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Iron Deficiency Anemia – Needs Attention and Proper Management

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INTRODUCTION

Iron deficiency is the most prevalent nutritional deficiency and the commonest cause of anaemia. It is a major health problem not only in India but world wide. 30% to 70% population in the developing world is iron deficient. As per WHO, over two billion people globally that is 30% of world population suffers from anaemia and more than half of them are due to iron deficiency. In spite of many national health programs, the situation in India continues to be bad with 56% women and 70% of children suffering from anaemia as estimated by the third National Family Health Survey (India) and more than half of these is because of iron deficiency.

Iron deficiency anaemia impairs cognitive ability and reduces physical capacity in general, affects proper growth of children and is an important contributor to maternal and peri-natal mortality, adds to the severity of many chronic diseases and often represents serious underlying cause so needs to be recognized and managed properly on individual basis together with population based National strategy of preventing iron deficiency.

IRON METABOLISM

Human body on an average contains 3gm to 4 gm total iron in male(50 mg/kg) and 2gm to 3 gm in women (40gm/kg) of which nearly 71% is present in haem compounds: 65% haemoglobin, 4% myoglobin and about 2% incorporated in enzymes like cytochromes, peroxidases and others subserving important and critical role in body metabolism. About 29% is in non-haem form stored as ferritin and haemosiderin in bone marrow, spleen and liver. Nearly 0.1% of total iron is bound to carrier protein transferrin flowing in plasma.

IRON ABSORPTION

Iron is absorbed in the duodenum and upper jejunum by a very carefully regulated process. At the brush border of the absorptive cell, the ferric iron is converted into ferrous form by a ferrireductase, then transported across the membrane by divalent metal transporter type 1 (DMT-1). Once inside the cell, iron is stored as ferritin or transported to plasma transferrin by ion exporter – ferroportin, during the process iron is reconverted to ferric form by a ferroxidase- hephaestin. The function of ferroportin is negatively regulated by hepcidin, the principal iron regulatory hormone whose level gets lower where demand is increased as in iron deficiency states.

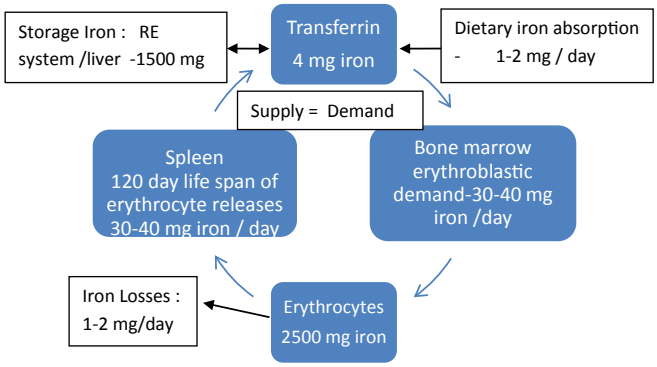

Fig. 1: Iron cycle : normal situation (Hb = 14 g/dl)

THE IRON CYCLE

Iron absorbed from diet or released from stores circulates in plasma bound to transferrin until it interacts with specific transferrin receptor on the surface of marrow erythroid cells, where then iron gets internalized and haem synthesis takes place, the excess iron in the cell gets stored as ferritin. This iron exchange mechanism also takes place in other cells of body expressing transferrin receptors specially hepatocytes and reticulo-endothelial cells where iron can be incorporated into haem containing enzymes or stored. The iron incorporated into haemoglobin subsequently enters the circulation as new red cell mass. 0.8 to 1% of red cells are replaced each day by reticulo-endothelial(RE) system and the iron released is recycled through the circulating transferrin. There is no regulated excretory pathway for iron, the only mechanism of iron loss is through the loss of epithelial cells and blood loss (Figure 1).

NUTRITIONAL IRON BALANCE

Most of the iron in body is recycled. The daily loss normally is approximately 1 mg in men and post menopausal women and about 2 mg in menstruating women which gets replaced by dietary iron normally absorbed.. Dietary iron usually amounts to 7mg/1000Kcal that is about 12 to 15 mg /day of which less than10% is from haem iron and more than 90% from non-haem iron. 30% iron of haem source and less than 5% of non-haem source is available for absorption. Normally only 10 to 15% of ingested iron is absorbed so when demand increases, dietary intake has to be increased. Pregnancy, anaemia, hypoxia and reduced iron stores increases the demand as also the growing infant, children and adolescent. However absorption can be raised only to the maximum of about 3.5 mg / day. Presence of amino acids and vitamin C increases the absorption of non-haem iron whereas phytates and phosphates in vegetarian diet, tannins in tea and alkali intake decreases the absorption implying the importance of rationalizing the timing of different food and iron tablets.

