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LITERATURE REVIEW

Optimizing iron adequacy and absorption to prevent iron deficiency anemia: The role of combination of fortified iron and vitamin C

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Abstract

Iron is a vital nutrient to promote the availability of tissue oxygen, cell growth and control of differentiation, and energy metabolism. Preventing Iron Deficiency Anemia (IDA) is necessary because iron is vital to central nervous system growth and development especially in the first years of life. Iron-rich complementary foods are recommended in infants around 6 months of age because iron store is depleted. Better understanding of iron absorption process and factors affecting its absorption and bioavailability is necessary to prevent iron deficiency and can be a dietary strategy to mitigate iron deficiency. Meat and iron-fortified food are the main sources of iron in the diet, and it is essential to introduce supplementary food to improve iron absorption. Additional foods such as cereals, cow milk and soybeans such as phytate, polyphenol and calcium are inhibitors which require care to prevent IDA. Ascorbic acid is an effective iron-absorbing enhancer, which is useful to reduce the effects of any known nonheme iron inhibitor. In iron-fortified foods, combination use of vitamin C (ascorbic acid) is recommended in molar ratio of 2:1 (with cow's milk and low-phytate cereal foods) and higher molar ratio of 4:1 (with higher phytate such as soybeans).

Keywords iron, iron absorption, vitamin C, iron deficiency anemia

Introduction

Iron is a precondition for all human cells and is part of almost all the living cells. Iron is required to promote tissue oxygen, cell growth and the regulation of differentiation and energy metabolism. Body iron levels are mainly managed by controlling iron absorption in small intestine, enabling accurate absorption to match unregulated losses. Depending on physiological demand, mechanisms regulating iron absorption often allow appropriate increases or decreases. Iron bioavailability is also limited, which explains why people vary in iron and iron stores. Various abnormalities and diseases can also influence regulation of iron absorption rate and iron storage. Therefore, dietary iron absorption by the proximal intestine is regulated precisely by cellular and systemic factors to ensure adequate body iron levels.[1]

Body iron present at birth is necessary in the first six months of life for the physiological requirements of infants with an adequate birth weight. The infant relies quickly on readily absorbed iron. The body iron content could increase around 70% in between 4 and 12 months. The average dietary daily requirement for iron in 7–12 months age was at 0.69 mg. The requirements reduced after 12 months, an

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average 0.63 mg/day for a child aged 18 months. Breast-fed babies with adequate weight rarely experience iron deficiency by 6 months. However there is a rapid rise in risk for those who remain breastfed for the next three months when there is no rich supply of iron in other dietary products.[2]

The World Health Organization estimates that an iron deficiency anemia (IDA) is an estimated 25 % of the world population. Most of this anemia due to lack of iron diet, but iron absorption and available iron can also be reduced due to infectious diseases and other chronic inflammation. Micronutrient deficiency is found worldwide, and iron deficiency (ID) is the most common. Young children have higher risk since they need high iron requirements to grow. Some risk factors include higher IDA prevalence, underweight baby birth, excess cow's milk, small intake of iron-rich complementary foodstuffs, low socioeconomic status, and immigrants.[3]

IDA prevention is needed, since iron is important for the growth of the central nervous system mainly throughout the first year old. *In vivo* experiments have demonstrated that iron is important for several brain development aspects, eq. Myelination, activity of the neurotransmitter, neuronal and glial energy metabolism and dendritogenesis of the hippocampus.[4] Some studies show strong correlation between infancy IDA and long-term low cognitive and behavioral performance. Children with IDA also have long term behavior issues such as discomfort, reluctance, and outsourcing and internalizing problems. ID without anemia was suggested to be correlated with poor cognitive/behavioral results, but this needed further research. There is still a lack of research connecting dose-by-dose indicators with later cognitive outcomes.[3,5]

