REVIEW ARTICLE

Iron Deficiency Anemia: Insights into the Prevalence, Causes, Iron Metabolism, Manifestations, Diagnosis, and Treatment

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ABSTRACT

Iron deficiency anemia (IDA) is considered the major public health problems and the most common nutritional deficiency around the world. IDA is characterized by a decrease of hemoglobin, serum iron, ferritin, and RBCs, and an increase in total iron-binding capacity (TIBC). Red blood cells become microcytic and hypochromic due to a decrease in iron content. The present study aimed to highlight the prevalence of iron deficiency anemia, causes, iron metabolism, manifestations, diagnosis, and treatment. Anemia is a major public health concern in preschool children, schoolchildren, and pregnant women in the developing world. It is a critical health concern because it affects growth and energy levels adversely, and damages immune mechanisms, and is also associated with increased morbidity. Young children from low-income families have a higher risk for developing anemia due to ID that occurs as a result of high demand for iron during the period of rapid growth. Causes of IDA in developing countries may be due to low intake of enough iron sources, high intake of cereals, and legumes, which contain iron absorption inhibitors, and/or low intake of iron enhancers (e.g., ascorbic acid). There is some evidence that ID without anemia affects cognition in adolescent girls and causes fatigue in adult women. IDA may affect visual and auditory functioning and is weakly associated with poor cognitive development in children. It produces many systemic abnormalities: the blue sclera, koilonychias, impaired exercise capacity, urinary discoloration by betanin in beetroot, increased lead absorption, and increased susceptibility to infection. Dietary iron is available in two forms: Heme iron, which is found in meat, and non-heme iron, which is found in plant and dairy foods. The bioavailability of non-heme iron requires acid digestion and varies by order of magnitude depending on the concentration of enhancers (e.g., ascorbate, meat) and inhibitors (e.g., calcium, fiber, tea, coffee, and wine) found in the diet. Foods containing plant phytates (grains) and tannins (non-herbal tea) are known to decrease the absorption of non-heme iron. ID results when iron demand by the body is not met by iron absorption from the diet. The clinical presentation of IDA can range from being completely asymptomatic to varying degrees of weakness, fatigue, irritability, headache, poor exercise tolerance, and work performance. The typical picture seen in IDA is low serum ferritin, low transferrin saturation, and increased TIBC. Serum iron, transferrin, transferrin saturation, and erythrocyte zinc protoporphyrin each have their limitations and are useful in supporting a diagnosis of IDA in situations. Transfusion should be considered for patients of any age with IDA complaining of symptoms such as fatigue or dyspnea on exertion. Oral iron therapy is usually the first-line therapy for patients with IDA. It can be concluded that IDA is a serious health problem among preschool children, schoolchildren, and pregnant women, especially in the developing world, and there is a need for national intervention strategies and programs to improve the socioeconomic status and health education which will help significantly in controlling anemia and IDA among preschool children, schoolchildren and pregnant women.

Key words: Causes, diagnosis, iron deficiency anemia, manifestations, prevalence, treatment

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INTRODUCTION

Anemia is a major public health concern in preschool children, schoolchildren, and pregnant women in the developing world. "Anemia" refers to a condition in which the hemoglobin content of the blood is lower than normal as a result of deficiency of one or more essential nutrients,[1] heavy blood loss, parasitic infections, and congenital hemolytic diseases.[2] Globally, anemia is a public health problem-affecting people in both developed and developing countries with bad consequences for human health as well as social and economic development.[3,4] Anemia is a critical health concern because it affects growth and energy levels adversely.[2] It damages immune mechanisms and is associated with increased morbidity.[3] It occurs in all age groups but is more prevalent in pregnant women and children.[2] Especially, young children from low-income families have a higher risk for developing anemia due to iron deficiency (ID) that occurs as a result of high demand for iron during the period of rapid growth.[5]

