Iron Deficiency Anaemia: A Short Review

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Abstract

Iron deficiency anaemia (IDA) is one of the most widespread nutritional deficiency and accounts for almost one-half of anaemia cases. It is prevalent in many countries of the developing world and accounts to five per cent (American women) and two per cent (American men). In most cases, this deficiency disorder may be diagnosed through full blood analysis (complete blood count) and high levels of serum ferritin. IDA may occur due to the physiological demands in growing children, adolescents and pregnant women may also lead to IDA. However, the underlying cause should be sought in case of all patients. To exclude a source of gastrointestinal bleeding medical procedure like gastroscopy/colonoscopy is utilized to evaluate the level of iron deficiency in patients without a clear physiological explanation. Inevitably, the accurate management of this disorder improves the quality of life, improves the symptoms of iron deficiency, and lessens the requirement for blood transfusion. The treatment options include oral iron supplement and intravenous iron therapy. However, this mode of treatment is not tolerable by some patients while it is insufficient in a certain subset of patients. Therefore, intravenous iron supplementation is considered undesirable approach and there is not much clarity on the safety concerns associated with this approach in case of very high doses or in the presence of very high ferritin levels. In addition, red cell transfusion is not recommended for IDA unless there is a need for immediate action. The objective of the review is to provide a critical summary and an update of the diagnosis and treatment options of IDA.

Keywords: Iron deficiency anaemia; Gastrointestinal; Insufficient iron intake; Microcytic

Introduction

Anaemia can be defined by a condition in which the total haemoglobin (Hb) level or number of red blood cells (RBCs) is poorly lowered. The World Health Organisation (WHO) defines anaemia as Hb<130 g/L in men older than 15 years, 110 g/L in pregnant women, and <120 g/L in non-pregnant women older than age 15 years [1]. Table 1 shows the definition of anaemia as defined by the World Health Organization (WHO) Iron deficiency anaemia (IDA) is a certain anaemic condition arising due to the inadequate iron to form normal RBCs. IDA is usually caused by insufficient iron intake, chronic blood loss, and increased iron demand [2]. The prevalence of IDA varies across the world [3]. Recognizing the original aetiology and the relevant diagnostic and therapeutic issues are primary keys in the management and assessment of this disorder.

<table>
<thead>
<tr>
<th>Population</th>
<th>Hb Diagnostic of anaemia (g/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged 6 months to 6 years old</td>
<td>&lt;11.0</td>
</tr>
<tr>
<td>Children aged 6-14 years old</td>
<td>&lt;12.0</td>
</tr>
<tr>
<td>Adult men</td>
<td>&lt;13.0</td>
</tr>
<tr>
<td>Adult non-pregnant women</td>
<td>&lt;12.0</td>
</tr>
<tr>
<td>Adult pregnant women</td>
<td>&lt;11.0</td>
</tr>
</tbody>
</table>

Table 1: World health organization definition of anaemia. *Values obtained from venous blood samples obtained at sea level.

Iron is an important dietary mineral associated with many body functions like oxygen transport in the blood. Iron deficiency anaemia is characterized by incomplete haemoglobin synthesis that results in microcytic and hypochromic red blood cells. Due to inadequate haemoglobin, the ability of blood to deliver oxygen to the other body cells and tissues is reduced [4-7].

Iron deficiency is defined as an imbalance of iron intake, absorption and iron loss. The iron deficiency is the first cause of anaemia. Pallor, fatigue and dyspnea are the most common symptoms of anaemia. Anaemia is classically associated with microcytosis and hypochromia in biological exams. Iron deficiency, inflammatory aetiologies, thalassemia and sideroblastic anaemia are the origins of microcytic anaemia [4-8].