ID and IDA risk factors in infants include birth weight underweight, early cord clamping, male, low socio-economic status, low intake of iron ingestion and iron fortified foods and excess consumption of milk from cows. [3] In Indonesia, several problems with hygiene and chronic infection worsen. Suggested ID prevention interventions are supplementation during pregnancy and infants, delayed umbilical cord clamping, meat products, cow's milk avoidance formula with fortification and/or complementary food, also iron-fortified milk use. A meta-analysis shows that iron supplementation has a modest positive effect on mental development and motor development.[3,6]

To prevent IDA, it is important to uunderstand the sufficiency of iron and how to improve it. High iron intakes can adversely affect iron adequate infants, so it is crucial to diagnose iron status in young children and understand intervention strategies such as enhancer or iron absorption inhibitors to achieve optimum iron adequacy.

The importance of iron adequacy and its challenges

During early infancy, the small iron in human milk meets iron requirements. Iron is found mostly in hemoglobin in the neonate, but a healthy infant has iron stores that depict 25% of total body iron. At birth, newborn goes to transition from hypoxic environment in the uterus to rich oxygen environment. This transition stopped hemoglobin synthesis and reduced hemoglobin to 120 g/dL in 6 weeks infants. Recirculating iron in erythrocytes is transferred to iron storage augmenting it size. After 6 weeks, iron is transferred back from the storage to blood as the infant continue to grow and expand their blood volume. This regulation maintains infant iron levels by themselves when they most needed it to grow at around 4 to 6 months of age. Exclusive breastfeeding during this period are adequate to fulfill iron requirements eventhough breast milk have low iron concentrations.[3]

Between age of 1 and 6 years old, the body iron content is again doubled. Between the age of 6 and 24 months, infants rely on complementary dietary iron and, due to higher requirements in growth than during any other lifespan. Iron levels between 6 and 24 months needs to be doubled from 300 mg.[3] Growth spurt in adolescents are also the time in need of more iron. Girls usually spurt before menarche, but boys shows increased hemoglobin concentration during puberty which marked rise of iron requirements.[7]

The iron role in brain development has been revealed by over 50 human studies, including observational studies, supplementation and iron therapy studies. The development of normal fetal brain anatomy, myelination, and dopamine, serotonin, and norepinephrine systems is important

with iron. The sooner the brain is prevented from being inferior to iron the better for instance, in prenatal and early infancy. Various findings have indicated that mothers who had iron supplementation during pregnancy, their children achieved better in multiple intellectual, executive, and motor tests than placebo. Moreover, mistimed or excessive iron can lead to worse neurodevelopmental outcomes, as shown in a decade follow-up study in a Chilean iron baby supplement. In the study, children aged 6 months receiving iron-enforced formulas with high haemoglobin performed in a series of neurodevelopmental tasks much poorer 10 years later and children receiving iron-enforced medicines with low-hemoglobin performed much better. These results emphasize that the nutrient benefits differ at one dose and can be toxic at another.[8]

The role of iron in neural transmitter synthesis makes it antenatally and postnatally important for brain development. Iron also alters brain epigenetic landscape. Iron deficiency could result in reduced myelin development, decreased synaptogenesis and decreased basal ganglia performance, adverse development of psychomotors and mental capacity.[5] Some research suggests that anemia is correlated with poor cognitive functions such as concentration, intelligence, memory and learning skills. A research by Hurtado et al. (1999) showed that the risk of moderately mentally delayed children below the age of a decade with IDA was increased. It was not based on maternity, gender, nationality, birth weight, social class, age and education. Children with hemoglobin below 100 g/dL with an IDA have a low score for international primary school development rates. These results show how important childhood anemia is to be monitored.[9]

Emotional and psychological behavior are also affected by iron deficiency. This linked to persistent changes in dopamine metabolism, GABA, function and structure of the hippocampus, and myelinization. Studies also shown that early iron deficiency can significantly impact cognitive and behavior also irreversible disturbance in motoric. Other consequences of iron deficiency anemia is extensive such as poor growth and development which also school accomplishment.[10] It is therefore important that the iron deficiency is monitored and detected as soon as possible.

