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Iron Deficiency Anaemia

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Abstract: ***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. 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.***

Keywords: anemia, blood loss, intravenous iron, iron deficiency, therapy

1. Introduction

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.[1,2] Iron deficiency anemia can result from inadequate iron intake, decreased iron absorption, increased iron demand, and increased iron loss.[3] Identifying the under-lying etiology and administering the appropriate therapy are keys to the evaluation and management of this condition.

2. Definition

Iron Deficiency (Id)

Microcytosis (mean corpuscular volume (MCV) lower than the normal range) is characteristic of ID but it may also occur in much less common conditions such as thalassaemia (when the red cell count is usually elevated). Haemoglobinopathies frequently cause microcytosis in certain ethnic groups but this should not be presumed to be the cause unless confirmed by laboratory testing. Microcytosis may be absent in combined deficiency (e.g. with folate deficiency) which may be recognised by a raised red cell distribution width (RDW). The anaemia of chronic disease due to the inability to use iron may also present with microcytosis. Serum ferritin concentration is the most powerful test for ID. [4] A serum ferritin concentration of <12 µg/dl is diagnostic of ID. [5] However, serum ferritin may be raised above 12–15 µg/dl in patients with ID and con-current chronic inflammation, malignancy, or hepatic disease, although if the concentration is >100 µg/dl, ID is almost certainly not present. A further test is usually only required in patients when doubt still remains as to the presence of iron deficiency. [6, 5] and advice from a haematologist should be sought. Red cell protoporphyrin concentration and transferrin saturation of <30% may help the diagnosis but a therapeutic response to three weeks of oral iron or a bone marrow aspiration are the only ways of confirming true deficiency. [4] New tests which involve measuring the serum transferrin binding receptor/ferritin ratio show promise in distinguishing between anaemia of chronic disease and iron deficiency but are not yet widely available. The need for investigation of patients with iron deficiency but no anaemia has not been assessed in clinical studies.

3. Causes of Iron deficiency Anaemia

In developing countries, low iron bioavailability of the diet is the primary cause of iron deficiency anemia;[36,37] however, in developed countries, decreased iron absorption and blood loss account for the more likely etiologies of iron deficiency.

Decreased iron absorption may also be the result of atrophic gastritis or malabsorption syndromes especially celiac disease.[38]

Postsurgical gastrectomy (partial or total) and intestinal resection or bypass may also produce iron deficiency anemia secondary to decreased iron absorption. Chronic blood loss from genitourinary, gynecological, or gastrointestinal tracts accounts for the majority of causes for iron deficiency anemia. The most common etiology of iron deficiency anemia in premenopausal women is excessive menstruation. Gastrointestinal bleeding is a common cause of iron deficiency anemia, whether the bleeding is acute or chronic. Patients may present with maroon-colored stools or blood in their stools with brisk bleeding but more often the blood loss is unrecognized by the patient as blood loss up to 100 ml/day from the gastrointestinal tract may be associated with normal-appearing stools.[39] The physiologic response of the small bowel to bleeding will be to increase iron absorption by twofold to threefold by upregulation of proteins duodenal cytochrome b, divalent metal transporter 1, ferroportin, and downregulation of hepcidin. However, iron loss greater than 5 mg/day over a prolonged period of time exceeds this compensatory response; the patient's iron stores will become depleted and iron deficiency anemia ensues.[40] Chronic gastrointestinal bleeding is associated with a variety of lesions and can occur at any location within the gastrointestinal tract. Iron deficiency anemia is especially prone to occur in those taking aspirin or non-steroidal anti-inflammatory drugs chronically. For those with angiodysplasia or other structural lesions, the site can often be visualized by endoscopic evaluation of the gastrointestinal tract. However, in 10 40% of patients with occult gastrointestinal bleeding the cause remains obscure.[41,42]

