Iron Deficiency Anemia and its Major Causes: A Literature Review

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Abstract: Iron deficiency anemia (IDA) is one of the most important micronutrient disorder affecting the people worldwide. It is characterized by insufficient hemoglobin level that results in the formation of abnormally small erythrocytes termed as microcytes. According to World Health Organization (WHO), prevalence of anemia is greatest in less developed countries, particularly in preschool children and pregnant women. The key factors responsible for the occurrence of IDA include nutritional deficiency, increased physiological requirements, parasitic or pathogenic infections, besides obesity and genetic factors. The present review summarizes the global prevalence of IDA, human iron metabolism, stages of iron deficiency, clinical manifestations and etiology of IDA, based on the findings of different research studies**.**

Index Terms **- IDA, micronutrient, hemoglobin, microcytes, nutritional deficiency.**

I. INTRODUCTION

Anemia is the most common nutritional deficiency that affects the people of all age groups in both developed and developing countries. It has severe implications on human health as well as socioeconomic development (WHO/CDC, 2008). Iron is an important micro nutrient, required for growth and differentiation of cells, hemoglobin synthesis, oxygen binding and transport , mental and physical growth, cognitive function, working of enzymes, immune function etc. Thus, iron deficiency due to any physiological or pathological reason can affect mental and physical growth which leads to reduced learning ability and work efficiency (Kumari et al. 2017). Iron deficiency anemia (IDA) is characterized by insufficient hemoglobin synthesis in the body, that results in the formation of red blood cells that are abnormally small (microcytic) and contain a deficient amount of hemoglobin. Consequently, the capacity of the blood to carry oxygen to body cells and tissues is decreased (Provan, 1999). Though there are various nutritional deficiencies such as vitamin B12, folic acid, and zinc which can cause different forms of anemia (WHO & FAO, 2004), iron deficiency is considered to be the most important factor that contributes to anemia worldwide. Nearly 50% of the cases of anemia are considered to be caused by iron deficiency. The percentage may vary among different population groups and areas, depending upon the local conditions (WHO, 2015). The level of hemoglobin concentration in the blood is commonly used as an indicative of anemia. According to World Health Organization (WHO), the hemoglobin values that indicate the threshold for anemia in a population living at sea level are shown in Table 1.

Table 1: Hemoglobin values indicating anemia in a population living at sea level

Population / Age group	Hemoglobin level (g/ dl)
Children 6 months – 5 years of age	< 11
Children 6 – 14 years of age	< 12
Adult males	< 13
Adult females (non – pregnant)	< 12
Adult females (pregnant)	< 11

Source: Preventing And Controlling Iron Deficiency Anaemia through Primary Health Care, A guide for health administrators and programme managers. World Health Organization, Geneva, 1989.

II. PREVALENCE

In 2002, one of the most important contributing factors to the global burden of disease was iron deficiency anemia (WHO, 2002). As per the global anemia prevalence surveys conducted by WHO between 1993-2005, anemia affected 1.62 billion people globally,

which comprised 24.8% of the population. The prevalence was highest in pre- school age children (47.4%) and lowest in men (12.7%). The population group with greatest number of individuals affected was non pregnant women (468.4 million). The WHO regions of Africa and South East Asia were found to be at highest risk where approximately two third of the pre- school age children and half of all women were affected (WHO/CDC, 2008). Further, in 2011, it was assessed that approximately 43% of children, 38% of pregnant women, 29% of non-pregnant women and 29% of all women of reproductive age suffer with anemia globally, which corresponds to 273 million children, 496 million non-pregnant women and 32 million pregnant women (WHO, 2015). Balarajan et al. (2011) in their study, estimated that the prevalence of anemia is around 9% in highly developed countries, and 43% in less developed countries with children and women of reproductive age at the highest risk. The Global Burden of Disease Study 2016 (GBD 2016) assessed the prevalence, incidence, and years lived with disability (YLDs) for 328 causes in 195 countries and territories from 1990 to 2016. This study mentioned that iron-deficiency anemia, was one of the five leading causes of YLDs in 2016, which affected 1.24 billion (1·21-1·28 billion) people (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators).

