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RESEARCH ARTICLE

IRON AND IRON DEFICIENCY ANEMIA - A REVIEW

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Abstract

Iron deficiency (ID) remains the most common mineral and nutrient deficiency and a public health concern worldwide. ID often leads to iron deficiency anemia (IDA), which affects about 30% of the world population. IDA presents with generalized fatigue and dyspnea in adults, decrement in learning, and behavioral abnormalities in adolescents. In children and pregnant women, a psychological disorder called pica is commonly seen. Delayed development and growth and decrease in cognitive function are the results of ID in neonates. A severe form of IDA can cause significant mortality in children and pregnant women. Investigations required to diagnose the IDA are complete blood count (CBC), serum iron, total iron-binding capacity (TIBC), transferrin saturation, but low serum ferritin is the best diagnostic test in IDA. Treating the underlying etiology is the initial step in IDA management. Oral iron salts remain the treatment of choice in most patients who do not have comorbid conditions. The patient who cannot tolerate oral iron due to gastrointestinal (GI) side effects newer generations IV iron therapy may be appropriate.GI evaluation is necessary for adult men and postmenopausal women whose respond is minimal to iron therapy. Red blood cells (RBCs) transfusion is indicated in severe unstable IDA patients.

Introduction:-

Anemia is defined as the hemoglobin (Hb) of less than 12g/dL (120g/L) in women and less than 13g/dL (130g/L) in men [1]. Globally, ID is the most frequent form of anemia and the leading cause of microcytic hypochromic anemia. About 50% of cases of anemia are due to ID and nearly a million deaths annually worldwide [2, 3]. Approximately 2-5% of post-menopausal women and adult men are suffered from ID in the developed world and leading cause being the chronic blood loss from the GI tract [4]. IDA incidence is significantly high in childbearing

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age women and children due to low dietary intake of iron. The situation is even worse in undeveloped countries. In this article, we reviewed the general physiology of iron, etiology, clinical features, diagnosis, and management of IDA, and aimed to play a positive role in ID prevention.

Iron:

Iron is one of the most abundant elements in the earth and an essential mineral required for metabolism in the human body [5]. The two forms of iron exist, the ferrous form (Fe2+) and the ferric form (Fe3+). There are many sources of iron which is divided mainly into two categories: haem iron and non-haem iron. The primary sources of haem iron are red meat, liver, and fish [6]. Out of the total dietary iron in the body, only 11%-15% is haem iron and is easily absorbed in the body. Non-haem iron is found in wholebread, vegetables, dairy products, and iron salts [7]. Non-haem iron is poorly absorbed, but total intake accounts for greater than 80%.

A Human healthy diet contains about 10-20mg of iron. The total body iron content usually is about 3.8gm in men and 2.3gm in women [8]. This iron is distributed in hemoglobin, myoglobin, haem enzymes (cytochromes, catalase), and in transferrin-bound iron. The storage pool, such as hemosiderin and ferritin, contains about 15%-20% of the total body iron. Approximately 1-2 mg of iron is lost through the skin, enteric, and minor blood loss every day. As free iron is toxic, the body must regulate the iron homeostasis. Iron is an essential mineral for red blood cells (RBC'S), so a proper understanding of iron metabolism is crucial in the diagnosis and management of many diseases such as IDA, hereditary hemochromatosis, and iron overload.

Iron absorption and transport:

Iron is absorbed in the small intestine, mainly in the duodenum and proximal jejunum [9,10]. Only 10-12% of the total dietary iron is absorbed, and absorption depends on the total body iron stores. Luminal non-haem iron is mostly in the (Fe3+) state and must first be reduced to (Fe2+) iron by ferric reductases such as cytochrome B and STEAPs (six transmembrane epithelial antigens of prostate proteins) which are present in the brush border of the duodenum. DMT1 (divalent metal transporter) is the primary transporter of Fe2+ iron, which is transported across the apical membrane [11-13]. The stored iron is transported out of the macrophages to plasma by ferroportin [14]. Various elements influence the absorption of iron. The factors that are favoring absorption are haem iron, ferrous form (Fe2+), vitamin C, pregnancy, reduced serum hepcidin, and ineffective erythropoiesis. An inorganic iron, ferric form (Fe3+), antacids, inflammation, increased serum hepcidin, and decreased erythropoiesis reduce iron absorption in the body.

After absorption to the blood, iron combines with an apotransferrin resulting in the formation of transferrin by the liver. A glycoprotein called transferrin helps to transport the iron in blood [15, 16]. Tf is used to evaluate ID and iron overload.