Iron metabolism

Iron is an essential element required for the maintenance of physicochemical processes. It is very much necessary to maintain its balance for proper physiologic functioning in the body. As the overabundance of iron can have extreme adverse effects like liver swelling and damage, in the same manner it is always advisable to avoid iron deficiency (ID) or iron overload [9,10]. The body absorbs 1 to 2 mg of dietary iron a day, which is balanced through body processes i.e., menstruation, sloughed intestinal mucosal cells, and other blood losses [11]. Dietary iron comprises heme iron (animal sources) and non-heme iron (vegetable and cereal sources). Heme iron bound to Hb and myoglobin is responsible for delivering oxygen to the tissues. Pancreatic enzymes digest heme to release it from the globin molecule in the intestinal lumen. This is followed by the absorption of heme iron into the enterocytes as metalloporphyrin takes place and it is further degraded by heme oxygenase-1 leading to the release of non-
heme iron. Subsequently, iron is exported by the only iron exporter ferroportin, present on the basolateral aspect of the enterocyte [12]. On the other hand, non-heme iron is less well absorbed. It is absorbed by intestinal luminal cells through a specific transporter and released into the circulation wherein the binding of transferrin occurs. Transferrin receptors on erythoblasts accept iron-transferrin complexes, which undergo the process of endocytosis leading to the incorporation of iron into Hb [13,14].

Iron absorption is maintained by increased erythropoiesis and iron deficiency, and down-regulated in iron repletion and inflammation. This dynamic process of iron absorption is mediated by hepcidin, which regulates the inflow of iron and blocks iron release from enterocytes and macrophages [15]. Iron stores in the body are regulated through the process of iron absorption. Non-heme iron is absorbed in the ferrous form (Fe$^{+2}$). Reduction of ferric iron (Fe$^{+3}$) by dietary ascorbic acid, stomach acidity, and luminal reductase improves the iron absorption. Non-heme iron is repressed by simultaneous consumption of tannins (in tea), phytic acid (in cereal and legumes), and calcium. Simultaneous consumption of ascorbic acid and heme iron sources also improves the process of absorption [14-16].

**Symptoms of IDA**

The two main types of iron deficiency are 1) absolute iron deficiency arising due to the lowered or exhausted level of total body iron stores are low or exhausted and, 2) functional iron deficiency wherein the total body iron stores are normal or increased, with the insufficient iron supply to the bone marrow. Absolute iron deficiency and functional iron deficiency can coexist. Functional iron deficiency is present in many acute and chronic inflammatory states [17].

The clinical features of iron deficiency anaemia depends on the following factors:

- Level of severity of the anaemia
- Age group
- Multiple disorders
- Illness consistency
- Speed of onset

Patients with iron deficiency anaemia present with symptoms that are associated with all anaemias such as pallor of the skin, conjunctivae, nail beds, fatigue, vertigo, syncope, exertional dyspnoea progressing to breathlessness at rest, tachycardia headache, and a cardiac systolic flow murmur [17-22]. The patients may also show dyspnoea at rest angina pectoris and haemodynamic instability in severe cases [21].

Iron deficiency rapidly affects the epithelial cells thereby leading to dryness and roughness of the skin, dry and damaged hair, koilonychia and alopecia. In mild-to-moderate iron deficiency loss of tongue papillaeis reported. Atrophic glossitis is also noted in severe cases. Iron deficiency may be associated with restless legs syndrome [23].

Anaemic condition tends to have negative impact physical performance, mostly work productivity due to reduced oxygen transport the reduced cellular oxidative capacity [13]. Perinatal iron deficiency is associated with tardy neurocognitive development and psychiatric illness [3,9-14,24,25]. Various symptoms associated with anaemia are listed in Table 2.