Kalaivani (2009) in his work mentioned that, India has the highest prevalence of anemia among the South Asian countries as per the estimation of WHO. Another notable fact is that about half of the global maternal deaths due to anemia occur in South Asian countries out of which nearly 80% of the maternal deaths due to anemia occur in India alone. Additionally, the data from National Family Health Survey (2015-16) (NFHS-4) indicated that 58.5 % of children in the age of 6-59 months, 53.1% of non-pregnant women (age 15- 49 years), 50.3% of pregnant women (age 15- 49 years), 53% of all women (age 15- 49 years) and 22.7% of men (age 15- 49 years) in India are anemic.

III. TYPES OF DIETARY IRON

There are two basic types of dietary iron: non-heme (inorganic) and heme (organic) (Bothwell, 1995). Heme is an important biological compound, as it is the major source of dietary iron. Heme iron is a component of hemoglobin and myoglobin and is present in meat, fish, poultry and blood products whereas, non- heme iron is found to varying quantities in all food products of plant origin (WHO, 1989).The bioavailability of heme iron is high (15-35%) and dietary factors slightly affect its absorption, while non-heme iron is less bio available (2%-20%) and its absorption is greatly influenced by the presence of other food components. Enhancers like ascorbic acid and inhibitors like calcium, phytic acid and polyphenols have a considerable effect on the absorption of non-heme iron (Hurrell & Egli, 2010; Baynes & Bothwell, 1990). In addition to the iron obtained from food, the diet may include exogenous iron originating from the soil, dust, water and cooking utensils. In case of developing countries, it is commonly observed that the quantity of contamination iron in the diet is many times higher than the quantity of food iron (WHO, 1989).

IV. HUMAN IRON METABOLISM AND ABSORPTION

Iron is required by the body for the formation of a various essential biomolecules such as hemoglobin, myoglobin, and other metalloproteins (Lynch, 1997). According to Bothwell (1995) around 65% of the body iron exists in the form of hemoglobin in a well-nourished adult. The rest of the iron is found in the form of myoglobin and other heme compounds or it is stored as ferritin in hepatocytes, bone marrow and spleen (Frazer & Anderson, 2005).The absorption of iron which is digested from the food takes place in the enterocytes of duodenum and proximal jejunum (Mckie et al. 2001).The dietary non heme iron that exists mostly in ferric(Fe^{+3}) form is first converted into more soluble ferrous (Fe^{+2}) form by a duodenal ferric reductase such as duodenal cytochrome b (Dcytb) (Latunde- Dada et al. 2002) and is subsequently transported across the apical membrane of enterocytes by a non-specific divalent metal transporter (DMT1) (Aisen et al. 1999). Dietary heme iron is also transported across the apical membrane by a mechanism that is unknown so far and then metabolized in the enterocytes by haem oxygenase 1(HO-1) to liberate Fe^{+2} (Wang & Pantopoulos, 2011). According to Shayeghi et al. (2005), heme carrier protein 1(HCP1) which is a polypeptide belonging to a group of transporter proteins plays important role in heme iron uptake. Cytosolic iron in the enterocytes is exported into plasma by the basolateral iron exporter ferroportin 1 (FPN 1) (Zoller et al. 2001). The actual mechanism by which FPN1 works is uncertain, however Fleming & Bacon (2005) are of the view that it is facilitated by the ferroxidase activity of a membrane bound oxidase known as hephaestin. The iron exported into the plasma, binds with transferrin (Tf) and is transported by blood to the places where it is utilized and stored (Bailey et al. 1988). Cellular uptake of iron occurs by transferrin receptor 1 (TfR) mediated endocytosis (Fleming & Bacon, 2005). After moving inside the cells, iron can either be incorporated into iron proteins like heme or stored in the form of ferritin for future use (Bleackley et al. 2009).

