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LITERATURE REVIEW

The role of iron for supporting children's growth and development

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Abstract

According to the World Health Organization (WHO), Iron Deficiency (ID) affects around 2 billion people worldwide. Early childhood ID has been associated with permanent cognitive deficits associated with CNS structural, metabolic impairment, growth retardation, impaired immune response, psychological abnormalities, and behavioral delays. This literature review will focus on the important role of iron in child growth and development.

Iron is necessary for various cellular processes in the growing brain especially when it comes to memory and learning. Children with early ID show cognitive deficits that persist; however, prompt iron treatment soothes the problem. A chronic ID group reported substantially lower scores of vocabularies, ambient sound perception, and motor measurements in a recent study relative to infants with normal nutritional iron status at 6 months and 14-18 months. Children's iron requirement differentiates based on individual age. The daily iron requirement for one- to three-year-old children is 7 mg. Some risk factors of infants and toddlers in developing ID are insufficient food intake, poor bioavailability, reduced absorption, increase demand, increase losses, cow's milk enteropathy hookworm infection, and maternal gestation.

Iron plays an important role in promoting children's growth and development. Physical health and nutrition are important in the first two years of life. Children who are unable to achieve iron adequacy will possibly show permanent cognitive deficit and impaired motor growth. Thus, iron supplementation may only be successful in early prescription after diagnosing iron deficiency.

Keywords iron, children, growth and development

Introduction

Every child has the right to gain optimum cognitive, social and emotional behavioral development. Children who have yet to meet their developmental and growth potential are likely to experience problems in school and lower their lifetime income, resulting in greater socioeconomic inequality and leading to more generational poverty.[1,2] It is widely accepted that health and nutrition are important in the first two years of life. This period is the window of opportunity that may also be ideal for mental growth, because the brain's intellectual potential reaches its greatest extent before the age of three years.[1, 3]

Nutritional deficits which affect brain growth and cognitive function have been shown to reduce global IQ by at least 10 points. Iron deficiency affects more than 2 billion people around the world. In preschool children, the prevalence rate is highest among 4- to 23-month-old (47.4 %). Iron is essential for the growth and the differentiation of different tissues. The neurons and brain tissue in the developing fetus and newborn are more sensitive to the lack of nutrition than the brain in later childhood and adulthood.[4]

Early childhood ID has been linked to many consequences, some of which have been potentially

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permanent cognitive deficits associated with structural and metabolic impairment of the CNS. Neuropsychiatric symptoms are of utmost concern even though they take place after treatment with iron and anemia.[4,5] A few medical sequences are linked to ID. These include impaired immune response, poor temperature control and compromised growth. In general, emotional regulations and affective responses are present in the literature as mental and physiological abnormalities or delays which follow ID; impaired motor growth and fine motor control; general and unique cognitive delays.[6]

The review of relevant literature will address the role of iron in children's growth and development, its effects on ID, and who are at risk of it. We also present a range of recommendations for iron consumption, how to fulfil the iron requirement in children, and recent research on the role of iron in children.

The role of iron for supporting growth and development in children

Iron is required to produce energy and cellular metabolism. For many mitochondrial enzymes, iron is an important mineral integrated for the development of oxidative phosphorylation and ATP, including cytochromes, NADPH and flavoproteins. Iron encourages cells to proliferate and grow through ways such as improving oxygenation and hemoglobin levels, and growth factors such as growth factor-1 (IGF-1). Iron deficiency anemia (IDA) induces a hypoxic condition in the body which consequently inhibits liver growth hormone, insulin-like IGF-1, and IGFBP-1. Stunting suggests both a sequential failure in development and a low total childhood iron status. The cause of stunting is diversified, but most include under optimal impact of infant and young child feeding (IYCF), infections and inadequate healthcare practices.[4,7]

Not only for physical growth, but iron is also required to sustain neuronal production and synaptic activity. At birth, the brain is made up of 50 % of the resting metabolic capacity. More than half of the energy used in the brain comes from what is required to maintain the Na^+, K^+, and Ca^{2+} gradients necessary for synaptic transmission. When creating and sustaining complex neuronal structures, a lot of energy is needed. A large amount of iron is required for multiple biological processes in the developing brain by incorporating iron into heme-containing proteins and non-heme iron-based proteins (e.g. hydroxylases, iron regulatory proteins, and enzymes involved in the metabolism of nucleic acids).[4]