It is critical to meet the daily intake of iron as the impact of iron deficiency on brain development may be irreversible. Recommended daily intakes of iron are as follow: 11 mg for 6 to 11 months, 7.0 mg for 1 to 3 years, 10 mg for 4 to 6 months, and 10 mg/day for 7 to 9 years.[11] This recommended daily intake (RDA) for children is directed towards children after 6 months as many authorities recommend exclusive breast feeding, but exclusive breast feeding after 6 months is strongly related to IDA. The iron-rich complementary food is recommended to avoid iron depletion after six months of age. This comprises meat, iron-enforced follow-up formulas and other iron-enforced products, such as cereals. There is some evidence that enhanced formulas reduce the risk of anemia in comparison with pure cow's milk (unmodified). Pure cow's milk should be avoided in infants under 12 months of age.[3]

In order to prevention ID and IDA in children, the early introduction of these iron rich additional foods such as meat and iron-fortified foods is likely to be important. Several analyses have assessed the effects of complementary iron-fortified foods on iron conditions in children. Iron-fortified complementary foods (6.2 g/L higher than controls) significantly affected hemoglobin. It is shown to reduced risk of anemia (defined as Hb<105 or 110 g/L), by 50% (95% CI 0.33–0.75) with complementary, iron-fortified food. High-meat supplementary foods are shown to improve hemoglobin. One study shows that a substantial meat intake affects the status of iron like iron-fortified cereals, even though the cereal group's daily intake is about five times higher. This is compatible with previous studies which show that the absorption of iron from meat is multiple times higher than cereals.[12] Supported by evidence, the European Society for Hepatological and Nutritional Paediatric Gastroenterology (ESPGHAN) recommends that all infants 6 months and older should be given supplementary food rich in iron (meat products and/or iron-enforced foods).[3]

Since the focus of ESPGHAN recommendation is on nutrition, the family availability of meat products, a low socioeconomic status, especially in Indonesia, is more sensitive to unmet iron adequacy. Indonesia is a low-to-middle-income country; in 2017, 10.6% of its population remained poor.

Poverty is the main cause of most undernutrition, such as iron deficiency. Children and adolescents with poor socioeconomic status are more vulnerable to iron deficiency due to low intake of iron, mainly eating plant-based diets (predominantly non-Heme iron sources) and low-level iron diets (mostly tofu or tempeh eating, which may inhibit iron intake), which are further compounded by chronic blood loss due to parasite and malaria infections. Other factors like chronic menstrual loss of blood and gastrointestinal iron malabsorption can cause IDA in older children and teenagers.[6]

The main goal of adequate iron intake is to prevent childhood delays and cognitive impairment. Iron is well absorbed in human milk but not enough to satisfy the needs of infants for 6 months old. Additional foods besides human milk must be developed to accommodate the needs of the child without replacing human milk. As additional foods are intake limited especially when the iron requirements are highest, it is crucial to provide the iron in a highly bioavailable form. Iron rich supplementary foodstuffs (meat products and iron-fortified foodstuffs) are recommended in infants after 6 months, but in the low socioeconomic status families this challenge is obvious.[3]

Iron absorption to achieve iron adequacy and how to obtain it

Most iron absorption takes place in the small intestines through polarized intestinal epithelial cells or enterocytes. Iron absorption is performed via divalent metal conveyor 1 (DMT1), member of the transported membrane protein solution carrier group. It is then transferred into the blood through the duodenum mucosa to produce red blood cells (RBC) in the cells or in the bone marrow. Feedback mechanisms are in place to improve the absorption of iron in iron-deficient individuals. Hepcidin is one pathway of reducing iron absorption in people overloaded with iron. Ferroprotein is also known to control iron absorption from the mucosal cell into the plasma.[7]

