Ray Peat's Newsletter

Resist much, obey little. … Walt Whitman

 Raymond Peat P.O. Box 5764 Eugene OR 97405 **July 2021**

Estrogen, iron, degenerative aging, and progesterone

On average, women's hemoglobin and hematocrit are both about 12% lower than men's, with little change in the ratio with aging. This difference has been ascribed to the loss of blood by menstruation, despite the fact that female animals generally (the great majority of which don't menstruate) also have a lower hemoglobin level than males. There is some evidence that estrogen slightly suppresses the formation of erythropoietin, the regulator of red blood cell formation, but most evidence indicates that it is estrogen's suppression of the bone marrow itself that accounts for most of the difference. Some evidence indicates that water retention caused by estrogen is responsible for the blood dilution (Ueda, et al., 1986).

Estrogen increases the stiffness of red blood cells and the viscosity of plasma (Solerte, et al., 1991), but women's whole blood is less viscous than men's (Kameneva, et al., 1999). This improved flowability of the blood, maintaining adequate oxygenation of tissues, results from the lower concentration of red cells.

For many years, this relative anemia of women led doctors to prescribe iron supplements for the correction of "iron deficiency anemia," with no indication of an iron deficiency other than low hemoglobin and low hematocrit. That practice has had various harmful consequences. Those consequences of consuming more iron than is needed have never been adequately explored.

While osteoporosis and dementia involve iron overload, they are associated with an increased likelihood of anemia.

While estrogen decreases the formation of blood, it increases the assimilation of iron from the diet, so that when a woman's estrogen is high her extraction of iron from food is several times as high as a man's. This increased affinity for iron can compensate for a greater need for iron resulting from menstrual blood loss and pregnancy, but it can also lead to the accumulation of toxic amounts of iron in the body if the diet supplies more than is needed. Both men and women accumulate iron with aging, and after menopause tissue iron increases more rapidly in women.

It has been known for a long time that calcium deposits in tissues such as arteries are mixed with iron (Peltomaa, et al., 1992; Langheinrich, et al., 2009), but there has been surprisingly little work to understand the reason for the association. In the 1960s, Hans Selye did a series of experiments in which a combination of injected iron salts and local tissue irritation caused deposition of calcium

in the irritated tissue, producing a scleroderma-like condition. If he treated the animals with vitamin E at the same time, the tissue didn't calcify. Vitamin E protects polyunsaturated fats from oxidation by iron, so the implication was that lipid peroxidation catalyzed by iron, triggered by slight stresses, was responsible for the tissue calcification.

Four day exposure of rats to hypoxia (10% O(2)) increased the level of lipofuscin-like pigments in erythrocytes up to 9 fold. This increase was completely prevented when the animals were exposed to hypercapnia (4.3% CO(2)) in addition to hypoxia.

Skoumalová, et al.

Until the 1960s, a paralytic disease occurring in some western Pacific Ocean islands, "amyotrophical lateral sclerosis/parkinsonism-dementia complex," was believed to be caused by heredity, and then it was thought to be caused by a virus transmitted by cannibalism, later by aluminum poisoning, and then by poison from a toxin in blue-green algae. Starting in 1976, a series of studies found that all of the affected areas, from western New Guinea to southern Japan, with a variety of cultural practices and diets, had in common a nutritional deficiency of calcium, because of the water and soil in the region. Their soils also contained a high level of aluminum.

When calcium is deficient, secretion of parathyroid hormone increases, removing calcium from bones to meet the regulatory needs of the rest of the body. This involves suppressing oxidative metabolism that produces CO2, and partially replacing it with glycolytic metabolism, producing lactic acid. When lactic acid is formed by a cell, the interior of the cell becomes more alkaline, causing the structural proteins to be more negatively charged. This can lead to an increase of positively charged metal ions inside cells. When metals other than calcium, such as aluminum, iron, or lead, are abundant in food and water, these will be accumulated in cells along with calcium, where they will—in proportion to the unsaturation of the cell's lipids—accelerate the processes of lipid peroxidation. The type of degenerative disease a person develops will depend partly on the types of metal and fat that accumulate in the tissues.