The fate and regulation of iron absorption:

An iron can follow one of two pathways, transport to the blood or storage as mucosal iron after entering the duodenal cells. Ferroportin transport (Fe2+) iron to the cytoplasm across the basolateral membrane. This process helps in the oxidation of (Fe2+) iron to (Fe3+) iron, which is carried out by the iron oxidases hephaestin and ceruloplasmin [17]. This absorbed (Fe3+) iron binds rapidly to the transferrin and delivers iron to progenitors of red cells in the marrow. Free iron is highly toxic, and iron must be sequestered [18]. So ferritin or hemosiderin binds to iron in the storage pool. In iron homeostasis, hepcidin plays the role of the primary regulator [19, 20]. It is produced by hepatocytes. Raised hepcidin levels inhibit the absorption of iron from the duodenum and lead to iron deficiency anemia, and low levels lead to iron overload. Hepcidin synthesis falls in response to low body stores iron, which facilitates iron absorption.

Storage of iron:

Ferritin is the main storage form of iron [21]. Lysosomes and cytosol stores the intracellular ferritin. Ferritin has properties of converting ferric to ferrous iron. Serum ferritin is increased in inflammation and iron overload. When the storage capacity of iron in ferritin exceeds a storage complex called hemosiderin is formed and stores the iron in overloaded cells [22]. Hemosiderin is found in macrophages in the liver, spleen, and bone marrow in trace amounts.

Functions of iron:

About 33% of the body iron is found in hemoglobin and myoglobin [23]. Hb is the main carrier of oxygen from the lungs to peripheral tissues. Hypoxia occurs when there is low hemoglobin in our body. Heart and skeletal muscles contain myoglobin, which helps in oxygen storage. Human iron is required to convert the food into adenosine

triphosphate (ATP). Enzymes such as cytochromes P450 help to convert the food into energy and also help in mitochondrial electron transport. If the body is deficient of iron, then less ATP is produced, which leads to fatigue. Iron dependent enzymes protein such as Ribonucleotide reductase (RNR), DNA polymerase, DNA helicase, and iron-sulfur (Fe-S) cluster proteins helps in DNA replication, repair, and cell growth [24]. It is also needed for the formation of cytochromes, peroxidase, and catalase. Other functions in our body, such as antioxidant and pro-oxidant, growth, healing, and healthy immune function, iron is crucial. The recommended daily allowance (RDA) of iron is shown in table 1[25].

Table 1:- Recommended Daily Allowance (RDA) for Iron.

Age	**RDA(mg/day)**
Birth-6 months	0.27(inadequate intake)
7-12 months	11
Children	7-15
Adult male	8
Menstruating female	18
Pregnant women	27
Breastfeeding	9
Non pregnant and Postmenopausal women	8

Stages of iron deficiency:

The main three-stage of iron deficiency is a negative iron balance, iron depletion in stores, and iron deficiency anemia [26]. If the requirement exceeds the ability of iron absorption, there is a negative balance of iron in the body. Thus increase the utilization of iron stores and serum ferritin level falls, but the hemoglobin and serum iron remains normal. An increase in iron-binding capacity or transferrin level is due to the compensatory increase in iron absorption. As the utilization of iron increases, there is a depletion in reticuloendothelial (RE) storage sites; the erythropoiesis is impaired, and the serum iron and transferrin saturation decrease. IDA is the final stage of iron deficiency where marrow iron is depleted, hemoglobin falls, and the microcytic and hypochromic erythrocytes are produced. So iron deficiency affects tissues resulting in signs and symptoms.

Causes of iron deficiency anemia:

Increased physiological demand for iron

The primary etiology of ID in underdeveloped countries is the inadequate intake of iron due to poor diet. In an adult male, it will take almost eight years to develop IDA due to a poor diet or malabsorption. Due to rapid growth in infancy and adolescence, the requirement exceeds the iron absorption. The RDA in non-pregnant women is 8mg per day, which is increased to 27mg per day in pregnancy. In pregnancy, about 300mg of iron is transferred to the fetus, and about 35% of maternal red cell mass is increased, and there is a loss of iron parturition, and the requirement of iron is increased [27]. So if there is less intake of iron during pregnancy, the development of IDA occurs. Lactation, erythropoietin therapy in chronic renal disease also increases the daily requirement for iron.