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 iron deficiency or iron overload.[7] 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 2mg is normally absorbed each day. 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 heme 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 (Feþ2) or ferrous (Feþ3) iron. The acidic environment of the stomach and certain foods are known to increase the bioavailability of dietary iron.[8] Vitamin C, for example, functions to prevent precipitation of ferric iron in the duodenum. Other foods containing plant phytates and tannins are known to decrease the absorption of non-heme iron.[9] After entry of ferric iron into the duodenum it must first be reduced to the ferrous form by duodenal cytochrome b prior to 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.[8] 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 the reoxidation of ferrous iron to ferric iron, which must occur prior to 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 transferrin occurs via the apotransferrin receptor pathway.[9] Once in the plasma the iron is transported by transferrin to the bone marrow for 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 the 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.[10] Some of the iron from senescent red blood cells is also stored in macrophages as ferritin or hemosiderin, and the majority of it is released via ferroportin into the plasma bound to transferrin for recycling. Around 70% of the total body iron is in heme compounds, 29% is stored as ferritin and hemosiderin, <1% is incorporated into heme-containing enzymes, and <0.2% is found circulating in the plasma bound to transferrin.[8] During states of intravascular hemolysis, red blood cells are destroyed and hemoglobin is released into the plasma. Haptoglobin is a protein synthesized primarily in the liver and functions to bind free hemoglobin. 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. In women, approximately 0.006 mg iron/kg/day is lost during normal menstruation. Thus, normally iron loss and gain is in balance with the amount lost daily being equal to the amount absorbed daily. The body has the ability to increase intestinal iron absorption dependent on the body iron needs. When the pendulum swings towards more iron being lost than is absorbed, iron stores become depleted and the patient develops iron deficiency. If the process continues the patient develops iron deficiency anemia. Iron deficiency is associated with upregulation 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 upregulates the expression of duodenal cytochrome b and divalent metal trans-porter 1; iron regulatory proteins upregulate the expression of divalent metal transporter 1 and ferroportin. These two pathways are vital for the enhancement of iron absorption associated with iron deficiency.[8] Within limits, iron absorption enhancement is proportional to the degree of iron deficiency. 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.[11] Hepcidin expression is most notably sup-pressed by hypoxia, erythropoietin, twisted gastrulation, and growth differentiation factor 15. The synthesis of hepcidin is unregulated 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.[8]

4. Consequences of Iron Deficiency Anaemia in Human

Iron deficiency has a great impact on the organism involved, as it interferes in all the reactions in which iron is involved. This will eventually result in well-known clinical consequences. The clinical presentation varies greatly from one case to the next, depending on the rapidity of onset of anemia, its severity, and the characteristics of the patient suffering from it. The cause of ID/IDA is another influencing factor, as well as the existence of other added nutritional deficiencies, or even a protein-calorie malnutrition. Thus, IDA or ID can be detected in subjects

that are asymptomatic or when they present with systemic symptoms, more or less important, such as weakness, tiredness, irritability, lack of concentration, headache, intolerance to exercise, or even a clinical presentation of heart failure in more serious cases. Some patients with ID, with or without anemia, can experience alopecia, atrophy of lingual papillae, or dry mouth due to decreased salivation. Other types of symptomatology, such as frailty of nails or spoon nails, chlorosis, or Plummer-Vinson or Paterson-Kelly syndromes have practically disappeared. The most dramatic consequences of ID are increases in both maternal and prenatal/perinatal mortality, apart from an increase in prematurity. In fact, 40% of perinatal maternal deaths are associated with anemia.[1] Iron deficiency has also been shown to impair cognitive performance and physical abilities, thus affecting performance at school and work.[43,44] The immune system is also affected by several mechanisms that influence the correct functioning of leukocytes,[45] thus increasing morbidity from infectious diseases. Thyroid function can be affected by various mechanisms that finally result in a reduction in triiodothyronine and an increase in thyroid peroxidase activity.[46] It is important to point out that not only IDA, but also "simple" ID can cause symptoms, as has been shown in several studies. Furthermore, it is necessary to outline that some of these consequences are hardly quantifiable. Hence, ID has a clear negative impact on the quality of life of people who suffer it, in spite of not being easy to estimate this correctly. It is even more complicated to analyze other effects it most surely produces. We are referring here to its impact on school and work performance as well as its economic implications for patients and society. It is highly possible that the development of human beings under conditions of ID results in a lower intellectual and educational development that, in the long term, will adversely influence their professional future and derived income. It could even be one of the reasons for slow development in poorer countries, hindering the adequate development of its human capital. Moreover, let us not forget that, in the event of ID in diet, there will most certainly be other deficiencies that will also have a negative impact on the adequate development of individuals. This is especially important in certain restrictive diets, since some diets have an evident indication for health purposes, such as gluten-free diets for celiac people, allergy diets, ketogenic diets in the management of metabolic disorders, and nutritional support diets in specific conditions affecting the gastrointestinal tract; thus, it is not rare to identify calcium, zinc, tiamine, riboflavine, niacin, and folate deficiencies in these kinds of diets/patients.[47]

