総 説
REVIEW ARTICLES

微量元素と貧血

前田 美穂

日本医科大学小児科

Trace elements related to anemia

Miho Maeda

Department of Pediatrics, Nippon Medical School
1-1-5, Sendagi, Bunkyo-ku, Tokyo, 113-8603 Japan

Abstract

Iron deficiency is the most common cause of anemia. Zinc, copper, manganese, molybdenum, and cobalt are also related to anemia. The body of an adult man stores approximately 4500 mg of iron. About 60% of this iron is in the form of hemoglobin, 20% is in the storage form of iron, 7% to 8% is contained in myoglobin in the muscle, and 12% to 13% is stored in iron-containing enzymes. The average amount of iron lost daily has been estimated to be approximately 1.0 mg in normal individuals. These losses are balanced by ingesting an equivalent amount of iron from the diet. Because of increasing iron needs of infants and adolescents during growth, and blood loss during menstruation in females, these patient groups may suffer from lack of iron, especially if they ingest inadequate amounts of iron from their meals.

Pica is one of the symptomes of iron deficiency anemia. Pacophagia is one of clinical manifestation of pica which is characterized by eating ice. Measuring serum zinc before and after iron treatment in patients with iron deficiency anemia, we observed decrease of zinc concentration in patients with pica whereas normal zinc concentration in patients without pica. However there was no significance between two groups.

Zinc deficiency leads to pathological signs related to impaired function of plasma membrane proteins such as erythrocyte plasma membrane. This impaired function causes hemolytic anemia. On the contrary, the excess of zinc also leads to anemia because suppression of iron absorption occur.

Hypochromic microcytic anemia has been observed in copper deficiency. Since the activity of cytochrome oxidase, which contains copper, decrease in this condition, iron will not be mounted in heme followed by anemia because of failure of iron reduction. Ceruloplasmin, which also have copper, make iron to combine with transferrin by converting ferrous iron to ferric iron through oxidative process. Therefore, lack of ceruloplasmin cause anemia similar to that in iron deficiency.

Key words：iron deficiency anemia, pica, zinc, copper, ceruloplasmin

Introduction

Although anemia has various causes, the most common one is iron deficiency. In addition to iron, several trace elements are involved in anemia, including zinc, copper, manganese, molybdenum, and cobalt. Some of these trace elements are thought to be associated with iron metabolism.

This review focuses on iron-deficiency anemia and discusses the relationship between anemia and other trace elements.

連絡先：〒113-8603 東京都文京区千駄木1-1-5
日本医科大学小児科

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Iron and anemia

Approximately 60% of the iron content of the body is in the form of hemoglobin (Hb), about 20% is in the storage form of iron, 7% to 8% is in myoglobin in the muscle, and 12% to 13% is in iron-containing enzymes. Iron undergoes closed transport in the body. About 4,500 mg of iron is present in an adult man, with about 3,000 mg incorporated in the hemoglobin within the circulating red blood cells, and about 1,000 mg stored in the reticuloendothelial system. In addition, the bone marrow, other tissues, and plasma contain approximately 150 mg, 150 mg, and 4 mg of iron, respectively. Approximately 1 mg of iron is absorbed from the daily diet, while about the same amount is excreted in the sweat, feces, and urine. Thus, most of the iron in the body remains in the red blood cells, and iron released when these cells are destroyed is re-utilized, thus maintaining the appropriate balance. The increased demand for iron that accompanies growth or the increased loss of iron that may occur with the onset of menstruation in females can upset this balance, causing the amount of iron in the body to become too low.

When iron levels are insufficient, the stores in the reticuloendothelial system of the liver are used first. Next, plasma iron levels decrease, while the level of transferrin (an iron-binding protein) increases almost simultaneously. Thereafter, hemoglobin levels decrease and iron-deficiency anemia occurs[1].

Generally, iron-deficiency anemia has a gradual onset, and symptoms do not appear in many cases until the Hb level falls below 8.0 g/dl. Symptoms of anemia include palpitations, shortness of breath, lassitude, fatigue, headache, dizziness, and sensitivity to cold. In addition, symptoms peculiar to iron-deficiency anemia include pica, glossitis, a smooth surface of the tongue, angular cheilitis, dysphagia due to formation of an esophageal web, achlorhydria, atrophic gastritis, spoon nail, and a decreased learning ability. The most common form of pica is pacophagia, which is defined as a craving for ice. Many patients do not realize that pica is a symptom of anemia, and there are almost no data about the overall frequency with which it occurs. However, pica is found in more than 50% of patients with iron-deficiency anemia. In zinc deficiency, the sense of taste is known to become abnormal, and Singhi et al. [2] reported decreased levels of zinc in patients with pica. We divided iron-deficiency anemia patients into groups with and without pica, and measured plasma zinc concentrations before and after treatment with iron supplementation. Plasma zinc concentrations before treatment were decreased in the group with pica, although differences between groups were not statistically significant, probably because of the small number of patients (total number of patients = 12) (Fig. 1).