Several studies have shown the negative effect of ID on learning and memory, behavior, affective and social behavior. In humans, late gestation through 2-3 years of age is associated with maternal iron deficiency which causes learning and memory deficits which persist beyond the time of maternal iron treatment. There are two types of memory: explicit and non-explicit (or implicit). Declarative memory is information and events that a person can consciously remember. Non-declarative memory refers to memory for tasks or skills that don't need to be consciously remembered. Neural structures responsible for long-term and short-term memory are intricate with multiple connected areas. Many factors can influence the proper growth and development of the brain such as growth factors, synaptic activity, and climate. As the hippocampal memory growth accelerates, it becomes most vulnerable to develop early IDs during gestation through age 2-3 years. During the developmental period when humans are most vulnerable to memory impairments, hippocampal function is at its peak. The hippocampus is responsible for memory formation and processing. Studies have shown that the hippocampus is especially vulnerable to early ID damage. The fragility is largely due to rapid maturation during the late fetal-neonatal phase in human and animal trials, which are iron-deficient. Early-life ID's impair brain function due to defects in iron-containing proteins.[4]

Observational research found relationships in children with low cognitive growth, poor school performance, and behavioral problems. Several possible pathways connect iron deficiency anemia (IDA) to cognition. Children with IDA tend to not move about or explore their world, which contributes to developmental delay. In children with IDA the neural transmission of auditory and optic nerve impulses occurs at a slower rate. A study demonstrated an association between changes in nerve myelination and deficiencies in iron status.[8] Behavioral issues are hypothesized by decreasing Da-Dd2 (dopamine Dd2) receptor functional activity. One of the main consequences of iron deficiency was the reversal of circadian pain threshold cycles, stereotyping, motor function, and thermoregulation. Beaton study from iron in the infant diet book concluded that circadian cycles of hemoglobin, hematocrit, serum iron, and transferrin saturation in male and female rats are consistent. The blood index levels are also age dependent. In normal populations, these levels at 0-13 years of age are higher than 14-20 years of age, and they rise later in life. Some researches have found that anemic infants were less sensitive to the examiner, their mother, and other people. In general, they were unhappier, less goal-driven, less attention spans, less verbal, and less moving.[9]

Impact of iron deficiency in children

Disruption of the supply and demand of fetal iron early in life results in total body and/or tissue-specific ID. There is a compelling evidence that infants (6-24 months) with intellectual developmental disorder are at risk of poorer short- and long-term development. Children with early ID show cognitive deficits that persist; however, prompt iron treatment soothes the problem. [4, 10] Changes in the mesolimbic pathway, where dopamine plays a critical role in behavior, can help explain altered socio-emotional activity in iron-deficient infants.[10]

A chronic ID group exhibited significantly lower scores on vocabulary, ambient sound perception and motor measurements in comparison to infants with regular dietary iron status at 6 and 14-18 months. Results from this study found that cognitive and motor functions were significantly reduced due to prenatal exposure to ID. Iron deficiency anemia slows down cognition in infants while limiting brain lesions. Children and teens who smoke often have impaired fine-motor skills and have weak gesture apraxia.[9]

For instance, 9- and 12-month-old children with IDA who have a short-term impact show a degraded memory processing. Iron-deficient diabetic mothers' new-born babies show diminished auditory memory of the mother's voice. Long-term effects of iron deficiency in children is that the deficiency of 3.5 years of age has impaired memory recall during imitation activities, and the degree of memory and learning dysfunction is directly associated with the degree of ID at birth. Low iron stores in 5-year-old children can affect how the children develop in terms of cognitive skills, fine motor skills, and problem solving. Children with IDA have lower psychomotor development scores, increased frequency of school grade repetition, reduced visual memory output, and increased anxiety, social issues, and attention problems as young as 11-14 years. These brain function defects persist despite the normalization of iron status in early childhood.On the other hand, 3.5-year-old children who have been iron-deficient at birth showed poorer memory performance during incited impersonation activities, and their degree of learning and memory deficiency was directly associated with the level of birth ID. At five years of age, children born with insufficient dietary iron showed a decline in language development, fine motor skills and handling ability which was not observed in children born with sufficient iron stores. As early as 11-14 years of age, children suffering from IDA had lower psychomotor development scores, increased frequency of grade repetition, reduced visual memory output, and increased problems with anxiety and attention, compared to those who were iron-deficient as babies. These cognitive defects persist into adulthood despite iron levels normalizing in early childhood.[4]