5. Signs and Symptoms

Individuals with iron deficiency may experience no symptoms. Findings common to all anaemias may be present or those rather specific to iron effects on rapidly turning over epithelial cells resulting in glossitis, gastric atrophy, stomatitis, ice eating, and leg cramping. The esophageal web syndrome is still reported to be related to iron deficiency, and at least some cases appear to respond to iron therapy.[12] Koilonychias or spoon nails may more commonly be due to fungal infections or hereditary variations.[13] Definitive diagnosis requires laboratory tests.[13] A bone marrow smear containing no stainable iron is definitive. Elevated total iron-binding capacity, low serum iron level, and a low serum ferritin concentration are considered diagnostic for iron deficiency. Transferrin saturation should be less than 10%. How-ever, serum iron is subject to diurnal variations, with higher concentrations late in the day, and may be increased after meat ingestion. Oral contraceptives increase serum transferrin and result in low transferrin saturation. The serum ferritin reflects body stores and is not affected by recent iron ingestion. Ferritin is an ''acute phase reactant'' and in the presence of infection or inflammation the ferritin may be high and the serum iron and transferrin low. Perhaps a better estimate of body stores is obtained by the ratio of serum transferrin receptor to serum ferritin.[15,16] Studies of the R/F ratio shows age dependence;[17] in males there is a Gaussian distribution, but in females there is a bimodal distribution. The R/F ratio can also be affected by inflammation. However, at least in the elderly, the R/F ratio may be more sensitive than the classic blood tests and may be more sensitive in distinguishing iron deficiency anemia from the anemia of chronic disease. [19] A major problem is the lack of standardization of the sTfR assay. There has been interest in using erythrocyte zinc porphyrin as an assay.[20] This may be useful in primary screening tests for assessing iron status. It is likely due to the increase transport of Zn across the intestine by the upregulation of the DMT-1 in iron deficiency. In individuals treated with recombinant erythropoietin, the increased production of RBCs exhausts iron stores rapidly, resulting in serum iron being reduced and transferrin becoming desaturated. In healthy individuals iron stores determine the response to erythropoietin, and baseline ferritin values <1,000 mg/L have been associated with a ''functional'' iron deficiency. Ferritin concentrations are not correlated to body stores in the setting of hyperthyroidism, malignancy, inflammation, hepatocellular disease, alcohol consumption, and oral contraception use. The percentage of hypochromic RBC and hypochromic reticulocytes may or may not be useful in identifying functional iron deficiency and in predicting response to erythropoietin and i.v. iron treatments. This percentage is not useful in the settings of thalassemia or chemotherapy patients.[21]

6. Screening

Men and Postmenopausal Women

Asymptomatic men and postmenopausal women should not be screened for iron deficiency anemia. Testing should be performed in patients with signs and symptoms of anemia, and a complete evaluation should be performed if iron deficiency is confirmed.[31]

Pregnant Women

The American Academy of Family Physicians, U.S. Preventive Services Task Force, and Centers for Disease Control and Prevention recommend routine screening of asymptomatic pregnant women for iron deficiency anemia.[22,29,32] The American College of Obstetricians and Gynecologists recommends screening for anemia and implementing iron therapy if iron deficiency anemia is confirmed.[33] The defined values consistent with anemia in pregnancy are hemoglobin levels less than 11 g per dL (110 g per L) in the first or third trimester, or less than 10.5 g per dL (105 g per L) in the second trimester.[34] A maternal hemoglobin level of less than 6 g per dL (60 g per L) has

been associated with poor fetal outcomes, including death.[33]

Children

The American Academy of Pediatrics recommends universal hemoglobin screening and evaluation of risk factors for iron deficiency anemia in all children at one year of age.[34] Risk factors include low birth weight, history of prematurity, exposure to lead, exclusive breastfeeding beyond four months of life, and wean-ing to whole milk and complementary foods without iron-fortified foods.[34] The Centers for Disease Control and Prevention recommends screening children from low-income or newly immigrated families at nine to 12 months of age, and consideration of screening for preterm and low-birth-weight infants before six months of age if they are not given iron-fortified formula.[32] The U.S. Preventive Services Task Force found insufficient evidence for screening in asymptomatic children six to 12 months of age and does not make recommendations for other ages.[22] A meta-analysis showed that infants in whom cord clamping was delayed for up to two minutes after birth had a reduced risk of low iron stores for up to six months.[35] Larger randomized studies that include maternal outcomes are needed before delayed cord clamping can be recommended for general practice.