V. STAGES OF IRON DEFICIENCY

Iron absorption is the key factor that regulates iron homeostasis. Thus, it is the concentration of serum iron that indicates the equilibrium between amount of iron absorbed and amount of iron used by the body. Iron deficiency occurs slowly, rather progressively until anemia is discovered (Cairo et al. 2014). The first stage of anemia is called “iron depletion” or negative iron balance, when dietary iron is insufficient to meet the body requirements. As a result, there is decrease in iron stores of the body, indicated by low serum ferritin levels with iron values below 12 ng/ml. The second stage, also known as “iron deficiency”, is characterized by iron deficient erythropoiesis. The biochemical abnormalities appeared due to iron depletion reflect that the hemoglobin production is not normal, though anemia is still not present. The transferrin saturation index is less than 16%, red cell distribution width increases more than 16%, mean corpuscular volume is below 80 fl, and a large number of microcytic and hypochromic erythrocytes are seen. The third stage is referred to as “iron deficiency anemia” in which there is a reduced iron delivery to the bone marrow, followed by reduction in both hemoglobin synthesis and content in erythrocyte precursors (Reeves et al. 1984).

VI. CLINICAL MANIFESTATIONS

The clinical features of anemia vary from one person to another and arise due to anemia itself as well as lack of iron. The speed of onset of anemia, its severity, and the characteristics of the patient are important factors which determine the symptoms. Thus, iron deficiency anemia or iron deficiency can be detected with the help of screening-analysis in an asymptomatic individual, or in a person who has symptoms such as general weakness, fatigue, poor concentration, intolerance to exercise, irritability, headache etc. These symptoms may appear even in cases of iron deficiency with normal hemoglobin levels. Some patients having iron-deficiency, with or without anemia, may have a dry mouth due to lack of salivation, alopecia or atrophy of lingual papillae. An eating disorder known as Pica may be seen in some cases, in which the person has an intense desire to eat non-nutritive substances like soil, chalk, gypsum, ice (pagophagia) or paper, that are normally not consumed in human diet (Bermejo& García-López, 2009).According to Rector (1989), pagophagia is considered to be quite common in women, and is not associated with the cause of bleeding. Pallor of varying intensity may be observed in some patients and there can also be a systolic murmur in cardiac auscultation (Bermejo & García-López, 2009). The problem of poor mental performance and cold intolerance in people having iron deficiency has been reported by Rosenzweig and Volpe (1999). Some unusual neurological disorders, such as the compulsion to move the lower extremities while at rest, has also been found to be associated with iron deficiency anemia. Goodman et al. (1988), have identified the restless leg syndrome as a reversible symptom of reduced brain iron levels that is particularly more common during pregnancy. Iron deficiency may lead to cognitive dysfunction, particularly if it occurs during infancy brain development and results in long-lasting cognitive challenges later in life (Lozoff et al. 1991).

VII. MAJOR CAUSES OF IRON DEFICIENCY ANEMIA

The etiology of iron deficiency anemia involves multiple and varied factors. Some important causes of IDA, as identified from the literature review are mentioned below:-

A. Diet and impaired iron absorption

The diet may become quite significant cause of IDA when the iron stores in the body are exhausted, or anemia has already developed, and there is a need of additional iron absorption from the gut for its restoration. This may happen in conditions like excessive blood loss, rapid growth during infancy, or infections like malaria, and hookworm. Thus, diet and iron supplements become essential for continuing the iron availability especially during pregnancy (Lee & Okam, 2011). Besides this, the bioavailability of iron for absorption is an essential aspect, which according to Sharp (2010), depends largely on the dietary components. López & Martos (2004) are of the view that heme iron is greatly bioavailable in comparison to non- heme iron. Also, the enhancers like vitamin C and inhibitors like tea present in the diet considerably affect the dietary availability of iron (Thankachan et al. 2008). In addition to dietary constituents, the impaired iron absorption from gut can lead to iron deficiency anemia. Certain infections, inflammation, or hepcidin up-regulating mechanisms can possibly inhibit non-heme iron absorption regardless of its high bioavailability in the diet. Vitale et al. (2011) in their work, found that diseases like *Helicobacte*r infections are associated with malabsorption of iron and increased iron loss. Bariatric surgery (Shankar et al. 2010) or decreased gastrin level (Kovac et al. 2011) are also found to have inhibitory effect on iron absorption. The research findings of Nicolas et al. (2002) have indicated that over expression of hepcidin during embryonic development, results in severe iron deficiency anemia in the fetuses. Further, celiac disease is also known to cause low iron absorption from the gut (Presutti et al. 2007).

