

The Nutritional Relationships of Iron

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Iron deficiency anemia has been considered the major nutritional problem throughout the world. However, it is now known that iron is involved, in many metabolic processes, particularly enzymes, and that many clinical manifestations (other than anemia) can develop as a result of iron deficiency. Iron is present in every cell and is involved in electron transport via cytochromes in the Krebs cycle, oxidases, and oxygenases.¹

Body Content and Requirements

The iron content of the body is approximately 25 mg per kg in adult women and 35 mg per kg in men. The RDA for iron is 10-15 mg for infants and children, 10 mg in adult males, 18 mg for teenagers and adult women, 45 mg during pregnancy and lactation.

Iron Assessment, Blood and Tissue

Routine serum tests for iron do not reflect intake of iron but are used to determine body stores, deficiencies, or overload. Alpers, et al, have indicated the inherent instability of serum iron, which fluctuates as much as 30% in the same person daily.² Statland and Winkel reported a considerable variation of serum iron levels in blood samples taken from the same patient at the same time each day.³ Due to a normal diurnal variation, morning values can be as much as 30% higher than evening values. This rhythm is reversed in night workers.⁴ Sleep deprivation can produce as much as a 50% reduction in serum iron levels.⁵ Serum levels of iron are also known to fluctuate with the menstrual cycle and oral contraceptive (OCA) use. Iron levels decrease just prior to menstruation and elevate during OCA use.

Due to the normal and induced variations in serum iron concentrations, single

iron determinations should be interpreted cautiously when assessing iron deficiency or iron overloads.

Tissue mineral analysis (TMA) has a unique advantage over serum in that it has the potential for detecting a tendency toward iron imbalance, either a deficiency or overload, before serum changes can be detected. TMA studies are not subject to the normal diurnal variations found in serum. Since iron deficiency can exist without anemia (sideropenia) and has been reported to be 2 to 3 times more predominant than iron deficiency anemia^{6 7}, TMA may serve as an appropriate screening tool for iron status.

TMA iron levels should also be interpreted carefully. Sample variations and possible exogenous contamination should be considered when interpreting TMA results.⁸ Trace Elements, Inc., has established the ideal tissue iron level at 2.8 mg%. However, tissue iron status should not be interpreted by the iron level alone, but more importantly in relationship with other minerals and, of course, in conjunction with serum test results and clinical findings. Significant ratios include calcium to iron (Ca/Fe), iron to copper (Fe/Cu), iron to lead (Fe/Pb), and iron to mercury (Fe/Hg). The ideal ratios are Ca/Fe = 15, Fe/Cu = 1.12, Fe/Pb = >5.6, and Fe/Hg = >28. Significant changes in these ratios (elevated Ca/Fe, lowered Fe/Cu, Fe/Pb, and Fe/Hg) can indicate the tendency toward iron deficiency, since each of the metals is known to interfere with iron absorption or the metabolic processes that require iron. Iron overload can also be assessed by using the tissue iron level in conjunction with copper and calcium (low Ca/Fe and elevated Fe/Cu).

Other routine serum indications that may be used in conjunction with TMA studies include total iron-binding capacity (TIBC), percentage saturation of transferrin, ferritin, hematocrit (HCT), mean corpuscular volume (MCV), and mean

1. Trace Elements, Inc., P.O. Box 514, Addison, TX 75001.

corpuscular hemoglobin (MCH). These serum changes usually only manifest when iron storage is becoming depleted. They are also subject to a number of variations such as altitude, physiological status, age, and sex. Further discussion of these and other tests are well described by Sauberlich, et al.⁹

Conditions Associated with Iron Imbalance

Prasad has reported that the recorded therapeutic use of iron dates back to 500 B.C.¹⁰ Iron was used to treat a condition known as chlorosis, which manifested in pallor of the skin, heaviness of the body and extremities, edema, dyspnea, palpitations, headaches, rapid pulse, prolonged sleep, cessation of menses, and aversion to eating meats. With the present knowledge of the biochemical functions of iron, this list can be extended to include anemia and non-iron deficiency anemia manifestations (sideropenia), which include emotional changes, immunodeficiency, endocrine, and other physical disorders.