Recent studies on iron role for supporting growth and development in children

Jáuregui-Lobera's studies demonstrate that harmful effects occur with ID, including cognitive deficit, actions and motor skills impairment. External variables such as socioeconomic status can confuse the causal relation between ID and the negative results. Iron deficiency, iron deficiency anemia, and non-iron deficiency anemia lead to certain cognitive deficits although it remains unclear if these deficits are the same. These cognitive deficits can happen at any time. Hemoglobin levels appear to indicate cognitive efficiency, but at the same time iron supplementation can enhance cognitive function regardless of hemoglobin levels. The ID hypothesis is linked to the brain damages such as changes to the hippocampus, mitochondrial damage, brain dopamine metabolism, and myelination. Supplements should be used only based on established indications, as not to abuse regular use. Using multi-supplements does not seem to add value compared to using individual supplements. Supplementation progress could be dependent on early prescription after diagnosing iron deficiency. Whether this supplementation is effective or not remains controversial, depending on therapy timing (e.g. critical periods).[10]

Iron deficiency (ID) may alter basal ganglia function, resulting in changes in dopaminergic activity causing reduced motor cortex myelination and related areas. Some of the processes underlying the processes arise late in pregnancy and early in infancy. Samantha McCann et al. found early childhood iron supplementation to be beneficial in promoting motor growth, but this effect may be minimized during later childhood. Their findings support the timing hypothesis and indicate that infant iron nutrition may be particularly relevant for motor development.[11]

Ana Ferreira *et al.*[12] revealed that iron deficiency and impairment correlated with motor and cognitive disability and changed social functioning. Studies showed that iron interventions could only effectively correct altered iron levels but failed to reverse cognitive or behavioral changes. The shortcomings of intervention studies was illustrated by claiming that iron dysregulation cannot be reversed by intervention. Cognitive stimulation and social interventions must be coupled with iron levels, a recommendation that is in accordance with findings from psychologists and sociologists.

David Mattei *et al.*[13] have proposed that early life environments, especially the fetal and early post-natal environment, affect health outcomes and risk of disease in multiple organ systems later on. Nutrition plays a central role in all environmental factors. The basis for lifespan functions is formed from conception to approximately 3 years. Well-nourished children are more likely to have positive social repercussions in their cognitive, motor, and socio-emotional capacity. Early exposure to these skills is essential for future neuropsychological disorders, mental diseases, poor school performance, early school dropout, low-skilled jobs, and poor care of future children. Epigenetics is the leading theory for the long-term effects of early environment, especially early childhood.

Required daily iron intake for children by stage

In the 1950s, studies of body iron in the human body found that the very first body iron is around 75 milligrams per kilogram at birth. In normal birth weights babies, there is most of the body's iron in the blood hemoglobin, but some is also contained in the body's stable term infant, normal birth weight equivalent to approximately 25 % of the body's iron. [14] When iron is recirculated from senescent cells by erythrocytes, it is moved from hemoglobin to iron stores. For the next few months, as the baby develops and increases blood volumes, iron is carried into the blood cell from stores, making the baby self-reliant with iron until the baby doubles its birth weight at around 4-6 months. Even though exclusive breastfeeding may be deficient in iron of a low concentration, it is meeting the requirements of infant iron.[15]