B. Increased iron requirements during pregnancy

The iron requirements are very high in pregnant as well as menstruating females. Lee & Okam (2011) in their study, estimated that during pregnancy ∼1200 mg of iron is required from conception till delivery. Anemia during pregnancy may be severe, moderate or mild depending upon the hemoglobin concentration. It is considered to be severe when the hemoglobin concentration is lower than 7.0 g/dL, moderate if the hemoglobin concentration lies between 7.0 and 9.9 g/dL, and mild when hemoglobin concentration is 10.0 to 11 g/dL (Bekele et al. 2016). Iron is required for the growth and development of all fetal tissues during pregnancy. According to Anderson & Holford (2008), the rate of human growth is virtually logarithmic in this period. A disproportionate increase in plasma volume, RBC volume and hemoglobin mass has been observed during pregnancy. Since, the plasma volume increase more than the RBC mass, hemodilution takes place which is known as physiological anemia of pregnancy. Nearly 1000 mg of iron is required during pregnancy, out of which 500-600 mg is required for RBC expansion, 300 mg for fetal and placental development and the rest of the iron for uterine growth. Around150 mg of iron is stored as a result of amenorrhea and therefore, there is an additional requirement of 850 mg of iron during pregnancy. The extra iron cannot be supplied by diet alone, due to which the stored iron gets depleted. In case the iron stores are already limited, iron deficiency anemia can occur in a pregnant woman (Sharma & Shankar, 2010). Thus, the diet need to be supplemented with medicinal iron, especially in the second half of pregnancy (WHO, 1968).

C. Blood Loss

In case of iron deficiency anemia, blood loss is considered to be one of the most significant factor. The blood loss from the body leads to loss of iron. There are various reasons for excessive blood loss such as long and heavy menstrual periods in women, bleeding fibroids in uterus, bleeding during child birth, internal bleeding due to ulcer, colon polyp, colon cancer, regular use of pain killers like aspirin or anti- inflammatory drugs like ibuprofen and urinary tract bleeding. Acute injuries, frequent withdrawal of blood, and

surgeries can also cause extreme blood loss (National Heart, Lung and Blood Institute, 2014).The decrease in the host's red cell mass and decreased supply of iron for erythropoiesis due to blood loss, results in the enhanced iron demand for erythropoiesis. There is ~1.0 mg of iron in each milliliter of packed RBCs (~2.5 mL of whole blood). Every day, nearly 1.0 mg of iron is absorbed from the diet and 20 mg of iron is accessible from older erythrocytes to support erythropoiesis. In case of heavy blood loss, the iron stores in body are depleted fast. Hence, the dietary iron and the recycled erythrocyte iron are not usually enough to compensate for acute blood loss (Miller, 2013).

D. Malaria

Malaria is a chief contributor to anemia in the developing countries. In most of the tropical regions of the world, iron deficiency anemia and malaria are found to exist together. Malaria infection in humans by *Plasmodium* species has been found to decrease the hemoglobin levels, frequently resulting in anemia, with *Plasmodium falciparum* causing the most severe and fatal anemia (Menendez et al. 2000). The primary cause of iron deficiency anemia in case of malaria is intravascular hemolysis. Consequently, there is loss of heme iron in the urine. This clinical characteristic of malaria was first described as blackwater fever by Connolly (1898). In a study on Indonesian school children, de Mast et al. (2010) found that serum hepcidin concentrations are increased in children with asymptomatic *P. falciparum* and *P. vivax* parasitemia that is accompanied by iron maldistribution, i.e. higher serum ferritin concentrations and lower values of serum transferrin saturation, serum iron concentration and mean corpuscular volume. This study supported the concept that prolonged repossession of iron into storage forms due to inflammation caused by malaria parasitemia is probably a chief cause of anemia in the developing countries. Burgmann et al. (1996) in their research findings indicated that malaria causes an immune response that suppresses erythropoietin production in patients suffering from acute *P. falciparum* malaria, which might be a factor responsible for prolonged anemia observed in these patients. The inhibitory role of hemozoin (HZ), and hemozoin-generated inhibitory molecule 4-hydroxynonenal (HNE) in the inhibition of erythropoiesis during malaria and subsequent anemia has been observed by Skorokhod et al. (2010) in their study.