ID and ID anemia (IDA) is considered the major public health problems and the most common nutritional deficiency around the world.[6] The prevalence of anemia in the world is 24.8%.[7] Furthermore, it is estimated that ID contributes toward 50% of the approximated 600 million global anemia cases in preschool and school-aged children.[8] This high prevalence of IDA in developing countries is associated with poor sanitation conditions, low socioeconomic conditions, restricted access to food, and lack of knowledge for good dietary practices.[9] Anemia has multiple consequences which can be extremely severe.[10,11] It affects the physical and mental development of an individual leading to decreased working capacity, which in turn affects the development of the country.[12] The causes of IDA in developing countries are many. It can be due to low intake of enough iron sources (meat/fish/poultry), high intake of cereals and legumes (which contain iron absorption inhibitors), and/or low intake of iron enhancers, that is, ascorbic acid. In addition, the poor socioeconomic status of the vast majority of people is reflected in the poor health services provided and unsanitary living conditions that cause diarrhea and worms infestation, thus leading indirectly to EDA.

IDA is characterized by a decrease of Hb (hemoglobin), serum iron, ferritin, and RBC (red blood cells) (shape and size). In addition, it is characterized by an increase in total iron-binding capacity (TIBC). Red blood cells become microcytic and hypochromic due to a decrease in iron content. Inadequate treatment of IDA leads to increased morbidity, poor life quality, and inefficient daily activities.[13,14] Early diagnosis, treatment, and prevention reduce healthcare costs through the reduction of unplanned hospital admissions and other health-services.

Objectives

The present study aimed to highlight the prevalence of iron deficiency anemia, causes, iron metabolism, manifestations, diagnosis, and treatment.

ANEMIA

Anemia is defined by a decrease in the total amount of hemoglobin or the number of red blood cells. IDA is a form of anemia due to the lack of sufficient iron to form normal red blood cells. IDA is typically caused by inadequate intake of iron, chronic blood loss, or a combination of both.[15,16]

IDA is the most common nutritional deficiency worldwide. It can cause reduced work capacity in adults and impact motor and mental development in children and adolescents.[17] There is some evidence that ID without anemia affects cognition in adolescent girls[18] and causes fatigue in adult women.[19] In addition, IDA may affect visual and auditory functioning[18] and is weakly associated with poor cognitive development in children.[19] The prevalence of Iron deficiency anaemia in differentWHO regions shown in the Table 1.

PREVALENCE OF IDA

In a study done by Tabib *et al*.[20] in Libya 2016, they found that Hb less than 7 g/dL reported in 22.5% of patients (11 male, 37 female) and Hb between 7–10 g/dL reported in 77.5% of patients (57 male, 108 female). The highest prevalence of IDA was found between 22 and 39 years of age, Hb mean was 7.9 ± 0.08. In the study by Achouri *et al*.[21] to detect the prevalence of IDA among schoolchildren in Kenitra, northwest of Morocco, the prevalence of anemia was 16.2%. The mean hemoglobin concentration was 12.53 g/dL in boys and 12.52 g/dL in girls. The results suggested that ID is an important determinant of anemia in this population. There was a significant relationship between education of the mother and anemia in children ($P = 0.004$) but not with the family income. In Sabratha in 1999, the prevalence of anemia (Hb<12 g/dL) was 11% among 370 male children aged 6–14 years and 13% among 341 female children of the same age.[22] In addition, the prevalence of IDA among schoolchildren in different countries was observed. Ethiopia 37.4%,[23] Yemen 34.2%,[24] Palestine 4.5%,[25] Morocco 16.2%,[21] India 23.1%,[26] Iran 29.1%,[27] and Pakistan 33.2%[28] [Table 2].

AETIOLOGY

Iron metabolism is controlled by absorption rather than excretion. Iron is only lost through blood loss or loss of cells as they slough. Men and no menstruating women lose about 1 mg of iron per day.[17] Menstruating women lose from 0.6 to 2.5% more per day. An average 60-kg woman might lose an extra 10 mg of iron per menstruation cycle, but the loss could

Table 1: The prevalence of iron deficiency anemia WHO region[12]

Region	Total population	Population affected by anemia	Percent affected
Africa	535	244	46
Americas	751	141	19
South East Asia	1364	779	57
Europe	860	84	10
Eastern Mediterranean	408	184	45
Western Pacific	1574	598	38
The Total	5491	2030	37

