Iron, Oxidative Stress, and Disease Risk

Based on epidemiologic evidence citing excess iron as a risk factor for many diseases, and oxidative stress as an underlying cause for those diseases, iron-induced oxidative stress has recently gained attention. Although iron can participate in oxidative reactions to generate free radicals under in vitro conditions, its involvement in vivo in the cause or progression of diseases is questionable.

Key words: iron, oxidative stress, cancer, cardiovascular disease, neurologic diseases

This review was prepared by Manju B. Reddy, Ph.D., and Laura Clark, B.S., Department of Food Science and Human Nutrition, Center for Designing Foods to Improve Nutrition, 1127 HNSB, Iowa State University, Ames, IA 50011.
Although iron deficiency is one of the most common nutritional problems existing today around the world, iron excess has recently gained attention owing to epidemiologic evidence based on its association with cardiovascular disease, cancer, and other diseases. The plausible explanation for this association is iron’s pro-oxidant property in generating free radicals.\(^1\) Iron is essential in the human diet and is needed for many important physiologic functions when bound to hemo-globin, myoglobin, cytochromes, several enzymes, and nonheme iron proteins. The bound iron is transported in the body by transferrin, while excess iron is stored as ferritin and hemosiderin. A small amount of body iron is also found as non-transferrin-bound iron (NTBI) and is associated with low–molecular weight ligands such as ATP, ADP, GTP, and citrate. The NTBI pool is small in healthy people but can be slightly elevated in people at risk for iron overload (i.e., hemochromatosis [HH], \(\alpha\)-thalassemia, and other disease conditions).\(^2\) Based on the involvement of iron in the Fenton reaction (i.e., producing hydroxyl radicals from \(\text{H}_2\text{O}_2\)) under in vitro conditions, the low–molecular weight iron complexes may presumably be involved in this reaction in vivo.\(^1,2\) Hydroxyl radicals are the most reactive radical oxygen species (ROS) and are known to have the ability to react with cellular constituents including amino acid residues and purine/pyrimidine bases in DNA; hydroxyl radicals are also able to attack cell membrane lipids causing lipid peroxidation.

Because the body’s capacity to store iron is more than adequate in normal individuals and iron in circulation is tightly bound to transferrin, only a negligible amount of catalytic iron is present in the body. Therefore, the Fenton reaction is unlikely to occur under physiologic conditions. Based on results of a recent study showing no relationship between NTBI and low-density lipoprotein (LDL) oxidation in 77 men and women with normal iron status (serum ferritin levels of 42–96 \(\mu\text{g/L})\),\(^3\) it is uncertain whether variations in iron status in the normal range have an effect on the availability of iron for intracellular oxidation. During oxidative stress, however, iron may be released from its proteins, further inducing oxidative damage. Rats treated with 5-aminolevulinic acid (ALA), a heme precursor that accumulates in inter-mittent porphyria and lead poisoning, had increased iron release from ferritin in a time- and dose-dependent manner, which may be related to its involvement in free radical generation. Based on the inhibition on the ALA-promoted iron release by superoxide dismutase (SOD), \(O_2^-\) involvement was suggested in releasing iron from ferritin.\(^4\) Although data do not indicate that oxidative stress induces iron release from proteins in vivo, this may partially explain why high levels of cholesterol (high oxidative stress condition) and iron have a synergistic effect in causing atherosclerosis.\(^5,6\)

Oxidative stress and free radical damage to the tissues may be involved in the development of diseases such as cancer, neurodegenerative diseases, and cardiovascular diseases (CVD). Published data suggests an association between iron and these diseases.\(^7–12\) Because iron chelation and deprivation in a variety of diseases has been shown to prevent oxidative damage in tissues and organs, there is reason to believe that iron could be involved in causing the damage.\(^13\) In an extensive review, Heath and Fairweather-Tait\(^14\) concluded that the data showing an association between elevated iron status and increased heart disease risk is not convincing; however, the authors stated that high iron intakes may be related to colorectal cancer in the general population. Increased accumulation of iron in tissue is associated with pathogenesis of many diseases, although the extent of this association is dependent on the type of cells. For example, cells that have higher antioxidant capacity, such as hepatocytes, are less susceptible, whereas brain cells, which have low antioxidant capacity, are more susceptible to iron-catalyzed oxidative stress. For instance, SOD and catalase concentrations are 7- and 140-fold higher in the liver than in the brain, respectively.\(^2\) Despite the high antioxidant capability in hepatocytes, accumulation of iron in the liver by iron dextran administration had a significant effect on thiorbarbituric acid–reactive substances (TBARS), indicators of lipid peroxidation; this effect suggests iron’s involvement in hepatic oxidative damage.\(^15\) Because oxidative stress is related to tissue damage resulting in many diseases, it is important to discuss the role of iron in some diseases.