E. Hookworm infection

Hookworms are bloodsucking nematodes that affect several million people in tropical and subtropical regions, with greatest number of infections in Asia followed by sub-Saharan Africa (Bungiro & Cappello, 2011). A study conducted by Brooker et al. (2006) on African school children reported that there is a significant overlap between malaria and hookworm infection in sub Saharan Africa. The infection of hookworm species like *Necator americanus* and *Ancylostoma duodenale*, commonly occurs through contact with contaminated soil or through oral ingestion of the larvae (Seidelman et al. 2016).The hookworm induces blood loss during attachment to the intestinal mucosa when it damages the mucosal capillaries and starts ingesting the blood. To ensure the blood flow, anticoagulants are released by the adult parasite. Nearly, 0.3 to 0.5 mL of blood from intestinal mucosa is consumed by each worm per day, which can result in anemia and contribute to impaired nutrition, particularly in patients with heavy infection (Hotez et al. 2004).

F. Obesity

Obesity is characterized by conditions like chronic, low-grade, systemic inflammation, elevated hepcidin, which consecutively has been found associated with anemia of chronic disease. Obesity-related inflammation may enhance hepcidin concentrations which reduces the iron availability. Aeberli et al. (2009) in their work compared the iron status, dietary iron intake and bioavailability, and circulating levels of hepcidin, leptin, and interleukin-6, in overweight children with normal weight children. They observed that there is decreased iron availability for erythropoiesis in overweight children probably due to hepcidin-mediated reduced iron absorption and increased iron sequestration. Nead et al. (2004) carried out a study on US children and adolescents which was based on the data of National Health and Nutrition Examination Survey III (1988-1994). They found that low transferrin saturation and low serum ferritin were twice as high in overweight adolescents as compared to normal weight adolescents. This study also indicated an increased prevalence of iron deficiency in overweight children.

G. Infection with HIV

Anemia is considerably more prevalent among individuals infected with HIV. It has been identified as a marker for disease development that significantly decreases survival among individuals having HIV (Sullivan et al. 1998).The prime cause of anemia in case of HIV infection is anemia of inflammation (AI), also known as anemia of chronic disease that is characterized by reduced RBC production through a series of mechanisms, partly mediated by pro-inflammatory cytokines such as tumor necrosis factor and interleukin-6 (Tolentino & Friedman, 2007). In a study by Ganz (2002), an association between inflammation and AI has been identified in the form of hepcidin. Hepcidin produced by the liver in response to inflammation, may suppress the normal response of bone marrow to erythropoietin, decrease the synthesis of erythropoietin, cause dyserythropoiesis and modify the iron metabolism. Consequently, iron is sequestered into storage forms, like ferritin, which make it less bioavailable (Means, 2000).

H. Gene mutations

Several important genes or mutations that modify iron metabolism can also be a cause of iron deficiency anemia. Iron content is considered to be regulated, by a gene named TMPRSS6. According to Finberg (2009), iron-refractory iron deficiency anemia (IRIDA) is an autosomal recessive disorder caused by a mutation in the TMPRSS6 gene that encodes a transmembrane serine protease in the

liver which regulates hepcidin expression. The research findings of Du et al. (2008) have shown that overexpression of TMPRSS6 blocks activation of diverse pathways for upregulation of hepcidin, with consequent iron overload whereas mutational inactivation of TMPRSS6 can reduce the body iron content.

VIII. CONCLUSION

Iron deficiency anemia is a global problem that adversely affects the human health, leading to a hampered social and economic development. The chief contributor in the etiology of anemia is iron deficiency, which according to various researches may occur due to poor nutrition, malabsorption, additional requirements, infectious diseases, obesity or genetic factors. Effective prophylaxis of any disease needs a thorough understanding of its etiology and pathogenesis. In view of the magnitude of this problem, recognition of correlation among multiple causative factors and their variation according to geographical location, nutritional status, level of development, and other social and economic factors becomes very important. In recent years, though a collaborative effort has been carried out to improve the treatment and prevention of iron deficiency and anemia, the problem still affects a large population worldwide. Further research, with regard to identification of higher risk groups of anemia at an early stage, can possibly help to design the strategies that can prevent the onset of the disease and its complications.

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