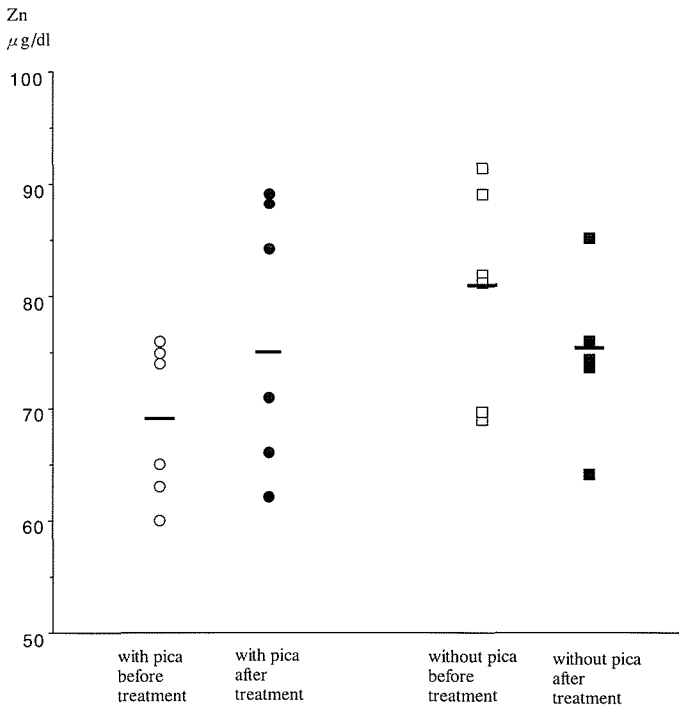

Fig 1. Zinc concentrations in patients with iron deficiency anemia

Although symptoms generally do not appear until anemia progresses, several symptoms (that the patients themselves remain unaware of) can occur when there is iron deficiency without anemia. These symptoms include a decreased ability to focus, excitability, diminished attention, decreased ability to learn languages, and decreased cognition. As iron deficiency is the causal factor of these symptoms, they are considered to be due to the impaired activity of iron-containing enzymes. For example, if there is a decrease of aldehyde oxidase activity, which is involved in the degradation of serotonin, the serotonin concentration of brain tissue increases, which leads to decreased regulation of emotions, impairment of mood and circadian rhythm, increased anxiety, and increased stress. In addition, there are enzymes such as monoamine oxidase for which iron is not a structural component but is still essential for enzymatic activity. When there is a decrease of monoamine oxidase activity, catecholamine metabolism becomes abnormal, which leads to diminished attention and excitability [3,4].

In children, iron deficiency is commonly seen in late infancy and adolescence. This occurs because of the increased demand for iron due to rapid growth in both periods. In the United States, it is reported that iron deficiency occurs in 9% of infants aged 1 to 2 years [5]. Our previous study showed that iron-deficiency anemia was present in 4.8% of infants aged 6 months to 18 months in Japan [6]. However, widespread testing of iron levels in young children has not been established in Japan, so the overall frequency of this disorder in children is unclear. On the other hand, during adolescence, when iron deficiency is common, testing for anemia in Japan is performed in junior and senior high school. Among males, the frequency of anemia in both junior and senior high school is 1% to 2%, a finding