From age 6 to 24 months, the infant is dependent on additional iron intake and the requirement for iron per kg of body weight is high as compared to any other lifespan due to rapid growth. According to previous studies, the total volumes of a person's total body iron must be double from 300 to 600 mg, assuming an average body weight of 7.5 kg at 6 months (or 70 mL/kg), and a 7 mg/kg (or 10 mg/kg) at 24 months. The theoretical requirement for iron is 0.076 mg/kg/day, but only 0.76 mg/kg/day is absorbed, which is less than half the required intake. After puberty, iron requirements are lower because an individual's body reaches a more mature stage of development. Various authorities recommended various daily intakes of iron, which are 6-12 months of 0.9-1.3 mg/kg, 5.8-9 mg at age 1-3, 6.1 to 10 mg at age 4-8 and between 9-13 years of age 8 and 11 mg/day.[15]

For children between 1 and 3 years of age the average RDAs in Europe are around 10 mg. Recommended iron for infant between 6 and 36 months of age is 7 to 8 mg per day in many European countries, including France, Germany, Italy, Spain, the Netherlands and the United Kingdom. Using the current analysis the estimated average (EAR) requirements for 6-12 months and 12-36 months are 6 mg/day and 5.3 mg/day and the intake of iron deficiencies for the 6-12 months at 7.8 mg/day and for 12-36 months at 6.9 mg/day in the United

Kingdom RDA.[16] The iron RDA in Indonesia is approximately 7 mg/day for 6-11 months, 8 mg/day for 1-3 years, and 9 mg/day for 4-6 years of age.[17]

Risk factors of inadequacy of iron intake

Infants and toddlers are at risk of developing ID. Here are some explanations about the risk factors of ID in children.

1. *Dietary inadequacy and low bioavailability.* Insufficient consumption in the developed world is the most common cause of malnutrition in infants. Iron is absorbed more effectively in infants fed breast milk than in infants fed formula milk. Therefore, the needed intake of breastfeeding infants is correspondingly lower. The iron found in cow's milk is less bioavailable. For adequate absorption of iron, one needs a diet containing a combination of meat, egg, fruit and vegetables.[14]
2. *Impaired absorption.* Malnourishment of proteins and energy may impede mucosal absorption, protein synthesis, exacerbation and deficiency caused in such children almost inevitably. Other disorders which are rare in infants include bowel disorders including celiac disease, inflammatory bowel disease, blind loop syndrome and gastric disease.[14]
3. *Increased demand.* Children have a high need for iron during their first year of existence and during rapid growth periods. Enough iron is available during a baby's early development to promote healthy development up to age 6. Children who are born prematurely will likely not have fully developed iron stores and may require additional iron. It is already well known that iron in milk alone is inadequate to sustain the continued rapid development of this child. Further dietary iron is necessary to avoid iron deficiency. Iron requirements are particularly high during a teenager's adolescent growth period.[14]
4. *Increased losses*. Iron deficiency results from blood loss. Chronic gastrointestinal failure in older children can also occur due to inflammatory bowel disease, which may be "silent" before anemia is progressed due to adaptation.[14]
5. *Cows' milk enteropathy.* Colitis in infants can occur in those fed on cow's milk, or in those fed on cow's milk-derived formula. The occult blood loss has a major impact on the iron reserves of younger babies. Studies show that the amount of occult blood decreases at a steady pace until it is essentially gone by age one. For one reason, it is recommended that children should not be fed whole cow's milk until after the first year. The only two good substitutes are iron-fortified formula or breast milk.[14]
6. *Hookworm infection*. Hookworm infection is caused by *Ascaris lumbricoides or Ancylostoma duodenale*, which affects 1 billion people worldwide. Eggs released through the digestive tract hatch into larvae that can survive for three weeks before humans come into contact with them when walking through polluted soil. The larvae enter the lungs via the respiratory vasculature, climb into the bronchi, and enter the larynx via the epiglottis. The larvae develop into the adults in the small intestine where they attach and feed off from the hosts. Adults worms are capable of living for 2 years or so. With a chronic lack of blood, an iron deficiency is observed. The prevalence of hookworm infection increases as one approaches adulthood, reaching a plateau in late adolescence.[14]
7. *Maternal gestational complications.* Neonates may also have impaired iron status due to extreme maternal ID, uncontrolled diabetes mellitus, high blood pressure, smoking, infection, placental insufficiency, premature birth, and rapid fetal development.[4]

How to meet iron intake adequacy

There is a responsibility to ensure adequate access to food that is rich in iron. Iron enrichment of agricultural crops (rice, maize, flour, cornmeal) is also practiced in some countries, including Asia, Africa and Latin America, and is suggested by the World Health Organization. For infants 6 to 23 months, the WHO recommends that the supplement to prevent ID/IDA should be 10-12.5 mg of iron per day (drops, viscous recipes or tablets), and children between 5 and 12 years of age should receive 30-60 mg of iron per day (tablet or capsule) for three months per year.[18] WHO recommends that all children between the ages of 6 and 23 months living in areas where the prevalence of anemia exceeds 20% should be given fortified complementary foods.

