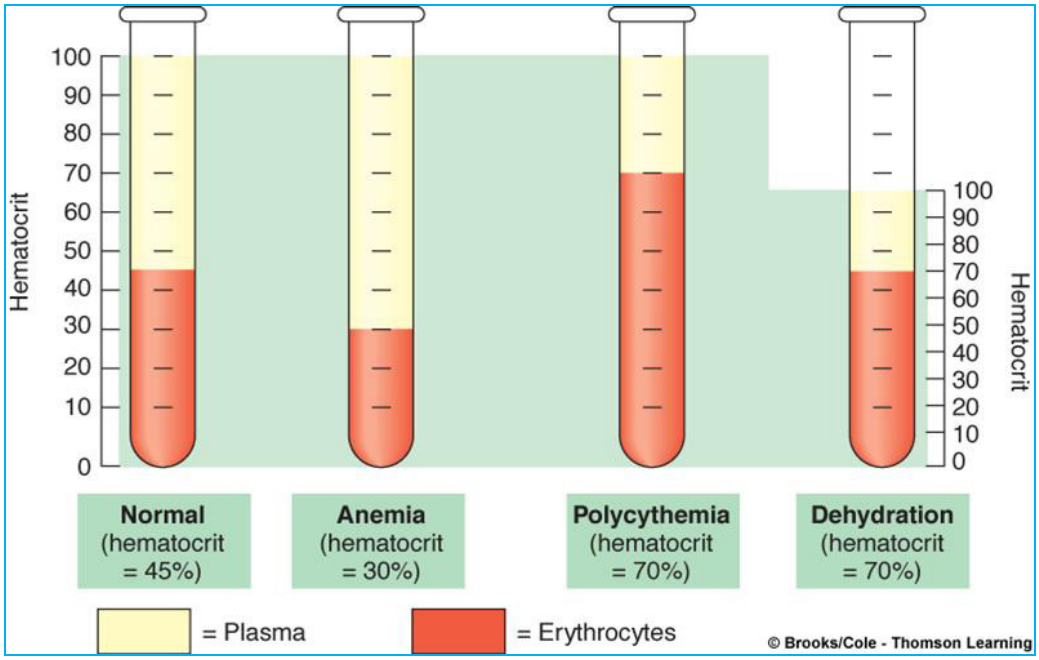

Figure (2): Normal, Anemia and Polycythemia blood

Global burden disease studies point out that one of the top cause-specific anemias is iron deficiency (ID). Recent advances in knowledge of iron homeostasis have shown that fragile patients are a new target population in which the correction of ID might impact their morbidity, mortality and quality of life (De Franceschi, Iolascon, Taher & Cappellini, 2017).

Iron is necessary not only in the haem of haemoglobin for oxygen transport (*see figure 3*), but also as a cofactor for several enzymes. For example, iron ions play central roles in the mitochondrial respiratory chain and in tissue oxygen storage in myoglobin (Haas & BrownlieIron, 2001).

Therefore, iron is necessary in cells that require sustained adenosine triphosphate synthesis, such as skeletal myocytes and cardiomyocytes, in addition to cells of the erythropoietic lineage (Cairo, Bernuzzi & Recalcati, 2006).