Mental Effects of Iron Deficiency

Early studies have reported a correlation between hemoglobin levels and intellectual performance in teenagers.¹¹ Other studies have confirmed these findings in adults as well as children.^{12 13} Further studies have concluded that iron deficiency occurring with and without anemia can lead to defects in attention and cognitive functions,¹⁴ minimal brain dysfunction, and hyperactivity.¹⁵ Disturbances in mental functions have been attributed to a number of defects in the metabolic pathways that require iron such as a simple reduction in oxygenation of brain tissues due to low hemoglobin. Iron is required for DNA synthesis in mitosis; therefore, a deficiency may lead to impaired neuronal development. Iron is also required in enzymes involved in neurotransmission. The iron dependent enzyme monoamine oxidase (MAO), is reduced in the presence of iron deficiency. A reduction in MAO activity leads to an increase of other neurotransmitters such as norepinephrine, dopamine, and serotonin. Studies have reported that in iron deficient children the urinary excretion of norepinephrine is increased.¹⁶

Through TMA studies, we have often observed that patients who show excessive tissue iron accumulation, or low Ca/Fe and elevated Fe/Cu ratios, are more intellectually oriented, indicating left hemisphere brain dominance. Decreased left hemisphere activity has been confirmed in iron deficiency patients through EEG studies.^{17 18} We have also observed that too much tissue iron accumulation leads to aggressive behaviour, hostility, and hyperactivity. It can, therefore, be tentatively concluded that elevated TMA iron levels, low Ca/Fe or high Fe/Cu indicate left hemisphere dominance (intellectually oriented), and low tissue iron, or high Ca/Fe and low Fe/Cu indicate right hemisphere dominance (emotionally oriented).

Other Physical and Metabolic Effects of Iron Imbalance

A number of physical effects are associated with iron deficiency. The symptoms of chlorosis were described earlier. Other symptoms include intracranial hypertension resulting in chronic dull headaches, enlargement of the spleen and heart, glossitis, angular stomatitis, and koilonychia (concave or spoonshaped nails).¹⁹ When anemia is present, the sclera of the eye may become pearly white or blue. The nails become brittle and ridged longitudinally.²⁰

Pica

Pica, a term used to describe an abnormal or unusual craving for foods or other substances, is associated with iron deficiency. This condition is found most often in children and women.²¹ The most common form of pica is geophagia, which is the ingestion of clay or dirt. Paper pica has been reported in individuals suffering from mercury toxicity in conjunction with iron deficiency. An example, involves a woman who constantly ate paper in the form of paperback novels, tissue paper and boxes, cigarette and candy wrappers. She was found to have mercury toxicity in both the blood and hair as well as iron deficiency anemia. Mercury is used to preserve paper products and acts as a fungicide. Oral iron therapy eliminated her desire for eating and chewing paper. Pagophagia, the compulsive eating of ice

common in adults, is controlled with iron therapy.²² The ingestion of or craving for laundry starch (amylophagia) is a form of pica that frequently occurs in women, particularly when pregnant, and is another sign of iron deficiency.²³ Pica is generally considered a phenomenon that occurs in underdeveloped countries or in poor rural areas, but it is not uncommon in the general population. It should also be noted that pica can occur in the presence of adequate or excessive iron stores. An increase in tissue retention of iron without the ability for it to be reutilized in the hemopoietic process produces the same effect as iron deficiency.