The iron state in the duodenum influences greatly its absorption. The iron ferrous (Fe^{+2}) is quickly oxidized to the ferrous insoluble (Fe^{+3}) at the pH of physiology. Gastric acid lowers the proximal duodenum pH.[13] This improves the solubility and absorption of iron ferric. When the production of gastric acid is impaired, the absorption of iron decreases considerably. Dietary heme can also be transported by unknown mechanisms via the apical membrane and subsequently metabolized by heme oxygenase 1 (HO-1) in enterocytes to release Fe^{+2}. This process is more efficient than inorganic absorption of iron and is pH-independent.[14]

Two forms of dietary iron are heme and nonheme. Hemoglobin and myoglobin from animal meat (cow, chicken and fish) are the primary sources of heme iron, while nonheme iron is made from cereals, legumes, fruit and vegetables. In contrast to heme iron with high bioavailability (15-35%) and unrelated nutritional conditions, non-heme is easily altered by other food elements and less bioavailable (2-20 %). This magnifies the problem as the amount of non-heme iron is plentiful in most meals. Iron nutrition is more influenced to non-heme iron intake than heme-iron despite the low bioavailability of nonheme iron.[15]

Animal meat contains well absorbed heme and promotes further absorption of iron from the diet. Vegetables, however are rich in factors which inhibit non-heme iron absorption. If the gastric juice can pass through a meal containing nonheme iron, it goes into a common pool. The interaction of iron in that pool is more absorbed than the others by iron inhibitors or enhancements in other food components. Vegetable foods, especially in developing countries, have inhibitory factors. Phytates in cereal grains, peanuts, and polyphenols in tea, coffee, cocoa, and certain vegetables and grains are the most important. The absorption of nonheme iron is reduced by calcium ,vegetable proteins and animal protein other than its flesh.[7]

Increasing iron needs after 6 months of age can be replaced by complementary food, but promoting breastfeeding remains the main nutritional intake during infancy and early childhood. It is important to make sure that supplemental with additional foods do not replace human milk. Iron source that used in fortification must be readily available because the quantity of complementary meals are small.[2] The incorporation of meat or fish products should be encouraged where possible due to their heme iron's high bioavailability. 25-50 % of the iron provided as heme is expected to be absorbed in children because

they don't have any significant iron storage.[15] Methods to enhance non-heme iron bioavailability are therefore important, particularly for complementary foods used in cereals. The balance between different dietary factors in weaning foods that influences iron bioavailability must be examined in order to identify ways to improve iron balance during the weaning period. Recent studies showed that increased meat intake in the weaning period is associated with better iron nutrition. Infants are unable to chew properly thus providing infant with meat and in a form that can accommodate this problem is tricky. Fine ground form of meat in weaning foods are expected to have a favorable effect in maintaining iron balance. Generally, prolonged breastfeeding during weaning can provide a small bit of iron but has other benefits.[12]

Some dietary factors that increase iron absorption, such as fructose, copper, vitamin A and β-carotene, major enhancer of the absorption of all ascorbic acid, are also noted for further strategies to enhance iron bioavailability.[1] Contrary to the striking effect of ascorbic acid on iron absorption, it was debatable to improve iron condition in extended vitamin C supplementation.[16]

Vitamin C and its Role in iron absorption

Ascorbic acid is the most effective iron absorption enhancer. Moore and Dubach (1951) first demonstrated ascorbic acid's enhancing properties. They reported dose-related enhancing properties and dependent on ascorbic acid in the upper gastrointestinal tract lumen. Ascorbic acid acts as a common nonheme pool ligand, increasing the absorption in gastric fluid of both innate food iron and iron fortified food. It works only when it is eaten with food. In a report, 500 mg ascorbic acid taken with the test meal was absorbed six times, compared to a low absorption in 4 and 8 hours before meal with the same quantity.[2]