7. Diagnosis

Diagnosis of iron deficiency anemia requires laboratory-confirmed evidence of anemia, as well as evidence of low iron stores.[22] Anemia is defined as a hemoglobin level two standard deviations below normal for age and sex.[23] 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 anaemia unless the mean corpuscular volume is greater than 95 µm, because this cut-off has a sensitivity of 97.6%.[24] Other causes of microcytosis include chronic inflammatory states, lead poisoning, thalassemia, and sideroblastic anemia. The following diagnostic approach is recommended in patients with anemia and is outlined in Figure 1.2,6 -11 A serum ferritin level should be obtained in patients with anemia and a mean corpuscular volume less than 95 µm. Ferritin reflects iron stores and is the most accurate test to diagnose iron deficiency anemia.[25] Although levels below 15 ng per mL (33.70 pmol per L) are consistent with a diagnosis of iron deficiency anemia, using a cutoff of 30 ng per mL (67.41 pmol per L) improves sensitivity from 25 to 92 percent, and specificity remains high at 98 percent.[26] Ferritin is also an acute phase reactant and can be elevated in patients with chronic inflammation or infection. In patients with chronic inflammation, iron deficiency anaemia is likely when the ferritin level is less than 50 ng per mL (112.35 pmol per L).7 Ferritin values greater than or equal to 100 ng per mL (224.70 pmol per L) generally exclude iron deficiency anemia.[27,28] In patients with no inflammatory states and in whom the ferritin level is indeterminate (31 to 99 ng per mL [69.66 to 222.45 pmol per L]), further tests can be performed to ascertain iron status. Values consistent with iron deficiency include a low serum iron level, low transferrin saturation, and a high total iron-binding capacity. Soluble transferrin receptor and erythrocyte protoporphyrin testing, or bone marrow biopsy can be considered if the diagnosis remains unclear. The soluble transferrin receptor level is an indirect measure of erythropoiesis and is increased in patients with iron deficiency anemia.[26] Another benefit of this test is that the soluble transferrin receptor level is unaffected by inflammatory states and can help identify concomitant iron deficiency anemia in patients with anemia of chronic disease.[30] Erythrocyte protoporphyrin is a heme precursor and accumulates in the absence of adequate iron stores.[29] If other tests are indeterminate and suspicion for iron deficiency anemia persists, the absence of stainable iron in a bone marrow biopsy is considered the diagnostic standard.

8. General Management of Iron Deficiency and Iron Deficiency Anaemia

In a simplistic manner, when ID or IDA due to poor iron intake is present, the mainstay of its treatment and prevention is to normalize the amount of dietary iron. The problem is that this is not so easy in most patients under these circumstances, as it involves an economic effort they may not undertake. Having said this, we will take a graphical overview of what should be the general management in these cases, and later we will comment on the particularities of some specific situations. Of course, if another etiology associated with an inadequate dietary iron intake is evidenced when investigating the cause of anemia, it should be treated specifically.

Iron supplementation

The first measure in initial treatment is to provide iron supplements until the values of hemoglobin and iron deposits have been normalized. This will usually be achieved by administering iron orally.[48] Even though it is broadly recommended to take it before breakfast in order to increase its absorption, there is no evidence supporting this, and it does significantly reduce tolerance; thus, it seems reasonable to administer it with foods. One tablet of any commercially available preparation of ferrous salts provides more iron than intestines are able to absorb in 1 day. All ferrous salts have similar bioavailability. Iron glycinate preparations are a therapeutic alternative due to excellent bioavailability and lower frequency of side effects, such as constipation.[49,50] Other formulations may serve as substitutes for ferrous salts, but there is no strong evidence showing these preparations are superior in terms of tolerance or clinical response. The treatment with oral iron is slow in reaching its goals, and a good compliance is necessary to be successful. The therapeutic goals are recovery from anemia and normalization of iron deposits. In any case, oral iron has important limitations. Often, the anemia is severe, and a quick response is needed. In other occasions, tolerance is poor, even following the precautions we have recommended, and this is especially frequent in chronic bowel inflammatory disease. Finally, in other patients, it may not be intrinsically effective due to a problem of inadequate absorption, or because losses are greater than the limited capacity of oral assimilation. In these situations, the use of parenteral iron is fully justified.[48] The efficacy and safety of iron sucrose have

been demonstrated in clinical trials and have been confirmed by broad practical experience.[51] The only inconvenience with iron sucrose is that the infusion of several doses is necessary in order to provide the total required dose. More recently, new formulations such as carboxymaltose iron[52] have appeared, making it possible to provide the entire required dose in just one or two sessions. In order to calculate the amount of iron a patient needs, a formula is used: Total iron deficiency (mg) = [weight (kg) × (target Hb − specific patient's

Hb (g/L) × 0.24) + 500 (approximate deposits), where Hb is hemoglobin and 0.24 is a constant. Side effects are very uncommon and nearly always mild, except for extremely uncommon anaphylactoid reactions; none-the less, observation and measuring of vital signs during the administration of the infusion are required.