Table 2: Iron deficiency anemia among young children in different countries[21,23-28]

No	Countries	% Prevalence
1	Morocco (2008)	16.2
2	Pakistan (2011)	33.2
3	Ethiopia (2013)	37.4
4	Yemen (2014)	34.2
5	Palestine (2009)	4.5
6	India (2011)	23.1
7	Iran (2007)	29.1

be more than 42 mg per cycle, depending on how heavily she menstruates.[17] A pregnancy takes about 700 mg of iron, and a whole blood donation of 500 cc contains 250 mg of iron.[29]

Iron absorption, which occurs mostly in the jejunum, is only 5–10% of dietary intake in persons in homeostasis.[29]

In states of overload, absorption decreases. Absorption can increase three-to-five fold in states of depletion. Dietary iron is available in two forms: Heme iron, which is found in meat, and non-heme iron, which is found in plant and dairy foods. Absorption of hem iron is minimally affected by dietary factors, whereas non-heme iron makes up the bulk of consumed iron. The bioavailability of non-heme iron requires acid digestion and varies by order of magnitude depending on the concentration of enhancers (e.g., ascorbate, meat) and inhibitors (e.g., calcium, fiber, tea, coffee, and wine) found in the diet.[17] ID results when iron demand by the body is not met by iron absorption from the diet. Thus, patients with IDA presenting in primary care may have an inadequate dietary intake, hampered absorption, or physiologic losses in a woman of reproductive age. It also could be a sign of blood loss, known or occult. IDA is never an end diagnosis; the workup is not complete until the reason for IDA is known.[29]

IRON METABOLISM

Iron is a trace element that is required for numerous cellular metabolic functions. As iron is toxic when present in abundance, tight regulation is required to avoid ID or iron overload.[30,31] The adult body contains 3–4 g of iron. The usual Western diet contains approximately 7 mg of iron per 1000 kcal; however, only 1–2 mg is normally absorbed each day.[32] The human diet contains two forms of iron: Heme iron and non-heme iron. Heme iron is derived from meat and is well absorbed. Pancreatic enzymes digest hem to free it from the globin molecule in the intestinal lumen. Iron is then absorbed into the enterocytes as metalloporphyrin and degraded by heme oxygenase-1 to release non-heme iron. Subsequently, iron is exported by ferroportin located on the basolateral aspect of the enterocyte. Non-heme dietary iron, which is found in cereals, beans, and some vegetables, is less well absorbed. Non-heme iron is present as either ferric (Fe^{+3}) or ferrous (Fe^{+2}) iron. The acidic environment of the stomach and certain foods are known to increase the bioavailability of dietary iron.[33-35] Vitamin C, for example, functions to prevent the precipitation of ferric iron in the duodenum. Other foods containing plant phytates (grains) and tannins (non-herbal tea) are known to decrease the absorption of non-heme iron.[34,35]

After entry of ferric iron into the duodenum, it must first be reduced to the ferrous form by duodenal cytochrome b before absorption. Duodenal cytochrome b is a reductase located in the brush border of the duodenum and proximal jejunum. Once reduced, the divalent metal transporter 1, the only currently known intestinal iron importer, transports ferrous iron from the proximal small intestinal lumen into the apical membrane of the enterocyte.[32] After entry into the cell, ferrous iron may either be stored as ferritin or transverses the cell to the basolateral aspect of the enterocyte, where the ferroportin is located. Ferroportin is present in the mucosa of the proximal small intestine, macrophages, hepatocytes, and syncytiotrophoblasts of the placenta. Ferroportin, along with ceruloplasmin and hephaestin, facilitates their

oxidation of ferrous iron to ferric iron, which must occur before exportation. Transferrin has a high affinity for ferric iron and binds it so quickly that there is essentially no free iron circulating in the plasma. Binding of iron to transferring occurs through the Apo transferrin receptor pathway.[32,35]