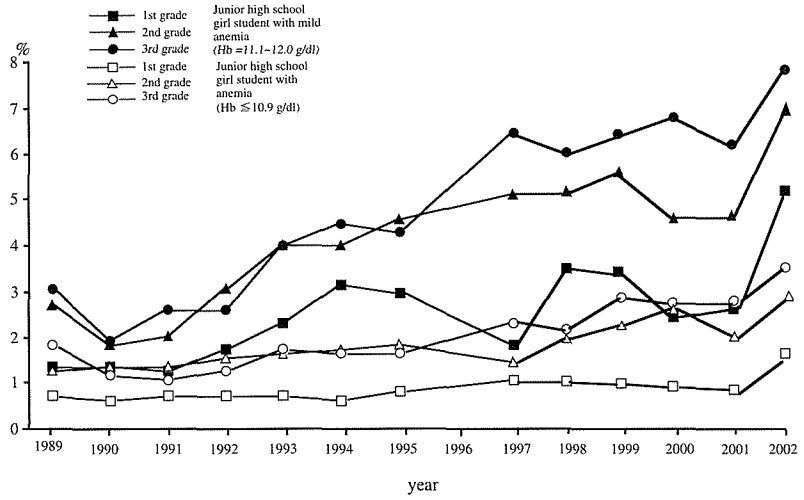

Fig 2. Changes in the percentage of junior high school girl students with anemia

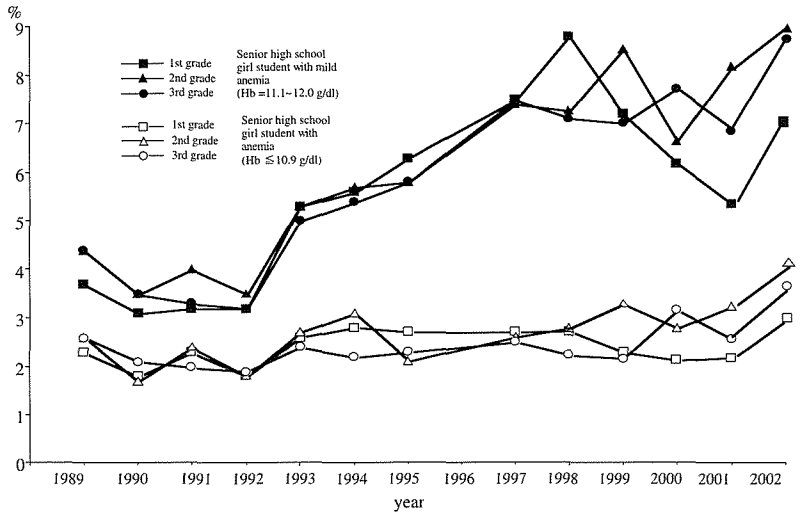

Fig 3. Changes in the percentage of senior high school girl students with anemia

that has not changed significantly over the past 10 years. However, in females, from 2nd grade of junior high school onwards, the frequency of anemia, according to World Health Organization standards, is 5% to 9%, and the prevalence of anemia has been shown to increase recently (Figs.2 and 3) [7,8].

Zinc and anemia

Zinc is present in red blood cells, white blood cells, and platelets, and is also found in various organs of the body. In addition, zinc is a structural component of many enzymes. In zinc deficiency, the resistance of the red blood cell membrane is weakened due to a decrease of sulfhydryl groups (SH; thiol), which are found in Na-K-ATPase and Ca-ATPase; this leads to hemolysis, which may be a causal factor for anemia [9]. Nishiyama et al. indicated that zinc deficiency could be a cause of sports-related anemia [10]. In addition, zinc deficiency leads to decreased activity of zinc-containing enzymes, such as DNA or RNA polymerase, causing impairment of nucleic acid metabolism that results in a decline of protein synthesis. It has been reported that anemia can occur as a result of reduced protein synthesis, but there is some controversy over this theory. It is also reported that patients with sickle cell anemia show a decrease in serum zinc concentrations [11], which demonstrates another link between anemia and zinc deficiency.

Excess zinc is also reported to cause anemia. Long-term use of zinc-containing medications has been reported to inhibit the absorption of copper, resulting in microcytic hypochromic anemia [12, 13] Excess zinc also inhibits the absorption of iron, which can lead to iron deficiency as well as copper deficiency [12, 14]. In addition, cases of sideroblastic anemia have been reported in association with excessive zinc intake [15].

Reports on the relationship between iron and zinc, particularly their intestinal absorption, have suggested that the absorption of zinc is compromised in the presence of iron [16, 17].

Copper and anemia

Ninety five percent of serum copper bind to ceruloplasmin which contains 8 copper atoms in each molecule. Ceruloplasmin has a ferroxidase action, oxidizing 2-valent iron to 3-valent iron, and it binds iron to transferrin. In addition, ceruloplasmin mobilizes stored iron and promotes the exchange of plasma iron. Thus, ceruloplasmin deficiency will trigger the onset of symptoms that are identical to those seen in patients with iron-deficiency anemia. Apart from the direct effects due to a lack of ceruloplasmin, copper deficiency also causes a decrease of cytochrome oxidase activity. This means that iron does not undergo reduction, so that its uptake by heme does not take place, and anemia occurs as a result. In the presence of copper deficiency,