### Table 2: Symptoms of iron deficiency anaemia.

<table>
<thead>
<tr>
<th>Very frequent</th>
<th>Frequent</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimness or Paleness</td>
<td>Diffuse and moderate alopecia</td>
<td>Haemodynamic instability</td>
</tr>
<tr>
<td>Exhaustion and tiredness</td>
<td>Atrophic glossitis</td>
<td>Syncope</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Restless legs syndrome</td>
<td>Kolonychia</td>
</tr>
<tr>
<td>Headache</td>
<td>Dry and rough skin</td>
<td>Plummer-Vinson syndrome</td>
</tr>
<tr>
<td>Dry and damaged hair</td>
<td>Cardiac murmur</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Neurocognitive dysfunction</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>Vertigo</td>
<td></td>
</tr>
</tbody>
</table>

**Common causes of anaemia**

Regardless of the various aetiologies, most anaemic patients usually have some component of iron deficiency, which responds to iron administration. With the elderly, the aetiology is attributed to iron deficiency in approximately one-third and chronic renal disease or inflammation accounts to another one-third. The aetiology in the remaining group is often unclear [26,27]. Latrogenic anaemia or drug-induced immune hemolytic anaemia (DIIHA) should be underscored with a growing list of commonly used medications being implicated [27]. Furthermore, data on blood loss due to excessive diagnostic phlebotomy in hospitalized patients have also been a cause of major concern [28].

**Diagnosis of IDA**

IDA diagnosis necessitates the laboratory investigation. IDA should not be presumed unless confirmed by laboratory testing in addition to...
and folate with or without the persistence, the absence of stainable iron in a bone marrow biopsy can be considered as the standard diagnostic measure [40].

Although microcytic anaemia is characterized by small red blood cells and iron deficiency, up to 40% of patients with IDA have normocytic RBCs [12,27]. Other reasons of microcytic anaemia include chronic inflammatory diseases, thalassaemia, lead poisoning, and sideroblastic anaemia [32]. The red cell distribution width (RDW) is a measure used in combination with the MCV to differentiate between mixed causes for anaemia from that of a single cause. An elevated RDW value signifies a variation in the size of the red blood cell. In addition, RDW may also be elevated at the early stages of IDA and folate with or without the deficiency of vitamin B12, both of which cause macrocytic anaemia [12,33]. White blood cell (WBCs) and platelet counts help to distinguish isolated anaemia from pancytopenia [31].

Patients suspected to have IDA should undergo iron studies test. The results determined from this test should be correlated with the red cell indices. The serum ferritin level is the most commonly available and useful index of iron deficiency [30]. Iron studies diagnostic for IDA consists of low haemoglobin (<13 g/dL and 12 g/dl in women), low transferrin saturation (<15%), a low serum ferritin (<30 μg/L), and high total iron-binding capacity (>13.1 μmol/l) [34,35]. However, one point to be noted is that ferritin is also an acute-phase protein and tends to be elevated in cases of infection, liver disease, inflammation, and malignancy. This can result in misleadingly elevated ferritin levels in iron-deficient patients with co-excising systemic illness [16,34]. Other markers such as C-reactive protein (CRP) may also help identify coexisting inflammation in cases of an underlying inflammation or infection [36,37]. Serum iron levels have significant diurnal variation, they tend to be low in both inflammation and IDA, and should not be used as a mode of diagnosis for iron deficiency [30].

Soluble transferrin receptor (sTfR) level is considered an additional iron index is the, which acts as a parameter for the diagnosis of IDA and as an indirect measure of erythropoiesis. It tends to be increased in patients with ID [38]. Another additional advantage of this test is that the soluble transferrin receptor level remains unaffected by inflammatory states and helps recognize concomitant IDA in patients with anaemia of chronic disease (ACD) [39].

If the other tests don't prove helpful and suspicion for IDA still persists, the absence of stainable iron in a bone marrow biopsy can be considered as the standard diagnostic measure [40].

As mentioned above, the diagnostic accuracy of ferritin is limited as it behaves as an acute phase reactant. The level of serum ferritin is often elevated independent of iron status by factors such as acute or chronic inflammation, infection, malignancy, liver disease, and alcohol use. Also, the levels of serum iron is reduced with infection, inflammation, and malignancy and elevated with liver disease [30]. On the other hand, past studies showed that the measurement of reticulocyte haemoglobin content (CHr) is identified as an indirect measure of the functional iron available for new RBC production [41]. In a study done by Mast et al. showed that CHr of <28 pg had an optimal sensitivity (74%) and specificity (73%) for diagnosis of IDA, using Prussian blue staining of the Bone Marrow (BM) aspirate to define iron deficiency [42]. Furthermore, Thomas et al. reported that functional iron deficiency was defined as CHr <28 pg. Therefore, CHr in combination with other parameters proves to be highly useful and reliable in the safe diagnosis of IDA [34].