The effect of all identified inhibitors of nonheme iron absorption including phytates, polyphenols, calcium, vegetable and certain animal proteins is useful in reducing ascorbic acid. Cereal grains, cow's milk and peanuts (especially soybeans) are generally used as supplementary foods in developing countries. Food sources and additional food can be combined.[12] Phytate is the major inhibitor of iron absorption in cereal foods and is expected to be the main inhibitor of these foods. Ascorbic acid reverses the inhibitory effects of phytate. Interaction among phytate, ascorbic acid and iron interest researchers in order to develop effective early childhood fortification strategies with specific recommendations for phytate removal and ascorbic acid addition to the cereal complementarity foods.[17]

Cook et al.[18] more rigorously evaluated ascorbic acid efficacy to improve iron absorption from several different cereal grains. From a practical perspective there is a need to measure how much iron is absorbed from complementary food such as cereal under optimal conditions. This measurement predict how much ascorbic acid are adequate to even lowest phytate level. Full-term infants averaging 32 weeks absorbed iron 8.5% of low-phytate meal from wheat flour and grain enhanced with 2.7 mg iron sulfate and ascorbic acid (ascorbic acid molar ratio to iron, 2:1). The food included 25 g of cereal. Lynch [2] stated that in food containing phytate (70-140 mg/d in additional products designed to supply enough of iron to meet the average calculated breast-feeding requirements) the molar ratio between ascorbic acid and iron should be between 2:1 and 4:1.

Human milk is better absorbed than cow's milk. The reason is that the milk of cows is higher in calcium and the milk protein prevents the consumption of iron. The addition of ascorbic acid is shown to improve iron in the cow's milk or cow's milk-based formula significantly. The addition of ascorbic acid to cow milk containing sulphate ferrous in a concentration of 100 mg/L (ascorbic acid-iron molar ratio, 2:1) increased absorption approximately double. Soybean protein is different for complementary foods or for milk with lower iron absorption. Studies show that more ascorbic acid is needed to ensure adequately bioavailable iron in complementary soy foods than in cow's milk or cereal-based foods. The molar ratio of 4:1 ascorbic acid to iron should be used when weaning high amounts of soy bean protein products in high phytate cereals, cerenic foods containing polyphenols or complimentary foods.[2] Iron level in human milk is very small and so it is important to have iron fortified foods with high bioavailability. The Estimated average requirement (EAR) and

Recommended Dietary Allowance (RDA) iron requirements for infants aged 7 to 12 months are 6.9 mg and 11.0 mg for selecting the iron fortification content in supplementary foods of all children. Noted that complementary foods used in developing countries are less bioavailable. The fortification iron is required at 170 μg/g for meeting the EAR and 275 μg/g for meeting the RDA for infants aged 7-12 months (daily consumption, 40 g). For children aged 13-24 months (daily use, 60 g) 115 and 183 μg/g are required, respectively.[19]

We can conclude that enough iron fortified in additional food should be added to ensure the infant's diet. Ascorbic acid is useful in reducing the effect of nonheme absorption inhibitors in cereals, soya, polyphenols and calcium in cow's milk, for example. Experimental studies have shown that absorption levels of approximately 10% for cow's milk and low-phytate or dephytinized grain foods can be anticipated if the iron molar ratio of 2:1 in ascorbic acid is increased by ascorbic acid and ferrous sulphate, while a molar ratio of higher 4:1 is required if inhibitors foods such as soya are used.

Conclusion

Iron belongs to nearly all living cells and is a necessity for all human cells. IDA prevention is important because iron is critical to the growth and development of the central nervous system, especially during the first 12 months of age. In infants around 6 months of age, iron rich supplementary food is recommended because iron shops are depleted. Meat and iron-fortified foods are the main iron sources of dietary use and it is essential to introduce complementary foods early to improve iron absorption. Ascorbic acid is a good iron absorption promoter and is useful to reduce the impact of all known non-hemic iron inhibitors that can help prevent IDs. Foods like cereal, cow's milk and soya contain iron inhibitors such as phytate, polyphenol and calcium. It is recommended that the molar ratio of ascorbic acid 2:1 (for cow's milk and cereal products) and the higher molar ratio 4:1 be added to the ratio (for higher phytate, such as soybeans).

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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