The physiological role of iron and the relationship of excess iron to chronic disease

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Iron is one of several trace minerals needed by the body to maintain healthy physiological function. Iron is utilized in the transport of oxygen, transport of electrons during ATP synthesis, and as a cofactor for dozens of enzymes (1). There is approximately 2-4 grams of iron present in the human body, with over 65% of it in hemoglobin, 10% in myoglobin, 1-5% in enzymes, and about 20% in the blood or storage (1). In both the human body and food sources, iron exists in one of two forms: ferric (Fe3+) and ferrous (Fe2+) (1). The U.S. Recommended Dietary Allowance (RDA) for iron is 6 mg/day for men, 8 mg/day for postmenopausal women, and 18 mg/day for premenopausal women (1). Iron deficiency is the most common micronutrient deficiency worldwide (2); however, iron overload is also possible. This paper will discuss the normal physiological role of iron in maintaining health, including the physiological functions of iron, as well as the processes of digestion, absorption, transport, and storage of iron in the human body. The evidence of excess iron and its relation to the incidence of chronic diseases of cardiovascular disease and diabetes will also be examined.

As mentioned above, iron is involved in several important functions for maintaining life. Perhaps the most important function is its involvement in the transport of oxygen to tissues. About 98.5% of total oxygen in the blood is carried by hemoglobin (1). Hemoglobin consists of a globin protein and four heme molecules, each of which contains an atom of iron in the center (1). Each red blood cell likely contains millions of hemoglobin molecules and carries up to a billion oxygen atoms, thus making heme synthesis the largest utilization of iron in the human body (1). Myoglobin is the oxygen transporter within muscle cells. Each myoglobin contains

consists of a single heme group and protein chain. It helps diffuse oxygen from hemoglobin into the cytosol and mitochondria of muscle cells (1).

Iron is also a key component in energy production. Cytochromes b and c in the electron transport chain both contain heme, and therefore iron. The oxidative properties of iron transfer the electrons along the chain (1). Iron is also found in other nonheme enzymes involved in electron transport, including NADH dehydrogenase, succinate dehydrogenase, and ubiquinone-cytochrome c reductase (1). Additionally, iron is required in the enzymes of several other pathways, including amino acid metabolism, carnitine synthesis, and procollagen synthesis. In each of these enzymes, iron is needed to add oxygen atoms to a substrate (1).

A majority of the body's iron (approximately 90%) is obtained endogenously from the recycling of iron from degraded red blood cells (3). The remaining iron supply must be provided by the diet. Dietary iron exists in two forms: heme iron and nonheme iron (1). Heme iron is found in meat and meat products as part of hemoglobin and myoglobin. Specific dietary sources include red meat, fish, poultry, liver, oysters, and clams (1). Nonheme iron is not bound to a heme group and is found in plant foods, such as beans, grains, nuts, vegetables, fruits, and tofu (1). Small amounts of nonheme iron are also present in dairy products (eggs, milk, and cheese) (1). Enriched grains fortified with iron and oral iron supplements are also comprised of nonheme iron (1). The two types of iron are absorbed through different pathways and with different levels of efficiency (4). Nonheme iron typically makes up a larger part of the diet; however, heme iron is absorbed more readily, making it the main dietary source of functional iron in the body (5). Overall, bioavailability of iron is poor; humans typically consume 12-18 mg/day of dietary iron, but only 1-2 mg is absorbed (6). Iron absorption varies depending on iron stores and can rise to 3-6 mg per day when the body's iron stores are low and can fall to 0.5 mg or less per day when

the iron stores are high (1); although this is thought to affect nonheme iron absorption more than heme iron absorption (3).

The absorption of heme iron is a fairly straightforward process. In order for heme iron to be absorbed, it must first be released from the globin portion of hemoglobin and myoglobin by proteases in both the stomach and the small intestine (1). Heme carrier protein 1 (hcp1), a protein found mostly in the duodenum of the small intestine, absorbs the released heme group across the brush border of the intestinal epithelial cells, or enterocytes (1, 7). Once inside the enterocyte, the heme group is broken down into ferrous iron (Fe2+) and protoporphyrin by heme oxygenase. The iron can then be used by the enterocyte, stored as ferritin, or transported across the basolateral membrane to the blood for circulation (1). Stored ferritin in the enterocyte is eventually lost when the brush border cell naturally degrades (8).

Nonheme iron absorption is more complex with several factors contributing to absorbability. Nonheme iron is bound to various food components in different ways. During nonheme iron digestion, hydrochloric acid and proteases in the stomach and small intestine hydrolyze the iron from the food compounds and release it in the ferric iron state (Fe3+) (1). Ferric iron gets reduced into ferrous iron (Fe2+) in either the acidic environment of the stomach or by reducatases on the membrane of the duodenum's brush border (1, 8). Ferrous iron can then be transported into the enterocyte by divalent mineral transporter 1 (DMT1) (1, 7). The amount of DMT1 molecules present on the enterocyte border is regulated by iron concentrations within the enterocyte (1). Once the ferrous iron is in the enterocyte, it has the same potential fates of the absorbed heme iron (1).