Blood loss:

An acute or chronic blood loss is one of the causes of iron loss, most common being occult GI blood loss. Peptic ulcer diseases (gastric, duodenal) are the most common cause of upper GI blood loss [28]. The most common lower GI lesion is colorectal carcinoma, mostly right-sided [29-31]. In an elderly patient, gastric and colon polyps lead to IDA. Parasitic hookworm infestation is the leading cause of IDA in developing countries. The common cause of ID in young adults is hemorrhoids.

Non-gastrointestinal causes such as uterine fibroids and menorrhagia are the common causes of iron loss in premenopausal women [32]. Menorrhagia is a loss of 80 ml or more blood at each mensuration cycle. Non-menstruating women lose an average of 1mg of iron per day, and a typical 60 kg menstruating woman loses an additional 10 mg of iron per day. So in menorrhagia, iron loss of 42mg per cycle has been reported [33]. One unit of blood (500ml) contains about 250 mg of iron. So there is loss of iron from blood donation, surgical losses, phlebotomy, hematuria, and epistaxis.

Decreased iron absorption:

Malabsorption is also the main factor that leads to IDA, and this should be considered if there is no history of blood loss and minimal response to iron therapy. The main causes of malabsorption are Helicobacter pylori (H. pylori) infections, celiac disease, Crohn's disease post gastrectomy, and medications are the leading causes of malabsorption. In Celiac disease, there is villous atrophy in proximal duodenum due to gluten intolerance and leads to iron malabsorption [34,35]. Chronic gastritis is caused by H. Pylori infection and the risk of IDA increased by two-fold, although the mechanism is unclear [36]. IDA is a common consequence after partial or total gastrectomy because the duodenum is bypassed, which is the main site of iron absorption, and there is a low availability of gastric juice [37,38]. The low or absence of HCL acid in gastric secretions is called achlorhydria. Proton pump inhibitors (PPI) and H2 blockers can impair the iron absorption since they decrease the HCL when used in the long term [39,40]. NSAIDs cause gastric mucosal inflammation, which leads to low iron absorption [41,42]. The etiology of IDA is shown in table 2.

Table 2:- Etiology of iron deficiency anemia.

Etiology of iron deficiency anemia
Increased demand for iron
Infancy, puberty, pregnancy, lactation,
Erythropoietin therapy
Poor diet
Increased iron loss
Gastrointestinal causes
Gastritis, esophagitis
Peptic ulcer disease (gastric, duodenal)
Gastric cancer, esophageal cancer
Colorectal cancer
Gastric and colon polyps
Parasitic hookworm infestation
Inflammatory bowel disease
Hemorrhoids
Non-gastrointestinal causes
Uterine fibroids
Menorrhagia
Hematuria
Phlebotomy
Blood donation
Decreased iron absorption
Celiac disease
Post-gastrectomy
Achlorhydria due to PPI, H2 blockers
NSAIDs
Inflammation

Clinical features of Iron deficiency anemia:

Initially, the symptoms of ID are nonspecific, and patients may not notice the symptoms until the IDA becomes more severe. The decreased oxygen delivery to the body gives symptoms. The most common initial presentation is generalized fatigue [43]. Features of iron deficiency are shortness of breath, headache, dizziness, cold hands and feet, brittle nails, reduced exercise tolerance, and restless leg syndrome. Geophagia, also called pica, is the consumption of soil, chalk, which has no nutritive value [44]. The consumption of ice noted in children, and pregnant women is called pagophagia [45].

On physical examination, the patient usually presents with shortness of breath, pallor of conjunctiva and skin, and tachycardia. A very severe form of anemia may have features of cardiac failure. Plummer-Vinson syndrome (PVS) can occur in people with chronic IDA. Dysphagia (difficulty in swallowing), glossitis, angular stomatitis, and esophageal webs in the post cricoid region are associated with PVS [46]. Treating iron deficiency may reverse the mucosal changes [47]. Koilonchyia is the spoon-shaped (concave) nails caused by IDA. These signs are not very specific, and the diagnosis is confirmed by laboratory results.

Diagnosis of IDA:
The standard tests done in clinical practice are CBC, RBC indices, serum iron and ferritin, total iron-binding capacity (TIBC), and peripheral blood smear. If the diagnosis is uncertain, then a bone marrow examination is done. To investigate the etiology, many other additional tests such as H pylori tests, occult blood tests, endoscopy, and colonoscopy may be required.