Women, under the effects of estrogen, accumulate (and synthesize) more of the extremely unsaturated fatty acids, such as DHA, than men do (Giltay, et al., 2004).

At birth, the brain contains a considerable amount of highly unsaturated fats, mainly of the omega-9 series, which our bodies can synthesize from sugar or saturated fats. The placenta normally functions as a barrier against highly unsaturated fatty acids from foods. The fats in the mother's diet enter her milk, with the result that the less stable omega-6 and omega-3 fats begin to accumulate in the breast-fed baby's tissues, especially the brain**;** if it receives a formula "enriched" with iron and DHA, the process is likely to be accelerated. Steady growth during childhood dilutes these environmental factors, but as growth slows their concentration increases. The result is an increasing tendency to produce lipid peroxides, that damage proteins and nucleic acids, causing progressive loss of function and increased calcification.

The presence of free, unbound iron in the tissues or in baby formula will degrade vitamin E, increasing the peroxidation of polyunsaturated fats. There are situations in which iron supplementation, without adequate vitamin E, can increase premature birth, increase the risk of hemolytic anemia in the newborn, and increase the risk of retinal

damage (Johnson, et al., 1982; Henderson and Torch, 1976; Casanueva and Viteri, 2003).

Some of the products of lipid peroxidation, interacting with iron and other cell materials, become the very complexly structured age pigment, lipofuscin. Among the substances in these dark granules are some heme molecules, protected against elimination, which can catalyze the conversion of oxygen to water, without producing usable energy; the pigment becomes a drain on fuel and oxygen, creating a constant reductive, oxygen deficient, stress. This tendency to reduce oxygen contributes to the formation of vicious circles, inducing hypoxia inducible factor, HIF, which is a crucial factor in promoting iron absorption, and which activates many potentially dangerous enzymes, including heme oxygenase, HO, which turns heme groups into free iron, carbon monoxide, and bilirubin. HIF also activates aromatase, increasing estrogen (Samarajeewa, et al., 2013).

About 60% of newborn babies are jaundiced for a few days, showing that the stress of being born has activated their HO, turning heme into its toxic components. The presence of free bilirubin is known to be associated with lipid peroxidation and DNA damage (Basu, et al. 2014). Better prenatal conditions would probably reduce the incidence of neonatal jaundice and stress, and this might involve avoidance of highly unsaturated fats and large iron supplements, and avoiding stressful medical procedures.

Stresses that increase exposure to excess iron and PUFA can shorten the life span of red blood cells, adding to the burden of heme and lipid peroxides. The well known association of the autoimmune diseases with excessive estrogen probably involves the increases of hypoxia, HIF, HO, iron, and PUFA under the influence of estrogen. Aldehydes produced by the breakdown of fats react with cell proteins, making them antigenic, while episodes of hypoxia and hypoglycemia make the immune system more reactive.

All microorganisms require iron to grow, so limiting the availability of iron will limit their ability to be infective. Our respiratory and digestive membranes secrete two proteins, lactoferrin and transferrin, which have a very high affinity for iron atoms, as well as other germicidal properties, and provide a first defense against infection. Milk contains these proteins, which provide anti-infective protection for the baby, while letting it safely assimilate iron by delivering it directly to proteins on the surface of the intestine that bind it. Since cancer cells' growth is stimulated by iron, the circulation of these iron-binding proteins in the blood and body fluids probably forms part of our defense against metastasis.

Another type of anti-microbial peptide (the cathelicidins and hepcidin) is able to kill viruses and bacteria directly, without binding iron. Hepcidin was discovered in the urine, and it's important for preventing bladder infections. Synthesis of the cathelicidins is dependent on vitamin D.

One of the ways in which estrogen increases iron retention is by inhibiting the formation of hepcidin (Balbouj, et al., 2018), since one of hepcidin's main functions is to limit the absorption of iron from the intestine, and to inhibit its release into the bloodstream. Progesterone increases the synthesis of hepcidin (Xiang, et al., 2016).

At the beginning of menopause, ovarian production of progesterone is suddenly interrupted, while the production of estrogen in fat, skin, muscles, and other tissues increases. Following menopause, the bones as well as the brain accumulate iron, and the effects include a much higher risk of osteoporosis and Alzheimer's disease in women than in men. While osteoporosis and dementia involve iron overload, they are associated with an increased likelihood of anemia.

