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Iron: A Two-Edged Sword.

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ABSTRACT

Iron is indispensable for life because of its significance in the cell biology and their disease-causing ability among humans. Lack of iron leads to growth arrest and anaemia while increased accumulation in the body is associated with toxic radical formation and progressive tissue damage. This article discusses the dual nature of iron, its deficiency and over load with various aspects of human health. Disorders of iron metabolism are among the most common diseases and comprise a wide spectrum of diseases with diverse clinical presentations, ranging from anaemia, and possibly to neurodegenerative diseases and malignancies.

Keywords: Anaemia, Iron, Iron deficiency, Iron overload, Infection.

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INTRODUCTION

In humans, iron is integrated into proteins as a component of heme (e.g., haemoglobin, myoglobin, cytochrome proteins, myeloperoxidase), iron sulphur clusters (e.g., respiratory complexes I-III, coenzyme Q_{10}, DNA primase), or other functional groups which are essential for vital cellular and organismal functions comprising of oxygen transport, mitochondrial respiration, intermediary and xenobiotic metabolism, nucleic acid replication and repair, host defence, and cell signalling [1, 12]. Therefore, iron is needed for a number of highly complex processes that continuously take place on a molecular level and are indispensable to human life [2]. It serves as a carrier of oxygen to the tissues from the lungs by red blood cell haemoglobin, as a transport medium for electrons within cells, and is an integrated part of important enzyme systems in various tissues including transfer energy within the cell and specifically in the mitochondria, synthesis of steroid hormones and bile acids; detoxification of foreign substances in the liver; and signal controlling in some neurotransmitters such as the dopamine and serotonin systems in the brain [2]. Both physical and mental growth require sufficient iron levels, particularly during childhood and pregnancy. The immune system is dependent on iron for its efficient functioning, in addition to its important role in innate immunity, nutritional immunity can also modulate adaptive immune responses, and indeed both iron deficiency and iron overload affect cellular immunity.

Forms of Dietary Iron and its absorption

Iron in haemoglobin, myoglobin, and enzymes serves as functional iron, whereas iron in ferritin, hemosiderin, and transferrin as storage iron [3]. Dietary iron is found in two forms: heme (10%) and nonheme (90%). The primary sources of heme iron are haemoglobin and myoglobin from consumption of red meat, fish [4] and poultry which are readily absorbed. By contrast, non-heme iron is found in both plant and animal sources (dried apricots, oatmeal, spinach, pine nuts, and beans) and its absorption is much lower and strongly influenced by the presence of other food components [4, 5].

Major inhibitors of iron absorption are phytic acid, polyphenols, calcium, and peptides from partially digested proteins and enhancers include ascorbic acid and muscle tissue which may reduce ferric iron to ferrous iron and bind it in soluble complexes which are available for absorption. Gastric acid and ascorbic acid promote reduction and solubilization of dietary ferric iron and thus improve absorption [1]. The chronic use of proton pump inhibitors for gastric acid reflux, helicobacter pylori infection, and inflammatory conditions (e.g., celiac disease) decrease nonheme iron absorption. Heme iron is absorbed into the enterocytes by a carrier protein; heme oxygenase, and stored intracellularly as ferritin or is released into the plasma by the iron transport protein ferroportin 1 (FPN). Once in the circulation, iron binds to transferrin (Tf) and is transported to various sites for its utilisation or storage [6]. Physiological body iron balance is maintained by hepcidin which assures maintenance of adequate systemic iron levels and is regulated by circulating and stored iron levels, inflammation and erythropoiesis.

Dual role of Iron

Iron is a critical element for many essential metabolic pathways of the body playing an essential role in immunosurveillance. Lack of iron leads to growth arrest and anemia while increased accumulation (overload) is associated with toxic radical formation and progressive tissue damage [6][8]. Iron overload can produce injury to the cells; it produces reactive oxygen species in the Fenton reaction (possesses redox activity), which cause oxidative stress and harm host tissues by oxidative damage of proteins, lipids, and nucleic acids. Iron is crucial for the proliferation of tumour cells and micro-organisms, due to its role in mitochondrial respiration and DNA synthesis. Hence, iron because of its key role in redox reactions it is considered as a two-edged sword. Given the vital functions of iron but the toxicity associated with iron excess, abnormalities in iron homeostasis are related to a number of diseases [12].