Laboratory diagnosis:
1. CBC: This is the initial test if we suspect IDA. Hemoglobin is less than 13g/dL (130g/L) in men and 12g/dL(120g/L) in non-pregnant women in anemia. In pregnant women, hemoglobin less than 11g/dL (110g/L) diagnoses the anemia [48].
2. RBC indices: MCV refers to the average size of a single RBC.MCH is the amount of oxygen-carrying Hb inside RBC's. MCHC is the average concentration of Hb in the RBC. All these indices are decreased in IDA, and RBC is microcytic and hypochromic [49]. Lead poisoning, sideroblastic anemia, thalassemia, anemia of chronic disease all are microcytic hypochromic anemia's [50].
3. Serum iron: Serum iron is the direct measurement of transferrin bounded circulating iron. In IDA serum iron is decreased to the level of <30 µg/dL. It is acutely and dramatically changed in case of inflammation, so this should be ruled out.
4. Serum ferritin: Within cells, iron is stored complexed to a protein called ferritin. For screening and diagnosis of ID, serum ferritin is the most specific and sensitive test as it indicates the iron stores [51]. There is a depletion of iron stores in the first stage of ID, which is associated with a decrease in levels of serum ferritin only. The decreased serum ferritin level of <15 µg/L diagnose the IDA [52]. In anemia of chronic disease, thalassemia and sideroblastic anemia serum ferritin may be normal or increased.
5. TIBC: It is an indirect measure of the circulating transferrin. There is an increase in TIBC as serum iron decreased. In IDA TIBC is >400 µg/dL [53].
6. Transferrin saturation: This is a measure of transferrin saturated with iron. This is measured as serum iron/TIBC X100.Normal transferrin level ranges between 30-55%. Transferrin Saturation<10% is seen in IDA [54].Diagnosis of IDA is shown in table 3.

Table 3:- Laboratory diagnosis in iron deficiency anemia.

Parameters	Normal values	Iron deficiency anemia
Hemoglobin(g/dL)	Male:13-17.5 Female :12-16	Male<13 Female <12 Pregnant women<11
MCV(fl)	80-100	Decreased
MCH(pg)	27-32	Decreased
MCHC(dL)	33-36	Decreased
Serum ferritin (µg/L)	Male and postmenopausal Women:20-300 Premenopausal women: 15-200	<15
Serum iron(µg/dL)	Male:78-178 Female:56-157	<30
TIBC (µg/dL)	300-360	>360
Transferrin saturation (%)	30-50	<10
Marrow iron stores	1-3+	0

Peripheral blood smear:
The RBCs in a peripheral blood smear are microcytic and hypochromic with occasional target cells [55]. Anisocytosis (unequal size RBCs) is the earliest recognizable morphologic changes of erythrocytes in IDA. With the increasing degree of severity, the red cells become microcytic and eventually hypochromic. A dimorphic blood film (new hemogloblinized normal-sized RBCs) is seen in a patient with IDA who recently treated with iron.

Bone marrow examination:
Bone marrow aspiration biopsy is a standard gold method to estimate RE iron stores and diagnose IDA. Bone marrow examination is high cost and invasive in nature and required only for complicated cases where other investigations cannot confirm the diagnosis. Perls' stain assesses bone marrow iron. The normal marrow iron stores are 1-3+ and indicated by blue staining in macrophages. The absence of blue staining due to the complete absence of iron from stores (macrophages) and from developing erythroblasts is seen in IDA [56,57].

Treatment of iron deficiency anemia:
Once the proper diagnosis is made, the treatment should start to replenish the iron stores. The treatment options may vary from patient to patient due to the cause and severity of IDA. The first step in the treatment is to treat the underlying cause. The major three treatment options available are oral iron therapy, parenteral iron therapy, and blood transfusion, usually RBCs.

Oral iron therapy:
The majority of younger patients with mild symptoms are treated with oral iron. Growing children and adolescents, pregnant women, patients with fewer episodes of bleeding will usually respond to oral iron. The most common oral iron preparation used is ferrous sulfate 325mg tid (three times a day), which contains 65mg of elemental iron [58]. Newer preparations such as ferrous gluconate, ferrous fumarate, and Polysaccharide iron have fewer side effects. Oral iron should be taken in an empty stomach preferred between meals and bedtime. However, the majority of patients take with food due to gastric upset. It is best to take iron with orange juice or oral 250-500mg as vitamin C increases the absorption of iron [59]. Oral iron should be given until anemia corrects and then continue to 3-6 months until serum ferritin returns to normal [60]. Common side effects of iron therapy are nausea, vomiting, abdominal discomfort, black stools, diarrhea, or constipation. The common oral iron preparations with their iron content are shown in table 4[61].

Table 4:- Oral Iron Preparations.