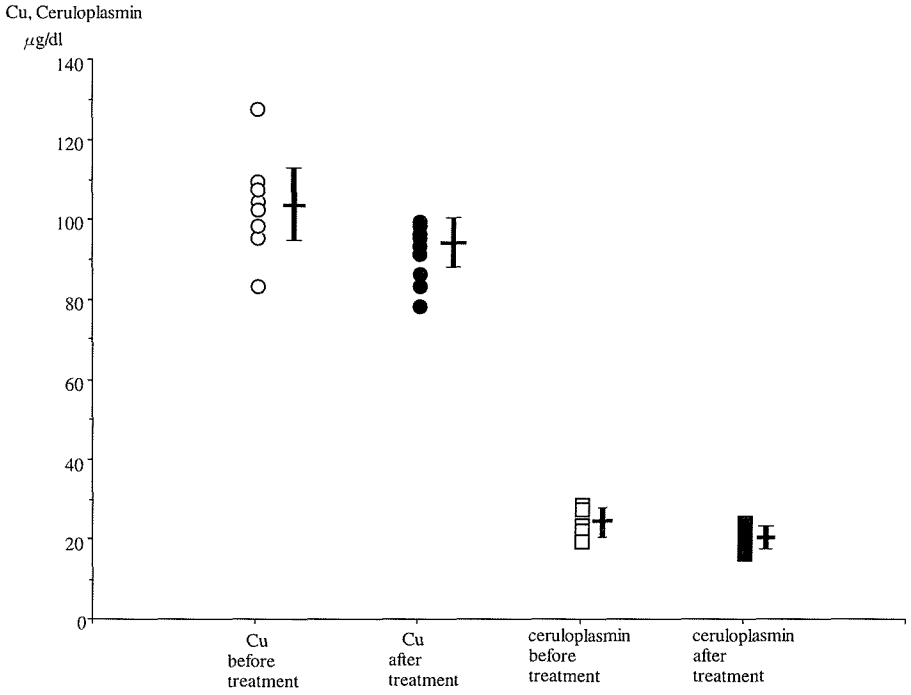

Fig 4. Copper and ceruloplasmin concentrations before and after iron supplementation in patients with iron deficiency anemia

iron is deposited in the mitochondria of bone marrow cells, resulting in an increase of ringed sideroblasts, which provides evidence of copper deficiency. Furthermore, the activity of superoxide dismutase, a copper-containing enzyme, decreases, which leads to impairment of red blood cell membranes due to oxidative damage. Thus, the lifespan of red blood cells is shortened, resulting in anemia.

Information about the effect of iron supplementation on other trace elements remains unclear. The relationship between iron-deficiency anemia and serum copper levels is also controversial [18]. We measured serum copper and ceruloplasmin levels before and after the treatment of iron-deficiency anemia, and found that serum copper levels were increased in patients with iron-deficiency anemia and that they decreased after treatment. However, there was no significant change in serum ceruloplasmin levels (Fig. 4). Previous reports on ceruloplasmin levels in the presence of iron-deficiency anemia are varied. When iron supplements are administered for anemia, the low ceruloplasmin levels also increase as the anemia recovers.

Manganese

Studies on manganese and anemia have shown that manganese absorption is increased by iron deficiency and decreased by the administration of iron supplements. In addition, administration of manganese has been reported to impair iron absorption and thus cause anemia [19].

Molybdenum

Studies on molybdenum and anemia have shown that iron-deficiency anemia is associated with molybdenum deficiency. Excess molybdenum decreases the availability of copper and promotes mobilization of copper from the tissues, which leads to copper deficiency and decreased ceruloplasmin synthesis, resulting in anemia [20].

Cobalt

It is known that cobalt and iron compete for intestinal absorption, and intestinal absorption of cobalt is said to increase in the presence of iron deficiency. Although cobalt is a component of vitamin B12, the relationship with abnormalities of this vitamin is not clear. Cobalt deficiency has been reported in the United Kingdom, Australia, and New Zealand. Anemia is one of the associated symptoms, and it can be either macrocytic or normocytic [21].

Conclusions

Iron deficiency anemia is the most prevalent anemia in young children and adolescents. Iron deficiency generally develops slowly and is not clinically apparent until anemia is severe (Hb levels fall below 8.0 g/dl). Pica, especially pacophagia, occurs more than half of iron deficiency anemia even though Hb levels dose not fall below 8.0 g/dl. The precise pathophysiology of pica is still unknown. We measured plasma zinc level in iron deficiency anemia with pica and without pica before and after iron supplementation. Plasma zinc concentrations before treatment were low in the group with pica, although differences between groups were not statistically significant, probably because sample size was small.

In addition to iron, several trace elements are involved in anemia, such as zinc, copper, manganese, molybdenum, and cobalt. Some of them are thought to be associated with iron metabolism. For example, the excess of zinc leads to anemia because the suppression of iron absorption occur. Ceruloplasmin contains 8 copper atoms in each molecule and has a ferroxidase action. Thus, copper deficiency leads to anemia similar to that in iron deficiency.

I reviewed the relationship between anemia and the trace elements.

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