Once in the plasma, the iron is transported by transferring to the bone marrow for the synthesis of hemoglobin and incorporation into the erythrocytes. Normal erythrocytes circulate for roughly 120 days before being degraded. Senescent red blood cells are engulfed by macrophages in their reticuloendothelial system, primarily in the spleen and liver, where they are degraded and catabolized by the cytosolic hemeoxygenase-1 to release the bound iron. Recycling of heme iron from senescent red blood cells is the primary source of iron for erythropoiesis and accounts for delivery of 40–60 mg iron/day to the bone marrow.[36] Some of the iron from senescent red blood cells is also stored in macrophages as ferritin (the major storage form of iron) or hemosiderin (the water-soluble form of iron), and the majority of it is released through ferroportin into the plasma bound to transferring for recycling. Around 70% of the total body iron is in heme compounds (e.g. hemoglobin and myoglobin), 29% is stored as ferritin and hemosiderin, <1% is incorporated into heme-containing enzymes (e.g., cytochromes, catalase, and peroxidase), and <0.2% is found circulating in the plasma bound to transferrin.[32,34] During states of intravascular hemolysis, red blood cells are destroyed and hemoglobin is released into the plasma. The hemoglobin-haptoglobin complex is then removed by the reticuloendothelial system and the iron salvaged. The binding potential of haptoglobin is limited by the amount of circulating molecules and quickly becomes saturated in moderate to severe hemolytic states. No physiologic mechanism for iron excretion exists and only 1–2 mg of iron is lost each day as a result of sloughing of cells (i.e., from the mucosal lining of the gastrointestinal tract, skin, and renal tubules). In women, approximately 0.006 mg iron/kg/day is lost during normal menstruation.[34] Thus, normally iron loss and gain are in balance, with the amount lost daily being equal to the amount absorbed daily.

The body has the increase intestinal iron absorption depends on the body's iron needs. When the pendulum swings toward more iron being lost than is absorbed, iron stores become depleted, and the patient develops ID. If the process continues, the patient develops IDA. ID is associated with up-regulation of iron absorption from the gut by way of an increase in the production of key proteins, such as duodenal cytochrome b, divalent metal transporter 1, and ferroportin. Hypoxia-inducible, factor-mediated signaling, and iron regulatory proteins also play critical roles in the local regulation of iron absorption. Hypoxia-inducible factor-signaling up-regulates the expression of duodenal cytochrome b and divalent metal transporter1; iron regulatory proteins up-regulate the expression of divalent metal transporter 1 and ferroportin. These two pathways are vital for the enhancement of iron absorption associated with ID.[33] Within limits, iron absorption enhancement is proportional to the degree of ID (i.e., the synthesis of key proteins, such as transferrin receptor, divalent metal transporter1, ferritin, and ferroportin, is regulated in an iron-dependent manner).[31] This system is checked by hepcidin, a hormone that is synthesized in the liver, secreted into the blood, and systemically controls the rate of iron absorption as well as its mobilization from stores. Hepcidin binds to, and negatively modulates, the function of ferroportin. Janus kinase 2 is activated upon binding of hepcidin to ferroportin and results in the internalization, ubiquitination, and degradation of ferroportin.

Thus, activation of Janus kinase 2 is associated with limiting iron exportation and ultimately decreasing erythropoiesis.[37] Hepcidin expression is most notably suppressed by hypoxia, erythropoietin (a hormone essential for erythrocyte differentiation), twisted gastrulation (a protein secreted by immature red blood cell precursors during the early stages of erythropoiesis), and growth differentiation factor 15 (a protein secreted by erythroblasts during the final stages of erythropoiesis). The synthesis of hepcidin is up-regulated by inflammatory cytokines (particularly interleukin-6), irrespective of the total level of iron in the body. This relationship most likely accounts for the development of anemia of chronic disease. The anemia of chronic disease is outside the scope of this discussion.[33,34]

MANIFESTATIONS OF ID

IDA produces many systemic abnormalities: Blue sclera, koilonychias, impaired exercise capacity, urinary discoloration by betanin in beetroot, increased lead absorption, and increased susceptibility to infection. Abnormal developmental performance and poor growth are particularly important features and are considered in more detail.[38]