There are several factors that influence the absorption of nonheme iron, particularly the presence of inhibitors or enhancers that may bind with nonheme iron. The strength of the bond

determines its solubility, which in turn affects its ability to be absorbed (1). Known inhibitors of nonheme iron absorption include phytates in plant foods, polyphenols in tea and coffee, calcium, and various proteins including casein, whey, egg white, and soy (3). Common enhancers of nonheme absorption include sugars, acids (ascorbic acid, citric acid, lactic acid), meat, poultry and fish (1, 5). Ascorbic acid is a particularly strong enhancer, as it can overpower all the inhibitors and will increase absorption of both natural and fortified iron (3). However, ascorbic acid loses its ability to enhance absorption if it is cooked, industrial processed, or degraded during storage (3).

The body's regulation of iron absorption is essential for maintaining the proper balance of iron in the body. The protein hepcidin is the main molecule involved in the regulation of iron absorption (1, 7). When the iron body stores are adequate or high, the liver releases hepcidin into the bloodstream, which blocks the transport of iron out of the enterocyte by binding to and degrading the transport protein ferroportin (FPT-1), found on the basolateral membrane of the enterocyte (1, 8). Thus, iron concentrations within the enterocyte increases and the synthesis of DMT1 decreases and the production of ferritin (the storage form of iron with in the cell) increases (1). Alternatively, if the body's iron stores are low, little hepcidin is released from the liver and the FPT-1 is left intact to transport iron out of the enterocyte and into the bloodstream (1).

In addition to ferroportin, several other proteins are involved in the transport of iron from the enterocyte to tissues. The first step in iron transport out of the intestine is for ferrous iron (Fe^{2+}) to bind to ferroportin, located on the basolateral membrane (1). The actual exit of the iron is also dependent on another simultaneous step. A copper-containing protein called hephaestin, also found on the basolateral membrane near ferroportin, oxidizes ferrous iron to the

ferric state (Fe3+) prior to being released from the ferroportin (1, 6). Iron must be in this ferric state to bind to its plasma transporter, transferrin, to form the Fe(III)-transferrin (TF) complex. This is the major form of iron found in the blood, although very small amounts of iron may also bind to albumin or citrate compounds (6). The latter is thought to occur only when transferrin is fully saturated and is classified as non-transferrin bound iron (NTBI) (5). In addition to newly absorbed dietary iron, transferrin also binds to recycled iron from the degradation of red blood cells and other iron-containing compounds already in the body (1).

The binding of iron to protein for transport through the bloodstream is crucial for several reasons. First, the receptors responsible for cellular uptake of iron are made to specifically recognize the TF complex. These receptors are known as TFR-1, found on most tissue cell membranes, and TFR-2, found mostly on the membranes of liver cells (6). Second, the binding of iron ensures that iron is not floating freely through the body in its oxidative ferric iron state. This limits iron's ability to potentially generate harmful free radicals that could be toxic to cells and organs (1, 6). And finally, bound iron is protected from any infectious bacteria using it for its own growth (1).

Once the TF complex reaches the tissues, the transferrin binds to TFR-1/TFR-2, enters the cell through endocytosis, and is transported through the cell's cytosol in an endosome vesicle (1, 8). From inside the endosome, ferric iron (Fe3+) is released and reduced by the protein known as steap3 to ferrous iron (Fe2+). Ferrous iron can then be transported out of the endosome by a DMT1 transporter protein. Once released into the cytosol, iron will be transported to other sites in the cell for functional use (i.e., mitochondria for cellular respiration) or oxidized and stored as part of ferritin (1). The amount of iron taken into the cell is dependent on the number of transferrin receptors on the cell membrane, which is regulated by intracellular

iron concentrations (1). Excess iron not needed by other cells gets stored in the liver, bone marrow, or spleen in the form of ferritin (1). Each ferritin molecules typically stores about 800 to 1,500 iron atoms, although it is capable of storing up to three times that amount (1). Ferritin is also found in the blood in small amounts thought to be proportional to ferritin found in body tissues with 1 ng of ferritin/mL serum equaling approximately 10 mg of tissue ferritin (1). Thus, serum ferritin levels are used to approximate iron stores within the body, although it is thought to be a limited marker because of ferritin's reactant nature (5). Also, its levels would be elevated during and following inflammation or illness, regardless of the level of iron stores; thus, causing a misrepresentation of iron stores (1). Still, serum ferritin concentrations remain the universal marker in both clinical and research settings (5).