Dietary improvement

Secondly, in order to prevent the new development of ID or IDA, it is necessary to correct the patient's diet. This is not always easy, especially in developing countries, due to economic determinants. The daily requirements of iron are 1–3 mg/day; these requirements increase during the growth period, in women of childbearing age, and in pregnant women, and decrease due to the cessation of menses. Because gastrointestinal absorption of iron is limited, the diet must contain between 15 and 30 mg/day. Food-frequency questionnaires combined with information on meal composition and food consumption patterns are necessary to analyze the amount of iron ingested by a person.[1] Several kinds of questionnaires in multiple clinical scenarios have been used to assess the quantity of daily iron intake; readers are encouraged to consult some especially interesting articles relating to such questionnaires.[53,54,55] The primary goal of dietary modification, that is, improving and maintaining the iron status of a population, involves changes in behavior, leading to an increase in the selection of iron-containing foods and a meal pattern that favors increased bioavailability. Efforts should be focused on promoting the access to iron-rich foods and foods that enhance iron absorption. Recommendations should be adapted to regional and local variations in diet and the age groups concerned. In the specific case of populations following diets based on vegetable consumption with scarce meat intake, frequent in developing countries, in which iron is non-heme, and hence, ID is more likely,[56] absorption may be increased by promoting the intake of foods that favor this, such as vitamin C,[57,58] and avoiding those that hinder it, such as calcium, very fatty foods, phytates, and others.[59]

Iron fortification

Another approach to improve ID in large populations is food fortification. Iron fortification is a practical and cost-effective long-term solution to control ID on a nationwide scale. A pro-gram of effective iron fortification mandates cooperation efforts among governments, food industry, and consumers. Iron fortification of foods is more difficult than fortification with other nutrients, such as iodine in salt. Iron compounds that are more soluble and absorbable, such as ferrous sulfate, often react with other ingredients in food, oxidize fats, and produce an unpleasant taste and color changes. Hence, other iron com-pounds are used, such as ferric pyrophosphate, or electrolytic iron, and the amount required is twice that of ferrous sulfate, as they are less absorbable in the gastrointestinal tract, but they produce no sensory changes in foods.[56,60,61] In any case, the appearance of these sensory changes should be monitored during the processing, storage, and preparation of foods. Moreover, it is necessary to identify an appropriate alimentary vehicle that reaches the entire target population, such as rice, pasta, or bread. Foods that are used most frequently in the fortification of populations are flours of staple cereals. Several fortifiers have been used successfully in nation-wide programs in different countries, and no significant side effects have been described with this fortification. In a meta-analysis of studies carried out in children receiving iron-fortified foods, no adverse effects occurred and a protective effect against the development of respiratory infections was observed with fortification.[61] It becomes necessary to use specific laboratory parameters relating to iron levels to evaluate the fortification needs in a population and to monitor subsequently the results of such intervention.

9. Treatment

Underlying Cause

Patients with an underlying condition that causes iron deficiency anemia should be treated or referred to a subspecialist for definitive treatment.

Oral Iron Therapy

The dosage of elemental iron required to treat iron deficiency anemia in adults is 120 mg per day for three months; the dosage for children is 3 mg per kg per day, up to 60 mg per day.[1] An increase in hemoglobin of 1 g per dL after one month of treatment shows an adequate response to treatment and confirms the diagnosis.[34] In adults, therapy should be continued for three months after the anemia is corrected to allow iron stores to become replenished.[25] Adherence to oral iron therapy can be a barrier to treatment because of GI adverse effects such as epigastric discomfort, nausea, diarrhea, and constipation. These effects may be reduced when iron is taken with meals, but absorption may decrease by 40 percent.[1] Medications such as proton pump inhibitors and factors that induce gastric acid hyposecretion are associated with reduced absorption of dietary iron and iron tablets.[69]