DIAGNOSIS OF IDA

Anemia cannot be reliably diagnosed by clinical presentation. The clinical presentation of IDA can range from being completely asymptomatic (found on routine testing) to varying degrees of weakness, fatigue, irritability, headache, poor exercise tolerance, and work performance.[12] Pica may be seen in some cases of ID with pagophagia (irresistible appetite for ice) being quite specific for ID.[39] Ask about overt blood loss as well as symptoms of gastrointestinal (GI) disease (abdominal pain, change in bowel habit, weight loss, and dysphagia). Use of medications such as aspirin or NSAIDs should also be noted. A family history of GI malignancy, hematological disorders, and bleeding disorders (e.g., hereditary hemorrhagic telangiectasia) is important,

as is the patient's ethnicity when suspecting thalassemia or coeliac disease. On examination, patients may have pallor (related to anemia), cheilosis, or atrophic glossitis. Severe, long-standing ID presenting as Plummer–Vinson syndrome (post-cricoid dysphagia, IDA, and oesophageal webs), koilonychias, blue sclera, and chlorosis have become extremely rare.[40] Urine testing for microscopic hematuria and a rectal examination should be included in the physical examination.[41,42]

LABORATORY DIAGNOSIS

The World Health Organization defines anemia as the level of hemoglobin below 13 g/dl in males over 15 years of age and below 12 g/dl in non-pregnant women over 15 years of age.[12] Although there is no consensus on the level of anemia that requires investigation, there is good evidence to suggest that even individuals with ID without anemia are at increased risk of GI malignancy compared with those without ID, especially if over the age of 50 years.[43,44] Therefore, any level of anemia should be investigated in patients with ID, with greater urgency placed on those with a hemoglobin level of less than 9 g/dl. Diagnosis of IDA relies on the interpretation of iron studies. The typical picture seen in IDA is low serum ferritin, low transferrin saturation, and increased TIBC. Serum ferritin is by far the best biochemical test as an indicator of iron stores and has replaced the more invasive bone marrow iron stores as the gold standard for diagnosis of IDA.[12,45-47] Hypothyroidism and acerbate deficiency, both of which interfere with ferritin synthesis, are the only two conditions other than ID capable of lowering serum ferritin.[46]

Serum ferritin of less than 15 ng/ml is essentially diagnostic of ID with a sensitivity of 59% and a specificity of 99%.[46] The diagnostic yield of serum ferritin may be improved by using a cut off of less than 30 ng/ml, which has a sensitivity and a specificity of 92 and 98%, respectively.[48] Best demonstrated the superiority of serum ferritin over other markers of ID, including serum transferrin, MCV, and erythrocyte zinc protoporphyrin in a review of 55 studies.[46] Since serum ferritin is an acute-phase reactant, its usefulness is limited in the presence of infection, malignancies, and acute or chronic inflammation.[12,45,48,49]

Elevation of ferritin out of proportion to iron stores is also seen in liver disease, alcoholism, and chronic renal failure.[47,49] A higher cutoff for serum ferritin such as less than 60 ng/ml[50] or less than 70 ng/ml[46] may be required to diagnose ID in this population of patients. Attempts to improve the diagnostic value of serum ferritin by using norm grams between ferritin and erythrocyte sedimentation rate or C-reactive protein have shown promise in some studies[51,52] but not in others.[53,54]

Serum iron, transferrin, transferrin saturation, and erythrocyte zinc protoporphyrin each have their limitations and are useful in supporting a diagnosis of IDA in situations where serum ferritin is equivocal.[47,49] Interestingly, the combination of serum ferritin and transferrin saturations offers no advantage over serum ferritin alone.[49]

Examination of bone marrow aspirate or biopsy was widely regarded as the gold standard for diagnosis of ID. However, expense, high interobserver variability, and invasive nature of the test have made it less favorable. Bone marrow examination should only be considered when the diagnosis of ID is still uncertain after biochemical investigations.[45] The concentration of serum transferrin receptor (sTfR) is a quantitative measure of total erythropoietin activity, which is elevated in ID but is not significantly affected by inflammation, infection, age, sex, or pregnancy.[12] This makes it a potentially useful test in identifying ID in patients with inflammatory disease and to discriminate IDA from anemia of chronic disease, although studies have shown conflicting results.[48,55-57] The accuracy of sTfR is limited in the presence of hematological disorders.[12,57] The incorporation of sTfR into the sTfR-ferritin index (log10 serum ferritin) has shown promise as a strong indicator of iron depletion in chronic disease;[55] however, this has failed to be adopted into common clinical practice.