Table 1: Causes of Iron Deficiency	
I	Increased Iron Loss / Blood Loss –
	1. Gastrointestinal blood loss Occult gastric or colorectal malignancy Gastritis Peptic ulceration Chronic use of aspirin or NSAIDS Varices Inflammatory bowel disease Diverticulitis Polyp Hemorrhoids Angiodysplastic lesions Hookworm, Schistosomiasis, Trichuriasis 2. Menstrual blood loss 3. Reapetd blood donation 4. Alveolar hemorrhage 5. Haemoglobinuria 6. Massive hemorrhage
II	Decreased Iron Intake or Absorption
	1. Inadequate diet 2. Malabsorption from disease (Coeliac disease), 3. Malabsorptin from surgery (gastrectomy, some forms of bariatric surgery) 4. Acute or chronic inflammation - H. pylori associated gastritis etc 5. Achlorhydria
III	Increased Requirements For Iron
	1. Rapid growth in infancy, childhood and adolescence 2. Pregnancy, lactation 3. Erythropoetin therapy

CAUSES OF IRON DEFICIENCY

Iron deficiency results when iron losses or physiological requirements exceed absorption (Table 1).

STAGES OF IRON DEFICIENCY

Iron deficiency passes through pre latent (negative iron balance) and latent (iron deficient erythropoiesis) phase to Iron deficiency anaemia.

1. Pre-latent Phase: When demands for or losses of iron exceeds the body capacity to absorb iron from diet resulting in iron deficiency, iron is mobilized from reticulo-endothelial storage to maintain erythropoiesis. Thus iron store decreases and is reflected by reduced – stainable marrow iron and serum Ferritin. Other parameters remains normal.
2. Latent Phase: Once the iron stores gets exhausted (serum Ferritin < 15ug/L), serum iron starts falling and Total iron binding capacity (TIBC) and erythrocytes Protoporphyrin begins to rise, and when transferrin saturation falls to 15 – 20%, hemoglobin synthesis gets impaired but RBC and haematocrit remains normal.
3. Iron Deficiency Anemia: Once the transferrin saturation falls to 10-15%, hemoglobin and haematocrit falls with the appearance of microcytic and hypochromic RBC.

CLINICAL FEATURES

Asymptomatic - diagnosed incidentally on routine laboratory examination, or may present with symptoms attributed to the anaemia or the iron deficiency proper beside to that of the underlying cause.

1. Related to Anemia: Fatigue, Breathlessness, Palpitation, Dizziness, Headache, Irritability
2. Related to Iron Deficiency:

- Impaired Growth and cognitive function, Poor concentration
- Skin and mucosal changes Fingernails may become brittle, fragile, or longitudinally ridged and then spooning (koilonychia) develop. Tongue may show soreness, mild papillary atrophy and absence of filiform papillae Angular cheilosis Dysphagia (Plummer-Vinson syndrome)
- Miscellaneous: disturbed thermoregulation, impaired immune function, increase in infection, decreased physical performance and exercise tolerance, Pica –craving for specific food (ice, clay, starch etc), Restless leg syndrome

SPECIFIC SITUATIONS

- Aggravates complication in pregnancy for both mother and fetus. Mother has increased likelihood to develop unpleasant symptoms, antepartum and postpartum hemorrhage, reduced quality and quantity of lactation and delayed wound healing etc. Fetus/ baby suffer low uterine growth, premature delivery, low birth weight etc.
- Aggravates the severity with increased morbidity and mortality of cardiovascular instability

INVESTIGATION

Blood Parameters

Erythrocytes: Blood hemoglobin falls below the lower limit of normal, RBC count and PCV decreased, mean corpuscular volume (MCV) decreased to less than 80 fl, mean corpuscular haemoglobin (MCH) < 28 pg/cell, and mean corpuscular haemoglobin concentration (MCHC)<30g/dl, increased red cell distribution (RDW) with low or inappropriately normal reticulocyte count.

Peripheral Smear: Characterized by microcytic and hypochromic RBC along with Anisocytosis (cells of varying size) and poikilocytosis (cells of varying shape – pencil/cigar shaped)

BIOCHEMICAL PARAMETERS

Serum Ferritin

Value less than 12ng/cc is a highly reliable indicator of depleted iron stores. However higher level are the rule in

Table 2: Differential Diagnosis of Microcytic Anaemia

Tests	Iron deficiency	Inflammation	Thalassaemia	Sideroblastic ana
Smear	Micro/hypo + Anisocytosis	Normal or micro/ hypo	Micro/ hypo	Variable
Serum iron (ug/dl)	<30	<50 or norm	Nor. To high	Normal to high
TIBC (ug/dl)	>300	<300	Normal	Normal
Percent saturation	<10	10-20	30-80	30-80
Ferritin (ug/L)	<15	30-200	50-300	50-300
Serum transferrin receptor	Increased	Normal	Increased	Normal
Free RBC Protoporphyrin	Increased	Increased	Normal	Increased
Haemoglobin pattern on electrophoresis	Normal	Normal	Abnormal (HbA2>35%)	Normal
Marrow iron	Low or absent	Normal or increased	Normal	Ring sideroblasts >15%

the presence of infection or inflammation.