Preparation	Tablet (mg)	Elemental iron content (mg)
Ferrous sulfate	300,325	60,65
Ferrous fumarate	325	106
Ferrous gluconate	325	36
Polysaccharide iron	150	150
Carbonyl iron	45,66	45,66

The monitoring of response to oral iron is crucial in treating the IDA. Usually, reticulocyte will increase after one week, and hemoglobin should be normalized by 1g/dL (10g/ L) per week if there is no blood loss [62]. The main reason that the patient does not respond to oral iron therapy is the failure to take tablets. Other reasons for treatment failure include continuing blood loss, malabsorption, anemia of chronic disease, wrong diagnosis by the physician.

An iron absorption test can be performed in the patients who doesn't respond to oral iron or have minimal response [63]. This test can differentiate poor absorption from other causes such as blood loss. This test is not so common in clinical practice but can be used in rural settings where other modern test is not available to diagnose malabsorption causes. An iron challenge test in shown in figure 1.

Parenteral iron therapy:
Intravenous (IV) iron is needed in conditions such as unable to tolerate oral iron due to severe GI side effects, whose needs are acute, and poor absorption of iron in the body, persistent GI blood loss, severe menstrual blood loss, and chronic hemodialysis patients. The total amount of iron required by the patient is calculated using Ganzoni formula: Bodyweight (kg) ×2.3× (15-patient hemoglobin/dL) +500 or 1000mg (for stores) [64].

There are several preparations of IV iron, such as iron dextran, iron sucrose, ferric gluconate, ferumoxytol, and ferric carboxymaltose. Iron dextran is cheaper and allows for high dose repletion in a single dose but have serious side effects. Second generations formulations such as iron sucrose and ferric gluconate have fewer side effects and can be given in a faster infusion rate than iron dextran, but multiple doses are required for the repletion of iron stores. Third generations formulations are ferumoxytol and ferric carboxymaltose which can be administered in high dose and rapid infusion. IV iron cannot be given in patients with fever and in a known case of hypersensitivity. The main side effect of IV iron is anaphylaxis, including fever, hypotension, and wheezing [65]. Delayed symptoms include skin rashes, arthralgia's, and low-grade fever that may occur after IV iron therapy. The currently available IV iron preparations are shown in table 5[66-69].

Table 5:- IV Iron Preparations.

Generation	Preparation	IV administration	Side effects	Advice
First	Iron dextran	1000mg diluted in 5%dextrose	Anaphylaxis	To test the

		or 0.9% NS can be given over 1h	Abdominal pain Diarrhea Nausea Vomiting	hypersensitivity reaction 0.5ml test dose should be given and wait until 1h before full dose
Second	Iron sucrose	100mg/200mg Undiluted slow injection over 2-5 min Diluted infusion: 100mg/100mL 0.9%NS over 10 min 300mg/400mg/500mg in 250mL 0.9% NS over 2h,3h and 4h respectively	Hypotension Muscle cramps Headache Dizziness Fatigue	Usually no test dose is required unless contraindicated
	Ferric gluconate	Injection:125mg IV over 15min Diluted Infusion: 125mg/100ml 0.9% NS over 1h	Diarrhea Nausea Vomiting	Contraindications: hemosiderosis, hemolytic anemia, hemochromatosis, ulcerative colitis
Third	Ferumoxytol	510mg IV infused over 20min; a total of two doses, the second dose is given in 8th day	Headache, Hypotension, Peripheral edema	Hypersensitivity reaction may occur.
	Ferric carboxymaltose	750mg IV infused over 30min; a total of two doses, the second dose is given after 8th day	Hypertension Flushing Dizziness	Contraindication: hypersensitivity

Blood transfusion:
Severe IDA is the main indication for red blood cell (RBC) transfusion [70]. Blood transfusion is indicated for those with excessive bleeding of an unknown source, cardiovascular instability, critically ill elderly patients, and who requires immediate surgery. The American Association of blood banks (AABB) recommends the RBC transfusion in hospitalized and stable anemic patients with hemoglobin 7g/L to 8g/L [71]. Transfusion helps to stabilize and decrease mortality in severely anemic patients. RBCs transfusion is contraindicated in patients with active infections and hypersensitivity.

Summary:
IDA is a global health concern. It is a significant burden in both underdeveloped and developing countries due to inadequate dietary intake. Therefore, early prevention is necessary. Treating the cause is the initial step in management. Patients who have mild IDA are treated with oral iron, and IV iron may have needed for those who cannot tolerate oral iron salts. RBCs transfusion is rarely needed. The GI evaluation is necessary mostly in postmenopausal women and adult men, where the source of iron loss is unknown.

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