Parenteral Iron Therapy

Parenteral therapy may be used in patients who cannot tolerate or absorb oral preparations, such as those who have undergone gastrectomy, gastrojejunostomy, bar-iatric surgery, or other small bowel surgeries. The most common indications for intravenous therapy include GI effects, worsening symptoms of inflammatory bowel dis-ease, unresolved bleeding, renal failure–induced anemia treated with erythropoietin, and insufficient absorption in patients with celiac disease.[70] Serious adverse effects have occurred in up to 0.7% of patients receiving iron dextran, with 31 recorded fatalities reported between 1976 and 1996.32,33 Iron sucrose and sodium ferric gluconate have greater bio-availability and a lower incidence of life-threatening anaphylaxis compared with iron dextran.[2] Approximately 35% of patients receiving iron sucrose have mild adverse

effects.[25] One small study cited similar adverse effect profiles between intravenous iron dextran and sodium ferric gluconate, with only one serious adverse effect reported in the iron dextran group.[72] If this finding is duplicated in larger studies, it could support the use of iron dextran over sodium ferric gluconate, because the total dose can be given in one sit-ting. A newer formulation, ferumoxytol, can be given over five minutes and supplies 510 mg of elemental iron per infusion, allowing for greater amounts of iron in fewer infusions compared with iron sucrose.[2]

Monitoring

There are no standard recommendations for follow-up after initiating therapy for iron deficiency anemia; however, one suggested course is to recheck complete blood counts every three months for one year. If hemoglobin and red blood cell indices remain nor-mal, one additional complete blood count should be obtained 12 months later. A more practical approach is to recheck the patient periodically; no further follow-up is necessary if the patient is symptomatic and the hematocrit level remains normal.[25]

Blood Transfusion

There is no universally accepted thresh-old for transfusing packed red blood cells in patients with iron deficiency anemia. Guidelines often specify certain hemoglobin values as indications to transfuse, but the patient's clinical condition and symptoms are an essential part of deciding whether to transfuse.[73] Transfusion is recommended in pregnant women with hemoglobin levels of less than 6 g per dL because of potentially abnormal fetal oxygenation resulting in non-reassuring fetal heart tracings, low amniotic fluid volumes, fetal cerebral vasodilation, and fetal death.15 If transfusion is performed, two units of packed red blood cells should be given, then the clinical situation should be reassessed to guide further treatment.35

10. Special Considerations

Co-Morbidity

The appropriateness of investigating patients with severe co-morbidity or other reason especially if the result would not influence management, should be carefully considered and discussed with patients and carriers when possible.

Pre-Menopausal Women

Menstruating women present a large healthy population in which IDA is common, occur-ring in 5–10%.[62] Menstrual loss, especially menorrhagia, pregnancy, and breast feeding are usually responsible.[63] History is unreliable in quantifying menstrual loss,[64] although pictorial blood loss assessment charts have been shown to have a sensitivity and specificity of around 80% for detecting menorrhagia.[65] There are little data on the yield of GI investigation in menstruating women with IDA[66.67] but significant GI pathology has been detected in these studies. Iron deficiency anaemia occurs in 5–10% of menstruating women. Because of the increasing incidence of important pathology with age, we recommend that those more than 45 years are investigated according to the above guidelines. In the absence of data in those less than 45 years, we recommend that only patients with upper GI symptoms have endoscopy and small bowel biopsy. The remainder should have anti-endomysial antibody determinations to exclude coeliac disease. Colonic investigation in patients less than 45 years should only be done if there are colonic symptoms, a strong family history of colorectal carcinoma, or persistent IDA following iron supple-mentation and correction of potential causes of losses.

Young Men

Although the incidence of important GI pathology in young men is low, there are no data on the yield of investigation in those with IDA. In the absence of such data we recommend that investigation of young men should occur according to the guidelines.

Post-Gastrectomy

IDA is to be expected after gastrectomy, both partial and total,[68] due to poor chelation and absorption of iron as a result of the loss of ascorbic acid and hydrochloric acid, and loss of free iron in exfoliated cells. It would seem reasonable, therefore, only to investigate those whose IDA persists on iron supplementation or who present with IDA many years after partial gastrectomy.

11. Conclusion

Unlike other prevalent anaemias and haemoglobinopathies, the diagnosis and treatment of iron deficiency anemia is achievable in most, if not all individuals. However, consideration of iron deficiency anemia must include the possible convergence of several causative factors. If resources are adequate, care must be given toward individualized approaches to therapy. In the underdeveloped world, more communal approaches are being taken to overcome the overlapping causes of iron deficiency anemia that affect hundreds of millions worldwide. Ultimately, it is predicted that increased research and understanding of fundamental iron biology will assist in devising new strategies aimed to-ward the global elimination of this disease.

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