Because mutagenesis caused by oxidative damage of DNA has been widely recognized as the primary step for cancer growth, the correlation between iron, ROS, and cancer has recently received great attention. More than two decades ago, data from the first National Health and Nutrition Examination Survey (NHANES) showed that body iron stores and dietary iron intake were positively associated with subsequent risk of colon cancer in men.\(^8\) Under in vitro conditions, both non-heme (ferric-NTA) and heme (hemoglobin) iron induced DNA damage in human colon cells (HT29 cells), indicating dietary iron involvement in colon cancer.\(^16\) In a case-control study, the risk for colonic adenoma was 4.3-fold higher in individuals with serum ferritin levels of 157 to 399 ng/mL than individuals in the lowest quartile (8–43 ng/mL), even after adjusting for other risk factors.\(^7\) By contrast, lung tumor size induced by urethane in rats was unaffected by iron status, and, in fact, a low-iron diet increased the incidence of lung adenoma by 86%.\(^7\)

Because liver is the primary site for iron accumulation, liver cancer is commonly associated with HH; it is
not clear, however, whether increased iron status in healthy individuals is of concern. Fisher et al.18 recently examined the effect of iron status on oxidative stress and nuclear factor-kappa B (NF-κB) in livers of rats treated with hepatogenic peroxisome proliferator (Wy-14,643). As expected, investigators observed a moderate increase in oxidative stress, as indicated by increased lipid peroxidation markers, in rats consuming a high-iron diet compared with rats consuming a low-iron diet, but no effect on DNA double-strand breakage was found. A high-iron diet did not increase NF-κB activity, which is influenced by oxidative stress, especially by H₂O₂. Current evidence suggests that oxidative stress can activate NF-κB by dissociating from its inhibitory protein in the cytosol. The active NF-κB enters into the nucleus and alters the transcription of genes implicated in carcinogenesis. Although the results of this study do not support the role of iron in inducing cancer through NF-κB activation, it does not rule out induction through other mechanisms. It is possible that the hydroxyl radical produced by excess iron may not have a similar effect as H₂O₂ on NF-κB activity, or that it requires the extreme iron concentrations as seen in HH. Tumor necrosis factor-α (TNF-α) protects from oxidative damage in hepatocytes exposed to tert-butyl hydroperoxide by inducing heavy-chain ferritin (H-ferritin) protein synthesis and making less non-protein–bound iron available in rats fed a normal diet. However, this protective effect was not seen in rats fed an iron-enriched diet.19

Excess iron may induce oxidative damage by depleting the body’s antioxidant defense. Iron overload induced by feeding carbonyl iron to rats reduced antioxidant concentrations (vitamin E and ascorbic acid in plasma) in the body, but did not affect lipid peroxidation; this suggests that iron-induced oxidative stress might be related to the depletion of antioxidants.20 Hence, adding antioxidants to the diet should have some protective effect on iron-induced oxidative stress. Existing data on the beneficial effect of vitamin E on reducing iron-induced cancer risk do support this hypothesis. In a recent rat study,21 feeding rats a high-iron diet (280 ppm) increased peroxides in feces and decreased colonocyte tocopherol concentrations compared to rats fed a 35-ppm diet. However, adding gamma tocopherol not only reduced the fecal lipid peroxides, but also reduced the expression of ras-p21, an oncogenic protein expressed in chemically induced colon cancer and over-expressed in patients with advanced colon cancer. These data suggest that vitamin E counteracts the effect of high iron-induced oxidative stress.

Although animal and in vitro studies show the role of excess iron in inducing cancer, dietary iron overloading in healthy individuals may not occur. This evidence does not rule out concern for people taking supplements, in which case the colon is exposed to large amounts of unabsorbed iron and thereby oxidative reactions. When human subjects consumed 19 mg/day iron for 2 weeks, there was a fivefold increase in free iron concentration and a 40% increase in free radicals in the feces compared with the pre-supplementation period.22 Excess unabsorbed iron may therefore cause mucosal damage and consequently colon cancer.

Overall, it is possible that iron is involved in free radical damage but that it doesn’t necessarily induce cancer because of the body’s antioxidant defense and the DNA repair process. More research focusing on the mechanisms involved in iron-induced carcinogenesis is needed, therefore, and should examine the role of antioxidants, enzymes, and DNA repair mechanisms.