If these tests are indicative of IDA, then iron therapy should be advised. Recommendation of additional evaluation of possible underlying causes of blood loss should also be considered for the patients with IDA. The British Society of Gastroenterology guidelines puts forward the best practice for upper and lower gastrointestinal (GI) study in all men and postmenopausal women with IDA and no history of clear blood loss from sources other than GI tract and offer an system to use various diagnostic measures [43].

Complication of IDA

Various physiological and pathological conditions promote iron deficiency anaemia. Blood loss, malabsorption, iron deficiencies are some complications associated with anaemia. Iron deficiency anaemia is frequently reported in chronic disorders [44], including inflammatory bowel diseases (IBD), [19,45] chronic kidney disease [46], chronic heart failure cancer and rheumatoid arthritis obesity [17,29,47]. Pathological disorders associated with iron deficiency anaemia are listed in Table 3.

<table>
<thead>
<tr>
<th>Blood loss</th>
<th>Malabsorption</th>
<th>IDA associated with anaemia of chronic disease</th>
<th>Genetic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>•Digestive tract diseases: colonic carcinoma, gastric carcinoma, inflammatory bowel disease</td>
<td>•Coeliac disease</td>
<td>•Chronic heart failure</td>
<td>•Iron-refractory iron deficiency anaemia</td>
</tr>
<tr>
<td>•Diseases, ulcers, angiodysplasia, parasites</td>
<td>•Gastrectomy</td>
<td>•Cancer50</td>
<td>•Divalent metal transporter deficiency anaemia</td>
</tr>
<tr>
<td>•Gynaecological disorders: endometriosis, hysterectomy</td>
<td>•Helicobacter pylori</td>
<td>•Chronic kidney disease</td>
<td>•Fanconi anaemia</td>
</tr>
<tr>
<td>•Surgery</td>
<td>•Gut resection, atrophic gastritis, bypass gastric surgery, bacterial overgrowth</td>
<td>•Rheumatoid arthritis</td>
<td>•Pyruvate kinase deficiency</td>
</tr>
<tr>
<td>•Haematuria, episaxis, haemorrhage</td>
<td>•Interaction with food, elements: tea, coffee, calcium, iron, flavonoids, oxalates, phytoflavonoids</td>
<td>•Obesity</td>
<td></td>
</tr>
<tr>
<td>•Non-steroidal anti-inflammatory drugs, aspirin</td>
<td>•Pica syndrome, pagophagia</td>
<td>•Inflammatory bowel diseases</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:** Pathological disorders associated with iron deficiency anaemia.

Prevention of IDA

It is necessary to expand public health initiatives in order to raise awareness and prevent IDA in children ultimately. Clinicians should not rely on traditional stereotypes and should be cautious of the possibility of iron deficiency leading to anaemia in all children [48].
Jaber et al. conducted a study to determine the effect of nutritional education and supplemental iron administration on the prevalence of IDA in Arab infants. A total of 310 infants were randomized into two groups. Mothers in the control group received standard information on prevention of IDA and mothers in intervention group received extensive information on the importance of an iron rich diet and were encouraged to give their children an iron polymaltose complex (IPC) preparation starting from age 4 months to 1 year. Anaemia was recorded in 28% in intervention and 34% in control groups. Frequency of anaemia was lower in infants who received iron medication ≥ 6 months and in infants breastfed for ≥ 6 months. After this study various questions were raised regarding the strategies of preventing iron deficiency anaemia in infancy [49].