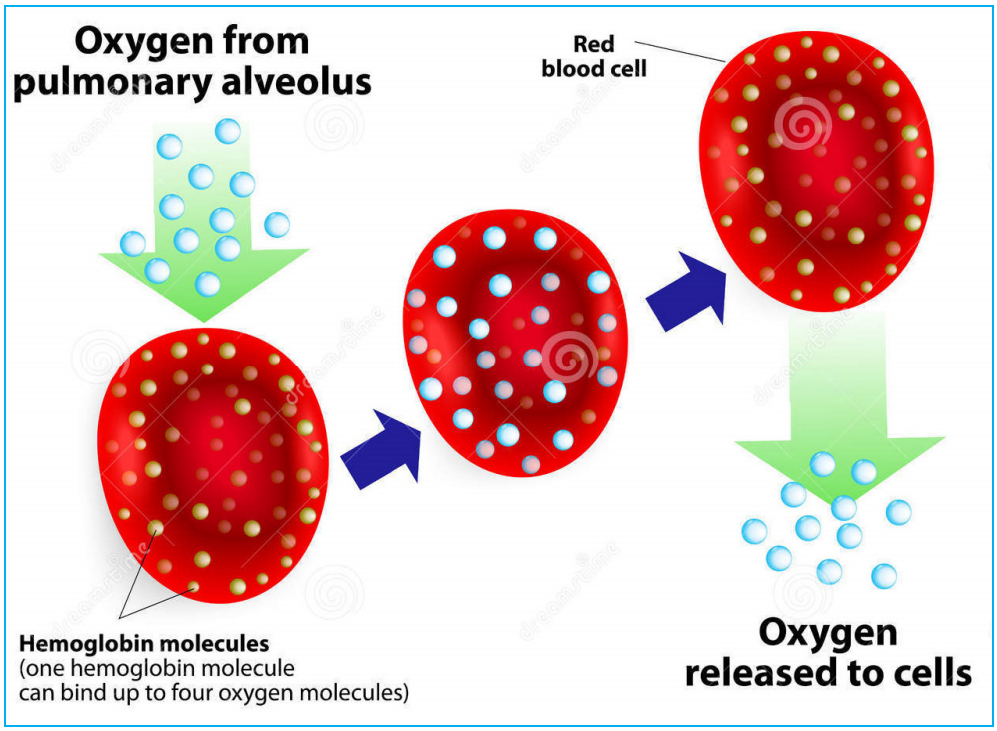

Figure (3): Haemoglobin for oxygen transport

In many cases, ID diagnosis appears simple with a low ferritin level. However, in some patients the diagnosis can be difficult between ID anaemia and anaemia of chronic diseases; therefore other specific indicators of ID are warranted. In recent years, new parameters have been developed to help physicians in the diagnosis of ID in complex clinical settings (Polin, Coriat, Perkins, Dhooge, Abitbol, Leblanc & Chaussade, 2013).

The underlying cause of ID must be sought, to achieve an etiological treatment and to identify a potentially serious diagnosis. In premenopausal women, iron deficiency anaemia is generally attributed to menstrual blood loss. Other aetiologies for ID are mainly gastrointestinal: digestive blood loss or iron malabsorption. ID warrants extensive investigations of the gastrointestinal tract including upper gastrointestinal endoscopy and colonoscopy since the probability of malignant tumours or ulcers, as the cause of excessive blood loss, is relatively high. If upper gastrointestinal endoscopy and colonoscopy are negative, further direct visualization of the small bowel is indicated in most situations. Recent advances have been made in the development of tools to examine the small bowel.

Treatment of ID anemia involves identifying and treating the cause of the condition, as well as replacing iron. Several methods of iron supplementation are currently available in oral or parenteral administration. In this review, we herein present recent advances in the understanding of ID, aetiological diagnosis and treatment

Problem Statement

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.

Terminology

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).

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).

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.

Iron metabolism and its regulation: physiology and pathology

Iron metabolism

Iron in the diet exists in ferrous or ferric form. 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) (Anderson, Frazer & McLaren, 2009).

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).