Iron overload

The term 'iron overload' can be used to describe a condition resulting in increased total body iron stores, with or without organ dysfunction. It was first described by Armand Trousseau in 1865 as a 'case of bronze diabetes and cirrhosis'. Von Recklinghausen in 1889 named this condition 'hemochromatosis' after discovering that these patients had an iron containing pigment in the liver cells. In 1935, Sheldon recognised the inherited nature of this disorder and the association with abnormal iron metabolism [3, 6]. However, the specific gene defect was discovered in 1996 when Feder et al. identified 2 gene mutations

(C282Y and H63D) of the HFE gene linked to primary iron overload [6, 9, 13]. Iron overload occurs when there are excess stores of iron in the body. Iron overload syndromes are broadly divided into two groups: Inherited or primary iron overload and secondary iron overload syndromes [6]. Primary iron overload is often inherited with specific gene defect identified as Hemochromatosis Gene (HFE) mutation [9].

Secondary iron overload generally arises due to transfusion, haemolysis, or excessive parenteral and/or dietary consumption of iron. Excess iron is deposited into organs especially liver, heart, and endocrine glands. Signs and symptoms are generally related to specific organ involvement. When the iron storage and iron-induced oxidative stress of the liver is exceeded, it can lead to oxidant-mediated liver injury, cirrhosis, and hepatocellular carcinoma [12]. Other chronic liver diseases like alcoholic liver disease, non-alcoholic fatty liver disease, and viral hepatitis are likewise linked with liver iron loading. Iron tends to accumulate in hereditary hemochromatosis and β-thalassemia associated with restrictive cardiomyopathy with prominent early diastolic dysfunction, arrhythmias, and progression to an end-stage dilated cardiomyopathy. The pathophysiology of iron-overload cardiomyopathy is multifactorial comprising of oxidant-mediated injury, interference with cardiac electrical function, and promotion of fibrosis [12].

Diabetes mellitus is a common complication of iron overload. In hemochromatosis, iron accumulates in pancreatic islets, having toxic effect on β cells by inducing oxidative stress and apoptosis, thereby impairing insulin secretion leading to elevated blood glucose levels and hyperpigmentation (bronze skin - bronze diabetes). Iron overload also causes insulin resistance by toxic effects on the liver. Iron overload can cause hypothyroidism and hypogonadism resulting in fatigue, hair loss, infertility, and decreased libido [9]. Osteoporosis is also prevalent in patients with hemochromatosis and β-thalassemia. Joint involvement can cause arthritis and neurological involvement can accelerate neurodegenerative diseases including Parkinson's disease, Alzheimer disease and depression [9]. The oral mucosal lesions of hemochromatosis include brown to grey diffuse macules that tend to occur in the palate and gingiva. Although these pigmentations are predominantly the result of iron deposition in the submucosa, basilar melanosis is also observed microscopically and may be the result of a secondary addisonian complication, whereby hemosiderin deposition within the adrenal cortex may lead to hypocorticism and ACTH hypersecretion [10, 12].

Increased iron metabolism is also associated with malignant transformation, cancer progression, drug resistance and immune evasion. Iron overload is believed to contribute to cancer development by means of the pro-oxidant effects of iron which can damage DNA and promote oncogenesis and secondly, cancer cells have an enhanced dependence on iron to maintain their rapid growth rate. Hence, iron chelators are being deliberated for use in cancer therapy by iron depleting cancer cells and/or promoting reactive oxidative stress to which cancer cells are predominantly vulnerable. Iron and iron-induced reactive oxygen species have also been implicated in the pathogenesis of chronic kidney disease (CKD) [12]. Serum ferritin greater than 300 ng/ml in males and greater than 150 to 200 ng/ml in menstruating females can be indicative of iron overload. Fasting, elevated serum transferrin saturation percentage greater than 45% can assist in further diagnosis. Genetic testing for the HFE gene associated with hemochromatosis and liver biopsy can be utilized in difficult to diagnose cases [9]. The treatment option for iron overload is reduction therapy through periodic phlebotomy and iron chelation therapy.