Due to iron's highly oxidative properties, iron balance is highly regulated within the body. The body has no known regulatory mechanism for excretion, so all iron regulation occurs through absorption and storage as previously described (6, 8). Iron only leaves the body in small amounts through urine, sweat, and shedding of the intestinal epithelial cells, or for premenopausal women, in large amounts through menstruation (3). Therefore, problems with the expression of any proteins involved in iron absorption regulation can result in increased iron stores (1). Iron overload is defined as "an increase in storage iron, regardless of the presence of tissue damage" (9). The most common reason for chronic iron overload occurs from a genetic mutation in the gene responsible for synthesizing hepcidin, the regulating molecule for iron absorption (1, 9). This genetic disorder is known as hereditary hemochromatosis (HH) and results in continued absorption despite high iron stores, leading to iron overload (1) from progressive iron accumulation in the heart, liver, pancreas, and other organs (10) and extremely high levels of circulating ferritin (5). In addition to chronic (primary) iron overload, secondary

iron overload can occur from blood transfusion iron overload, long term hemodialysis, chronic liver disease, or dietary iron overload, usually through iron supplements/pills or from diets high in heme iron, which is highly absorbable (1, 8). The excess iron exceeds the ability of both TF and NBTI to safely transport iron, leaving unbound iron to travel freely through the blood, potentially causing free radical damage to the small intestine and other tissues (1) and eventually organ disease and failure (7).

The excess levels of iron in the blood and tissues are thought to play a role in the development or advancement of chronic diseases, particularly cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Links between excess iron and both CVD and T2DM are suspected because of an increased prevalence of both conditions in people with HH (5). Cardiovascular disease is a complex and multifactorial health condition that cannot be tied to any one cause; however, research is consistently done to understand correlating risk factors. Iron overload has been studied as a potential risk factor and contributor to CVD with mixed results over the years; however, several recent studies have found a possible link. A 2013 study in Iran found a positive association between high iron stores and CVD most likely due to iron causing oxidative stress and lipid peroxidation, both of which have been linked to atherosclerosis (11). The researchers concluded that CVD patients should not take supplemental iron and should avoid foods rich in iron (11). In a 2011 study from Argentina, patients with iron overload had several markers associated with high risk for CVD, including higher triglyceride and lower HDL-C levels, higher levels of oxidized LDL, and a higher proportion of small, dense LDL particles compared to control subjects (9). A 2012 study in *The Journal of Nutrition* examined the diets of over 6,800 adults to determine the association of micronutrient consumption, including heme and nonheme iron, with incidence of CVD, metabolic syndrome, and type 2

diabetes. They found dietary intake of heme iron and zinc specifically from red meat was associated with greater risk of both CVD and metabolic syndrome. The intake of nonheme iron and heme iron from sources other than red meat had no effect on the incidence of CVD (12).

Type 2 diabetes mellitus (T2DM) is another chronic disease commonly studied in search of associated risk factors. Insulin resistance and prediabetes are potential precursors to T2DM so these are often studied as well, including their link to excess iron stores. People with T2DM typically have higher serum ferritin levels compared to those without diabetes, and serum ferritin levels have been shown to positively correlate with plasma levels of insulin and glucose (5). Additionally, numerous animal studies have shown excess iron to cause diabetes (10). One recent study on mice explored the effects of a high fat diet and iron supplementation on risk factors for T2DM compared to mice fed low fat diets with and without iron supplementation. Iron supplementation, regardless of the amount of fat in the diet resulted in higher plasma glucose levels, lower HDL-C levels, an increase in iron stores in the liver, and an increase in hepatic ferritin protein expression; while levels of insulin and insulin resistance were higher in both the high fat diet group and the high fat with iron supplementation group. The researchers concluded that iron loading led to hyperglycemia, hyperinsulinemia, and insulin resistance, which are all significant precursors to T2DM (13). A recent meta analysis conducted in China reviewed human studies on iron overload and T2DM. The analysis concluded that heme iron intake and high body iron stores were significantly associated with an increased risk of T2DM, while total dietary iron, nonheme iron, or supplemental intakes were not significantly associated with T2DM risk (10). The researchers explained some possible reasons for this correlation. First, pancreatic beta cells, responsible for producing and secreting insulin, are highly susceptible to oxidative stress due to a decreased expression of antioxidant enzymes in beta cells.

Additionally, excess iron may decrease glucose metabolism and increase fatty acid oxidation in muscle cells, resulting in increased insulin resistance and increased glucose production in the liver (10). A 2008 review article by American researchers reported similar conclusions and explanations after reviewing numerous studies regarding iron body stores and the increased risk of T2DM (5).

The physiological role of iron is crucial for every day human health and its homeostasis is essential. Because iron is a highly reactive pro-oxidant, it has potential to cause an increase in oxidative stress in the body. This oxidative stress can contribute to elevated risk factors associated with both CVD and T2DM. However, both conditions are the result of many cumulating factors in the body, and iron cannot be identified as a direct contributor to either condition. Still, it is essential to understand that excess iron stores could be harmful and is best avoided when possible. Due to heme iron's high absorbability, it is recommended to avoid a diet high in heme iron and instead, eat a balanced diet that includes both heme and nonheme sources.

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