The increase of tissue iron in aging is a factor in the greater susceptibility to infection. Iron not only supports the growth of infective organisms, but increases the formation of inflammatory cytokines and weakens the barrier function of the intestine, contributing to endotoxemia (Visitchanakun, et al., 2020). These factors are involved in the corona virus sickness, and iron overload is increasingly recognized as a factor in susceptibility to that infection and in its main characteristics, extreme inflammation, the cytokine storm, and hyper-coagulability. Removal of the iron by chelation has been proposed to reduce the inflammation and coagulation (Vlahakos, et al., 2021; Perricone, et al., 2020; Edeas, et al., 2020; Nielsen and Pretorius, 2020). Commonly used chelators can move harmful metals from the bones, where they were inactive, into the brain and kidneys; some chelators taken orally can move metals from the intestine into the mitochondria. Lactoferrin, currently being tested, seems to be safer, and besides reducing free iron it is antiinflammatory, reducing iron absorption, while blocking viral infection in multiple ways (Habib, et al., 2021; Campione, et al., 2021).

The long history of prescribing iron pills to women, regardless of their diet, has created a culture that has little interest in considering the harmful effects of excess iron. That attitude exists within the fraudulent "science" tradition created and sustained in the last 80 years by the estrogen industry that, to create a market for their product, has identified menopause and old age as a time of estrogen deficiency.

The fact that unopposed estrogen contributes to a toxic accumulation of iron, and promotes the retention of highly unsaturated fats (forming lipofuscin) in the brain and other organs, degrading immunity, brain function, and bone strength, gives us numerous opportunities to intervene to remedy and to prevent some serious health problems, including those that have been thought to be inevitable consequences of aging.

When we act to correct one part of this interlocking system, we are usually improving other things as well. For example, estrogen's effect on hepcidin that increases iron can be reversed by increased progesterone, with its opposite effect on hepcidin (Xiang, et al., 2016), while estrogen's effect on intracellular calcium is also reversed by progesterone (Luoma, et al., 2012; Xu, et al., 2005; Zhang, et al., 2002).

Besides progesterone, two other steroids cause an increase of hepcidin—epitiostanol, an anti-estrogen used to treat breast cancer, and mifepristone, which antagonizes cortisol as well as estrogen and progesterone. The importance of non-toxic substances to lower iron is widely recognized: "Small molecules capable of inducing hepcidin could also be of great therapeutic benefit to patients with hemochromatosis or other disorders complicated by iron overload, such as β-thalassemia. Unfortunately, there has been limited progress in identifying small molecules that increase hepcidin biosynthesis" (Xiang, et al., 2016).

Oxidative metabolism is the basic factor in resisting the degenerative processes; for example, the CO2 that the mitochondria produce prevents iron toxicity in a variety of ways. It inhibits the formation of lactic acid, eliminating that cause of iron and calcium deposition in cells, and it acts directly on iron to make it less toxic; for example it stabilizes lysosomes (Gerby, et al., 2019), and reduces the activity of free radicals produced by lipid peroxidation, reducing formation of lipofuscin (Skoumalová, et al., 2008). One of its effects is probably by stabilizing transferrin, increasing its affinity for iron: "It was found that hypercapnia in vivo protects against the damaging effects of ischemia or hypoxia. Several mechanisms have been suggested to explain the protective role of CO2 in vivo. The most significant appears to be

stabilization of the iron-transferrin complex which prevents the involvement of iron ions in the initiation of free radical reactions" (Veselá & Wilhelm, 2002).

Because of the close interaction between iron and calcium, vitamin D and adequate calcium in the diet are important for protection against chronic iron overload (Esparragoza, et al., 2020; Lee, et al., 2021). In general, avoiding foods with added iron is good, and having coffee or tea with naturally iron rich foods is protective for most people. Even during pregnancy, slightly low hemoglobin isn't enough to justify using an iron supplement—slightly low hemoglobin is protective against infections and stress. Very low serum ferritin and transferrin saturation are reasonable indicators of low tissue iron stores.

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