The treatment should involve iron replacement in addition to the diagnostic steps that are focussed towards correcting the fundamental cause of iron deficiency anaemia. Oral iron replacement is effective and cheap, but parenteral therapy may be sometimes required due to intolerance, disobedience or failure of treatment via oral therapy. Iron needs are tripled during pregnancy, because of expansion of maternal red cell mass and growth of the fetus and placenta [50].

Severe iron deficiency anaemia is associated with considerable morbidity and is preventable. There are three potentially modifiable feeding practices associated with iron deficiency anaemia that may present opportunities for preventive interventions through primary care as well as public health settings: 1) Cow's milk intake should be limited to 500 ml/d after 1 year of age, 2) Use of bottle should be discontinued by 12-15 months or earlier, 3) Infants should not be put to sleep with a bottle. Healthy infants have adequate iron stores until 4–6 months of age, and iron deficiency anaemia peaks between 1 to 3 years of age [43]. Therefore, it is critical to identify optimal feeding practices beyond the first 6 months of life to prevent iron deficiency anaemia. Canadian Paediatric Society, Health Canada, Breastfeeding Committee for Canada and Dieticians of Canada confirm their recommendation of exclusive breast-feeding for the first six months [51,52].

Management of IDA

Once IDA is confirmed, the choice between intravenous and oral forms of iron therapy should be made based on the clinical circumstances on a case-by-case basis.

Dietary therapy

Increasing dietary iron consumption alone is insufficient to treat IDA and higher supplemental doses of iron are essential. However, increasing the iron intake and enhancing the absorption by minimising the inhibitors and maximising the enhancers may be valuable for secondary prevention of iron deficiency [30].

Oral iron therapy

The dosage of iron required to treat IDA in adults is 120 mg/day for three months; the dosage for children is 3 mg/kg per day, up to 60 mg/day [32]. In a study done by Baker et al. an increase in haemoglobin of 1 g/dL after one month on treatment showed an adequate response to treatment and confirmed the diagnosis of IDA. In adults with IDA, the treatment should be continuously undergone for three subsequent months after the anaemia is corrected for the replenishment of the iron stores [53].

Physicians often face the challenge of managing IDA with oral iron intake especially when the iron losses in patients exceeds the maximum amount of iron that gut is able to absorb [12]. Additionally, the amount of iron absorbed by the body from GI tract is frequently limited to a few milligrams per day, and consequently, oral iron supplementation may not be able to keep up with the on-going losses. Adherence with oral iron is poor because of frequent GI side effects such as epigastric discomfort, nausea, diarrhoea, and constipation, which limit the usefulness of oral iron [54,55].

Parenteral iron therapy

Parenteral treatment may be used in patients who cannot absorb or tolerate oral iron, such as those who have undergone gastrectomy, bariatric surgery, gastrojejunostomy, or other small bowel surgeries [55]. Parenteral iron therapy can offer a number of clinical advantages, especially newer formulations with better safety profiles in addition to their ability to efficiently restore the body iron stores [56]. The most adverse effect of intravenous therapy includes GI effects, worsening symptoms of inflammatory bowel disease, renal-failure-induced anaemia treated with erythropoietin, unresolved bleeding, and insufficient absorption in patients with celiac disease [57].

Red cell transfusion

Transfusion of red cells is a warranted treatment for severe anaemia [58]. Recommendations often specify certain haemoglobin values as indications to transfuse, but the patient's clinical condition and symptoms are critical mode of determining whether RBC transfusion should be carried out or not [59]. Transfusion is associated with adverse consequences, including fluid overload, and a range of immunological hazards. Therefore, it should be kept for immediate, targeted management in patients with severe anaemia and end-organ function, or where IDA is complicated by series acute on-going bleeding. Iron treatment must always follow transfusion to restore iron [30].

Conclusion

IDA remains a common and important disorder and accounts for approximately one-half of the cases of anaemia. The diagnosis of anaemia is confirmed by the findings of low iron stores and haemoglobin level below normal. In cases of IDA, oral iron treatment should be initiated for the replenishment of iron stores. Intravenous therapy may also be used in patients who cannot tolerate or absorb oral iron formulations.

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References