TREATMENT

Transfusion should be considered for patients of any age with IDA complaining of symptoms such as fatigue or dyspnea on exertion. It also should be considered for asymptomatic cardiac patients with hemoglobin less than 10 g/dL (100 g/L). However, oral iron therapy is usually the first-line therapy for patients with IDA.[58] Iron absorption varies widely based on the type of diet and other factors. Bone marrow response to iron is limited to 20 mg per day of elemental iron. An increase in the hemoglobin level of 1 g/dL (10 g/L) should occur every 2–3 weeks on iron therapy; however, it may take up to 4 months for the iron stores to return to normal after the hemoglobin has corrected.[59] Iron sulfate in a dose of 300 mg provides 60 mg of elemental iron, whereas 325 mg of iron gluconate provides 36 mg of elemental iron. Sustained-release formulations of iron are not recommended as initial therapy because they reduce the amount of iron that is presented for absorption to the duodenal villi. GI absorption of elemental iron is enhanced in the presence of an acidic gastric environment. This can be accomplished through simultaneous intake of ascorbic acid (i.e., Vitamin C).[60] Although iron absorption occurs more readily when taken on an empty stomach, this increases the likelihood of stomach upset because of iron therapy. Increased patient adherence should be weighed against the inferior absorption. Foods rich in tenants (e.g., tea)[61] or phytates (e.g., bran, cereal)[62] or medications that raise the gastric pH (e.g., antacids, proton pump inhibitors, and histamine H2 blockers)[63] reduce iron absorption and should be avoided if possible. Some

persons have difficulty absorbing the iron because of the poor dissolution of the coating.[64] A liquid iron preparation would be a better choice for these patients. Laxatives, stool softeners, and adequate intake of liquids can alleviate the constipating effects of oral iron therapy.

Indications for the use of intravenous iron include chronic uncorrectable bleeding, intestinal malabsorption, intolerance to oral iron, non-adherence, or a hemoglobin level less than 6 g per dL (60 g per L) with signs of poor perfusion in patients who would otherwise receive transfusion (e.g., those who have religious objections).[65] Until recently, iron dextran has been the only parenteral iron preparation available in the United States. The advantage of iron dextran is the ability to administer large doses (200–500 mg) at 1 time.[66] One major drawback of iron dextran is the risk of anaphylactic reactions that can be fatal. There also is a delayed reaction, which consists of myalgias, headache, and arthralgias, that can occur 24–48 h after infusion. No steroidal anti-inflammatory drugs will usually relieve these symptoms, but they may be prolonged in patients with chronic inflammatory joint disease.

Sodium ferric gluconate (Ferrlecit), a safer form of parenteral iron, was approved by the U.S. Food and Drug Administration in 1999. The risk of anaphylaxis is drastically reduced using sodium ferric gluconate. In a study of 2534 patients on hemodialysis, 0.04% receiving sodium ferric gluconate had life-threatening reactions compared with 0.61% receiving iron dextran.[67] Sodium ferric gluconate is usually administered intravenously in eight weekly doses of 125 mg for a total dosage of 1000 mg. No test dose is required.

Another intravenous preparation, approved for use in the United States in 2000, is iron sucrose (Venofer). In ID not associated with hemodialysis, 200 mg is administered intravenously 5 times over a 2-week period. Safety profiles are similar to sodium ferric gluconate, although published experience is more limited.[68]

CONCLUSION

It can be concluded that IDA is a serious health problem among preschool children, schoolchildren, and pregnant women, especially in the developing world, and there is a need for national intervention strategies and programs to improve the socioeconomic status and health education, which will help significantly in controlling anemia and IDA among preschool children, schoolchildren, and pregnant women.

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