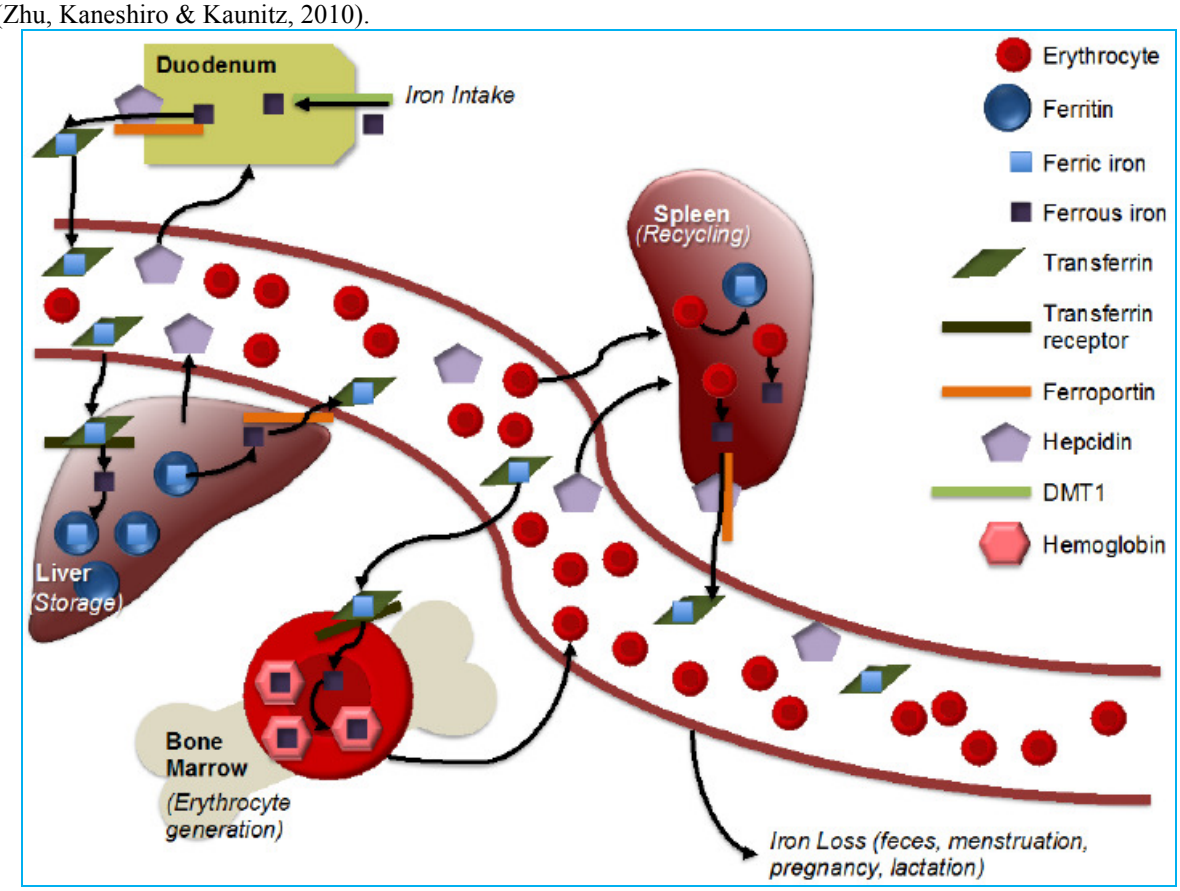

Figure (4): Iron metabolism

Homeostasis of iron metabolism

Hepcidin, a protein first described 10 years ago by Nicolas et al., is an iron regulatory hormone, which plays the role of sensor for the body's iron demands. This polypeptide is produced by the hepatocyte. The binding of hepcidin to ferroportin leads to the endocytosis and degradation of ferroportin. The direct consequence of this phenomenon is the decreasing of iron transfer into the blood plasma from the enterocytes, macrophages and iron-storing hepatocytes. The production of hepcidin is influenced by iron plasmatic concentration, erythropoietic requirements for iron and inflammation in chronic diseases. In ID and in haemorrhagic or haemolytic anaemia, the production of hepcidin in hepatocytes decreases and both iron absorption in the duodenum and the release of iron from stores are greatly increased. In anaemia of chronic disease, hepcidin is over expressed by the action of cytokines such as IL6. The direct consequences of this inflammation are the iron sequestration in hepatocytes and macrophages and the decreasing of intestinal iron absorption. These disorders result in a "functional" ID since iron store is not available for the needs of the body, mostly erythropoiesis (Ganz, 2011).

Anemia in iron deficiency

Erythropoiesis in physiological conditions consumes 25 mg of iron daily. Iron from the circulation is transported by plasma transferrin and delivered to the erythroblast via the transferrin receptor. Iron is essential for the synthesis of the haemoglobin molecule (one molecule of haemoglobin contains four iron atoms). ID leads to a reduction of the synthesis of haemoglobin molecule. The direct consequence is the increasing number of mitoses of erythroblasts leading to microcytosis and hypochromia (Jolobe, 2000).

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.4

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).

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).

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 (Wish, 2006).

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 (Harrington *et al*. 2011).

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.

Intravenous iron therapy and its limitations

Intravenously administered iron is one approach to replacing iron losses in patients with chronic gastrointestinal bleeding in which blood loss exceeds 10 ml/day (around 5 mg iron). With the use of intravenous iron the desired serum iron levels, in which the marrow production can increase by fourfold to eightfold, can be achieved.

Hillman and Henderson previously showed that the maximum iron delivery from reticuloendothelial iron stores is 40–60 mg of iron/day to the bone marrow for erythropoiesis. Supplementation with oral iron provides 60–80 mg iron/day, whereas intravenous iron or nonviable red cells provide 80–160 mg iron/day. They found that the maximum red blood cell production achieved by patients with a mean serum iron less than 70 µg/100 ml was between 2.5 and 3.5 times normal. With oral iron supplementation, patients were able to achieve serum iron values between 70 µg/100 ml and 150 µg/100 ml, and red blood cell production was able to increase to four to five times normal. Only when nonviable red cells or intravenous iron dextran was administered was the iron supply sufficient to increase the serum iron to values greater than 200 µg/100 ml with a concomitant increase in marrow production to 4.5–7.8 times normal (Figure 5).

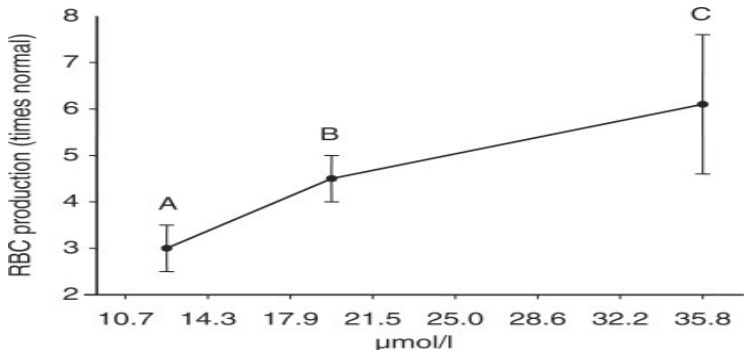

Figure (5): Response of the bone marrow in relation to the level of serum iron

It is important to note that this response was transient lasting only 7–10 days as the excess iron was subsequently sequestered in the reticuloendothelial system. The physician can estimate a patient's total iron deficit and then decide how much to administer intravenously.

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