Endocrine Effects of Iron Imbalance

In 1938 Cecil described the relationship between hypothyroidism and iron deficiency anemia. He stated that both thyroid extract and iron therapy are indicated for iron deficiency anemia.²⁴ More recently researchers have found that iron deficiency can impair thyroid function and that iron status may reflect thyroid activity.²⁵ Lehmann, et al, recently reported that the conversion of L-phenylalanine to L-tyrosine was reduced over 50% in iron deficient subjects.²⁶ Since there is a reciprocal relationship between the thyroid and adrenal glands,^{27 28 29} it can be speculated that iron status may also indicate adrenal activity. TMA studies have revealed that subclinical hyperparathyroidism may contribute to iron deficiency. This would be expected due to the increased absorption of calcium influence by the parathyroid, thereby decreasing iron absorption.

Dysphagia

A condition known as the Plummer-Vinson Syndrome (PVS) is associated with iron deficiency and characterized by esophageal stricture causing difficulty in swallowing. Vinson originally described these cases as hysterical dysphagia. PVS is known to respond to iron therapy.³⁰ It is possible that a decrease in thyroid function may have the effect of exacerbating PVS. Difficulty in swallowing or a frequent need to clear the throat is a classical sign of hypothyroidism or enlargement. As discussed previously, iron deficiency is related to low thyroid activity. Perhaps those

patients who complain of difficulty in swallowing, especially pills, should have their thyroid and iron status evaluated.

Infections

During an infectious condition (bacterial), iron is shifted into storage compartments — the liver, spleen, and bone marrow. This is a protective mechanism rendering the iron unavailable to the bacteria, which requires iron for its growth.^{31 32} Iron also becomes unavailable for incorporation into red blood cells, resulting in an infectious anemia that does not respond to iron therapy until the infection is controlled. Chronic infections (bacterial) are indicated on TMA studies by an elevation in the Fe/Cu ratio, usually greater than 2 to 1. Other conditions in which iron reutilization is impaired include rheumatoid arthritis and some types of malignancies. The above conditions result in iron deficiency anemia, even though tissue concentrations of iron are more than adequate. Iron deficiency is also a predisposing factor in infections due to a decrease in humoral immunity.³³ The decreased immunity is probably due to other accompanying nutritional deficiencies. Low iron and hemoglobin levels have been found to be associated with vitamin A deficiency.³⁴

Iron deficiency is also found in individuals suffering from chronic candidiasis and recurring herpes viral infections.³⁵

Factors Contributing to Iron Deficiency

Iron deficiency can be caused by many factors: increased physiological requirements (such as during pregnancy and growth), excessive blood loss, low iron intake, poor absorption, dietary antagonists, infections, parasites, poor nutrition, and vitamin and mineral deficiencies.

Sources and Absorption

Heme iron (iron attached to a heme molecule) is the most available form of iron for absorption and is found in animal protein. Even though iron from vegetables is not as readily absorbed when consumed alone, absorption is enhanced in the presence of animal proteins. Dairy products such as milk and cheeses can reduce iron absorption by as much as 80%.³⁶ Tannin

contained in teas also decreases iron absorption.

Iron requires an acid medium for complexing with proteins in the stomach for later release and absorption in the small intestine. A deficiency of hydrochloric acid markedly inhibits iron absorption. In an alkaline medium, iron forms insoluble complexes and becomes unavailable for absorption.

Minerals Antagonistic To Iron Absorption

Figure 1 indicates the minerals that are antagonistic to iron.^{37 38 39 40 41 42} Excessive intake of any one or combination of these trace elements can contribute to sideropenia and iron deficiency anemia or exacerbate an existing deficiency. Antagonism of iron by these minerals occurs either by inhibiting absorption, compartmental displacement, or interfering with cellular iron enzymes. Iron therapy can also be used in antagonizing the effects of toxic metal accumulation.

A deficiency of the synergistic trace elements can also lead to iron deficiency. The synergistic minerals include the following:

Minerals Synergistic to Iron

- | | |
|----------------|----------------|
| Copper (Cu) | Chromium (Cr) |
| Sodium (Na) | Nickel (Ni) |
| Selenium (Se) | Potassium (K) |
| Manganese (Mn) | Phosphorus (P) |

Some elements are listed as both antagonistic

and synergistic because of a dual relationship of some elements with iron. As an example, copper is considered synergistic due to its requirement in ferroxidase activity. However, excessive intake of copper competes with iron for absorption.