Serum Iron and TIBC

Serum iron level (normal 30 ug/dl to 160 ug /dl) represents the amount of circulating iron bound to transferrin and is decreased in iron deficiency. TIBC (normal 220ug/dl to 420 ug/dl), an indirect measure of circulating transferrin is increased. Transferrin saturation which is normally 25-50% is always reduced to less than 16% in IDA.

Soluble Transferrin Receptor

Soluble transferrin receptor (sTfR – normal 4-9 ug/L) is markedly increased in IDA and helps to distinguish IDA from anaemia of chronic disease(ACD).

Red Cell Protoporphyrin Level

Free erythrocyte Protoporphyrin (FEP-normal <30ug/ dl of RBC) gets increased with impaired haem synthesis in IDA and sideroblastic anaemia and helps distinguish these from thalassaemia where it is normal.

Bone Marrow

Decreased or absent stainable iron in marrow macrophages is indicative of iron deficiency.

DIFFERENTIAL DIAGNOSIS

IDA needs to be differentiated from three other important causes of microcytic hypochromic anaemia- 1. Thalassaemia resulting from inherited defect of globin synthesis, 2. Anaemia of chronic disease resulting from impaired iron utilization and 3. Sideroblastic anaemia resulting from impaired haem synthesis because of impaired iron incorporation in haem. Body iron stores are increased in all these three situation where as it is decreased in IDA (Table 2).

MANAGEMENT

Management of IDA needs not only the correction of anaemia but also requires replenishment of depleted iron stores. It also warrants careful search of the underlying cause and their proper treatment. The common and usual sufferers –pregnant women, growing children and adolescents must always be looked and properly managed for IDA to prevent untoward complications. Treating hookworm infection empirically is justified in Indian context. Cardinal rule of considering gastrointestinal blood loss as a cause of unexplained IDA until otherwise proved in adult male and post-menopausal women should be observed. Patients with recurrent or not responding IDA should be screened for celiac disease or other causes of mal-absorption.

There are three major therapeutic approaches for treating iron deficiency-

BLOOD TRANSFUSION

Reserved for patients with severe symptomatic anaemia, anaemia with cardio-vascular instability, and those with continued and excessive blood loss.

ORAL IRON

Usually treatment with oral iron is adequate. Ferrous sulphate 200 mg 8-hourly (120 mg of elemental iron/day) is usually more than sufficient. Usual adult dose is 150mg to 200mg of elemental iron per day and the dose for children is 3 mg /kg/day. Absorption is better when taken on empty stomach. If not tolerated, dose reduction to 12 hourly and taking after meal may help or shift to other ferrous salt. Haemoglobin should rise by 1g/dl every 7 to 10 days and a reticulocyte response will be evident by 1 week. After correction of anaemia, sustained treatment should be continued for 4 to 6 months to replenish the iron store.

PARENTERAL IRON THERAPY

Needed in patients who are non-compliant or intolerant to oral iron, who suffers mal-absorption states, whose need is relatively acute as in pregnancy or cardiovascular instability or in conjunction with erythropoietin in renal failure and other causes of qualitative iron deficiency. Iron dextran requires test dose and may cause anaphylaxis but the newer Parenteral preparations (iron sucrose, ferric carboxymaltose, ferumoxytol) are relatively safe as reactions are very rare and is given intravenous. Parenteral iron excepting iron sucrose can be given to deliver total dose.

Total iron (mg) needed = Body weight (kg) x 2.3 x (15 –

patient's haemoglobin, g/dl) + 500 or 1000 mg (for stores).

Iron sucrose (100mg in 5cc)- only iv use, maximum single dose 100mg can be given as slow iv injection over 5 minutes or as infusion in 100 cc saline over 30 minutes. Maximum 600 mg/week.

Ferric carboxymaltose – 1000mg /week as iv infusion over 6 to 15 minutes, (not > 15 mg/kg).

Comparative clinical trials showed a faster, better tolerated & more prolonged effect with better quality of life on IV iron than with oral iron in the indicated situation.

CONCLUSION

National program to prevent iron deficiency needs to be instituted more effectively. Iron deficiency warrants meticulous evaluation and proper management to prevent mortality and morbidity and use of IV iron where indicated.

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