Iron deficiency

The most widely recognized clinical manifestation of iron deficiency is anemia. Iron deficiency anemia (IDA) occurs when the balance of iron intake, iron stores, and the body's loss of iron are deficient to upkeep production of erythrocytes. Common causes include malabsorption (e.g. celiac disease, gastric/gut resection, Helicobacter pylori colonization, chronic use of protein pump inhibitors/H2 antagonists), increased iron requirements during pregnancy and rapid growth in children, or increased blood loss (e.g. due to gynaecological losses or gastrointestinal losses from parasites, slow, chronic bleeding due to colon cancer, uterine cancer, intestinal polyps, hemorrhoids, etc., ulcers, malignancy, aspirin/nonsteroidal anti-inflammatory drugs) [12]. CKD patients are prone to iron deficiency due to nutritional deficiencies, use of medications like phosphate binders and antacids that interfere with enterocyte iron uptake, increased iron utilization induced by erythropoiesis stimulating agents, and increased blood loss from haemodialysis, frequent phlebotomy, and uremic platelet dysfunction. Rarely IDA can be a consequence of mutations in genes involved in duodenal iron uptake, iron mobilization from body stores, or erythroid iron uptake or utilization, including DMT1 (*SLC11A2*), ceruloplasmin (*CP*) and

transferrin (*TF*) [12, 18]. Iron deficiency can exist with or without anemia. Some functional changes may occur in the absence of anemia, but the most functional deficits seem to occur with the development of anemia.

Iron deficiency anaemia rarely causes death, but the impact on human health is significant. In IDA not only tissue delivery of oxygen is affected, but proliferation, growth, differentiation, myelinogenesis, immunofunction, energy metabolism, absorption and biotransformation are compromised leading to abnormal growth and behaviour impaired brain development and cognition, reduced cardiac performance, and infections etc. are observed [11]. Iron deficiency during pregnancy is related to a range of adverse outcomes for both mother and infant, including increased risk of sepsis, maternal mortality, perinatal mortality, and low birth weight [9]. Iron deficiency can lead to premature hair loss, alopecia areata, greying of hair, and increased formation of free radicals that speed up the aging process.

Easy fatiguability, diminished attention span, depression, disturbances of sleep rhythm and reduced mental alertness also occur in this condition. Iron deficiency causes thrombocytosis and also several non-haematological consequences like glossitis, angular stomatitis, koilonychia, dysphagia with postcricoid oesophageal web etc. due to the necessity of iron for cellular proliferation and differentiation [11]. Iron deficiency is known to effect immune function with increased incidence of furunculosis, candidiasis, and upper respiratory infections. Studies on cell mediated immunity, phagocytosis, bacterial killing, and humoral immunity showed changes in iron deficiency patients. Iron is also required for growth of various microorganisms [15]. However, iron deficiency anaemia in a community where certain infections are rampant may also offer some protection against these infections as was evidenced by increasing incidence of malaria in an African population when iron supplement was given [11, 16]. Low iron levels are also known to cause heart failure and increase risk of cancers. The role of iron in the treatment of cancer has been studied in two directions. Depriving cancer cells from iron with iron chelators has been proposed as a therapeutic approach for cancer. Manipulation of iron stores in cancer cells for treatment of cancer has been considered in the other direction as well, so that iron overload in cancer cells results in inhibition of cancer growth by generating oxidative assault [3, 14].

Serum ferritin is a good indicator of body iron stores under most circumstances, examined and evaluated in the context of nutritional and medical history. The four principle strategies for correcting iron deficiency in populations include education combined with dietary modification to improve iron intake and bioavailability; iron supplementation, iron fortification of foods and the new approach of biofortification [17].

SUMMARY

This review has discussed the dual nature of Iron as a double edge sword. Although iron is essential for all cells, it could be potentially hazardous. Excess or deficiency can affect many vital functions in the body. Hence, attaining control over iron homeostasis is one of the dominant fields in deciding the fate of an infection with intracellular pathogens or course of a malignant disease or drug resistance [3].

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