Vitamins Antagonistic To Iron

The vitamins that are considered antagonistic to iron are shown in figure 2. The mechanism of antagonism may be direct or indirect. As an example, vitamin D, by enhancing the absorption of calcium, can lead to poor iron absorption. Cobalt, which is an integral part of vitamin B₁₂, competes with iron and vice-versa on an absorptive level.⁴³

The antagonistic effects of iron and vitamin E occur on a cellular level, either through increased metabolic demands of iron produced by vitamin E or by free radical production caused by excess tissue iron accumulation. Excess tissue iron levels contribute to lipid peroxidation,⁴⁴ thereby increasing the antioxidant requirement for vitamin E.⁴⁵

Rarely does a single mineral deficiency develop without other nutritional deficiencies. A deficiency of synergistic vitamins may also be found with iron deficiency. Vitamins that are considered synergistic to iron are listed below.

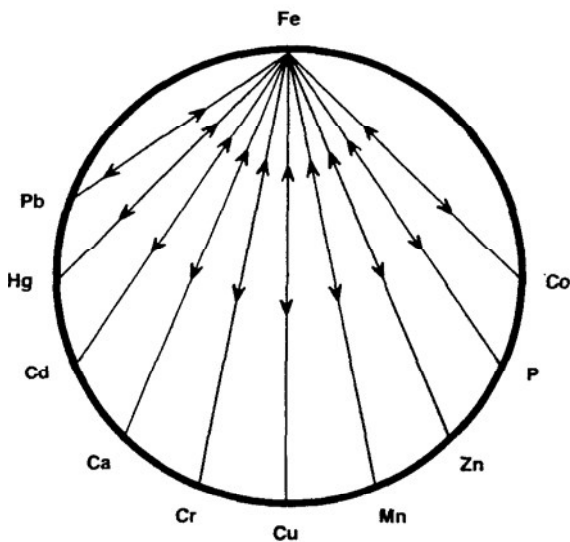


Figure 1.

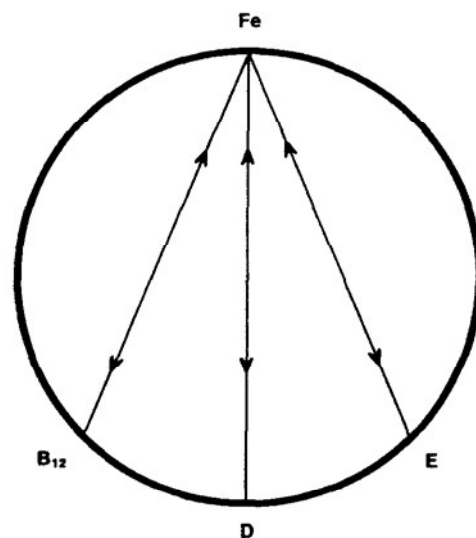


Figure 2.

Vitamins Synergistic To Iron

Vitamin E	Vitamin B ₆
Vitamin B ₁	Vitamin B ₁₂
Vitamin B ₂	Vitamin C
Vitamin B ₃	Vitamin A

A deficiency of one or combination of the synergistic vitamins can both lead to iron deficiency and may also be required to correct it.

Iron Overload

Acute iron toxicity is the second most common cause of accidental poisoning in small children as a result of consuming large quantities of iron supplements.⁴⁶

Fairbanks describes two types of iron overload. Hemosiderosis is described as a general increase in tissue iron without fibrotic changes. Hemochromatosis is more serious and describes tissue iron accumulation with fibrotic changes occurring in the liver, spleen, and pancreas.⁴⁷ Hemochromatosis and hemosiderosis develop as a result of such metabolic disturbances as hemolytic anemias, liver disease, multiple transfusions, and the ingestion of excess amounts of iron over a long period of time. Idiopathic hemochromatosis is apparently a hereditary disorder characterized by uncontrolled iron absorption. Iron overload affects men more commonly than women.