Although oxidative damage may be one of the underlying causes of neurodegenerative diseases, the role of excess body iron as a source of free radicals in the pathogenesis of these diseases is not well understood. Parkinson’s and Alzheimer’s diseases are associated with elevated brain iron concentrations relative to the iron storage protein, ferritin. A rise in iron levels without concomitant change in ferritin provides free iron for free radical generation. Brains of Alzheimer’s disease patients show a disruption in iron metabolism, such that there is an accumulation of iron in senile plaques and altered distribution of iron transport and storage proteins.10 Studies on postmortem brains of Parkinson’s disease patients also revealed iron accumulation in the substantia nigra. Cell death in this region is associated with oxidative stress, which may presumably be exacerbated by the excess iron in this region. Whether iron plays a causative role in cell death is controversial. H-ferritin plays a role in protecting the brain from damage by helping to keep the intracellular iron concentrations low. Thompson et al.13 recently examined the role of H-ferritin in protecting from neurodegenerative diseases in a mouse model that is heterozygous for H-ferritin. Mutant mice brains had less than half the levels of H-ferritin but had similar iron content as compared to wild-type animals. As expected, high oxidative stress was reported in terms of reduced SOD activity coupled with increased oxidized proteins and increased apoptosis measures (Bax and caspase-3) in the neurons of the mutant model. Protection against 1-methyl-4-phenyl-1,2,3,6-tetrapyridine (MPTP)–induced Parkinson’s by the oral administration of a metal chelator or by transgenic expression of ferritin, as shown in a recent study in mice, strongly supports the role of iron in neurodegenerative diseases.23 It seems that changes in iron homeostasis are a major contributing factor in neurodegenerative diseases, but it is not clear why those changes occur in aging. There is no data suggesting that excess iron in the body can be a risk factor for developing neurologic
disorders. Although more research is needed in this area to understand the underlying mechanisms of iron-mediated neurodegeneration, new studies show that metal chelation therapy is a promising approach to improve the quality of life of the aging population.

Because free radicals can also induce lipid oxidation and atherosclerosis, a major underlying cause of cardiovascular diseases, the relationship between iron and CVD has recently gained significant attention. Iron from transferrin may be released at pH values that can be seen at atherosclerotic lesions in the arterial wall (slightly lower than physiological pH) and may cause LDL oxidation. An in vitro study showed that lipolysis induced by lipoprotein lipase reduced the physiologic pH from 7.4 to 7.0, and these lipolytic events triggered iron release, which in turn increased LDL oxidation. Knowing the pH-dependent iron-binding chemistry of transferrin, it is reasonable to suspect iron involvement in causing the oxidative damage even in individuals with normal iron stores. However, no information is available on what pH exists at atherosclerotic lesions in vivo. Data from human epidemiologic studies relating excess iron to CVD are conflicting. Based on 10-year age-related CVD rates between sexes, Sullivan first proposed that women are more protected from CVD than men because of their lower body iron stores before menopause. It is interesting to note that factors known to have an effect on CVD also are known to affect iron. For example, the negative relationship of CVD to aspirin use and positive relationship to oral contraceptive use may be indirectly related to iron losses in these situations. In addition, blood donors experienced fewer (0.7%) myocardial infarctions (MI) than non donors (9.8%), indirectly suggesting that reduction of body iron may be responsible for the protection. However, it is possible that lower incidence of MIs might have been related to overall health consciousness in blood donors. A decade ago, a study showed that elevated iron stores with serum ferritin levels of >200 μg/L had 2.2-fold higher risk of acute myocardial infarction than men who had serum ferritin levels of <200 μg/L.11

Contrary to the above studies, other studies found no association between iron status and CVD risk.26,27 The Atherosclerosis Risk in Communities (ARIC) study showed that after adjusting for age, smoking status, hypertension, LDL cholesterol, diabetes, and waist-to-hip ratio, there was no association between serum ferritin and asymptomatic carotid atherosclerosis.27 Using the data from three controlled feeding studies in 24- to 65-year-old subjects, a recent study also reported no association between iron status (serum ferritin and NTBI) and LDL oxidation, an underlying cause of atherosclerosis.3

This association between iron and CVD seems stronger with hypercholesterolemia in both humans and animals.5 Iron overload achieved by iron dextran injections in hypercholesterolemic rabbits caused significantly higher atherosclerotic lesions and produced higher concentrations of lipid peroxides; these effects suggest the synergistic effect of cholesterol and iron excess.6 It is possible that high-fat diets may induce oxidative stress and thus create conditions favorable for iron to participate in causing more tissue damage. The existing data are weak in relating iron excess or free iron in the body to atherosclerosis, and thus the risk for CVD, but do not rule out the possibility of iron involvement in oxidative stress when the diet contains a high proportion of fat or the body’s antioxidant defense is compromised.

Although iron is involved in free radical generation in vitro, its participation in oxidative reactions in vivo is questionable. While it is commonly accepted that free radical damage is involved in many diseases, no direct evidence is available to indicate that iron excess is causing these diseases. There is stronger evidence for the mismanagement of brain iron in neurologic diseases and for excess dietary intake in colorectal cancer than for iron’s involvement in CVD. In conclusion, iron excess in a healthy population is not a major concern, but in those with high oxidative stress and hyperlipidemia, there may be increased risk for developing cardiovascular diseases.

9. Thompson K, Menzies S, Muckenthaler M, et al. Mouse brains deficient in H-ferritin have normal iron concentration but a protein profile of iron deficiency
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