Factors Contributing To Iron Overload

The most well-known incidence of dietary iron overload has been reported in the Bantu Africans who consume large quantities of beer brewed in iron pots. The acidity of the beer leaches large amounts of iron from the pots resulting in daily intakes of iron of over 200 milligrams.⁴⁸ Cooking in iron skillets and pots can increase the iron content of foods prepared in them by as much as 3 to 400 percent.

Generally, excessive alcohol intake increases iron absorption, thereby contributing to liver cirrhosis commonly seen in alcoholics. The iron content of the liver in patients with cirrhosis can be several times higher than normal. The iron content of some alcoholic beverages is high, particularly in red wines and foreign beers.

Water is often a source of iron in regions with high iron soils. Iron water pipes are

also a source of iron, especially if the water being directed through them is acidic.⁴⁹

Herbs can contribute to high iron intake. Our analysis of some of the more common herbs has found the following significantly high in iron (above 50 mg%): Peppermint Leaves, Comfrey Root, Black Chohosh Root, Chickweed, Goldenseal Root.

As with other trace elements, iron absorption and retention may be affected by individual metabolic characteristics. As an example, iron absorption is increased in individuals who have a deficiency of pancreatic enzyme excretion.⁵⁰ Supplementation with pancreatic enzymes is known to decrease excessive iron absorption. Copper deficiency decreases iron elimination and therefore can contribute to increased tissue burdens.⁵¹ In the presence of a copper deficiency, excessive vitamin C intake can contribute to iron overload due to the ascorbic acid-copper antagonism, and the ascorbic acid-iron synergism. Any factor that antagonizes copper retention can potentially contribute to iron overload.

Conditions Associated With Iron Overload

In hemochromatosis, excess iron accumulation is known to deposit extensively throughout the body as hemosiderin. Most notably involved are the liver, heart, pancreas, joints, lymph nodes, and skin. Iron deposits have also been found in the anterior pituitary, thyroid, adrenal cortex, and brain.

Conditions commonly associated with excessive tissue iron accumulation observed through TMA studies include the following: Cirrhosis, Diabetes, Rheumatoid Arthritis, Allergies (Histamine), Migraines, Hypertension, Hyperactivity, Hepatitis (Bacterial), Chronic Infections (Bacterial), Emotional Disturbance.

Dexter, et al, reported their findings of autopsied brain tissue from individuals who died with Parkinson's Disease and a control group who had no history of neurological disease before death. Their results revealed a 35% increase of iron in the substantia nigra of the parkinsonian brain as compared to the controls. The copper was reduced by 34%.⁵³ They found that lipid peroxidation was increased in the parkinsonian nigral tissue, adversely

affecting dopamine-containing cells.⁵⁴ Since excess iron promotes lipid peroxidation and copper inhibits it, an imbalance of Fe/Cu may play a role not only in Parkinson's Disease but other neurological diseases as well. Excessive tissue iron or elevated Fe/Cu ratios have often been noted on TMA studies of patients with Amyotrophic Lateral Sclerosis (ALS). The future may reveal that conditions such as ALS, Huntington's Chorea, and others are conditions of free radical pathology, contributed to by excess tissue iron accumulation, copper deficiency, and other factors disturbing the balance of these trace elements.

Our observations indicate that excess tissue iron levels in patients experiencing hostility and aggression may be due to iron accumulation within the amygdala, an aggressive center. Stimulation of the amygdala produces aggressive behaviour, which could be mediated by iron-induced lipid peroxidation.

Conclusion

This has been a brief overview of iron and its involvement in metabolic processes. Since iron deficiency without anemia is more prevalent than iron deficiency with anemia, TMA may serve as a useful tool in evaluating individual iron status. As with other important trace elements, iron assessment should be evaluated in conjunction with its nutritional co-factors, either synergists or antagonists.

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