Minimal Nutrient Platforms (MNPs) are single-dose containers of liquid-coated iron paired with other micronutrients that can be blended into food to provide micronutrient intake. MNPs are emerging as the preferred community-based solution to address iron deficiency in children; Over 16 million children were treated with MNPs in 2017.[19]

Iron levels are low in human milk, but absorption is high. Exclusive nursing delivers high levels of iron during the first few months of life. After the second half of the first year, human milk cannot meet the increased iron needs; rather, iron-fortified formulas must be used. Using infant formula can also help mitigate this type of issue. In developing countries, there are numerous additional foods that can be added to the infant diet for about 6 months. However, they are usually low in iron and do not replace the iron that is depleted in breast milk.[6] Currently, about 45% of children under 5 years old have ID with anemia while the number is less than 7% in developed countries. From two years ago until the present day, an estimated 2 % to 6 % of European children are affected. The introduction of enriched food and supplements led to this reduction.[10]

Premature babies (less than 37 weeks in gestation.) who are exclusively breastfed should receive 2 mg of elemental iron supplementation each day from birth until at least 12 months of age, except for those who have received multiple blood transfusions. In full-term safe babies, hematologic components are enough to manage the first six months of life. The American Academy of Pediatrics (AAP) suggests that the first four months of a baby's life is the optimal time to supplement with iron. **Table 1** lists the daily iron supplements recommended for children. **Table 2** demonstrates different oral iron formulations and suggests which product is best suited for treatment of anemia. *Ikatan Dokter Anak Indonesia* (IDAI) or Indonesian Pediatric Society recommends iron supplements for all infants and children below two years of age who live in areas where there is a high prevalence of iron deficiency, or those who are not receiving fortified foods. Infants who were breastfed exclusively and didn't take in enough iron from their diet are recommended to take a supplemental iron supplement of 1 mg/kg per day **Table 4**.[21]

Adults at risk for iron deficiency anemia are suggested to take iron supplements without screening if the prevalence of iron deficiency is over 40%. Iron supplementation given as 2 mg/kg/day equivalent for 3 months can be effective. For young children, iron supplementation is generally recommended at a dosage of 60 mg per day. By feeding infants formula which has enough iron in it, formula-fed infants rarely need additional iron. For children aged one to three, the approximate 7 mg daily iron requirement is met by eating iron-rich foods. Inadequate intake of iron can lead to iron deficiency. Greater improvement in hemoglobin concentration can be achieved through iron supplementation, but healthy children are more likely to tolerate iron-fortified foods. **Table 3** lists various infant foods and their iron content in milligrams. If iron supplementation is difficult, supplement given intermittently would still increase hemoglobin concentration and reduce the risk of iron deficiency.[20,21]

Summary

Exposure to iron plays an important role in the health of children. Cell metabolism and proliferation are required to produce energy. As well as, iron supports neuronal activity and the growth of the brain. Physical and nutritional health is critical for the child's health in the first 24 months of life, as this is when the brain is most malleable. It affects cognitive function, motor functions, socio-emotional development, and neurophysiological development. The iron requirement differs between individuals, depending on age. Children who do not receive sufficient iron will often develop permanent cognitive deficits and motor deficits. Iron supplementation is only effective when prescribed early on after the patient is diagnosed as being iron deficient. In the end, it is best to meet the iron needs according to children's age to avoid irreversible effects, and for further research to be conducted so that iron supplementation can repair those negative effects.

Table 1. Elemental iron supplementation or requirement in children[20]

Age	Iron supplementation or requirement
Preterm (<37 weeks' gestation) infants: 1 to 12 months	2 mg per kg per day supplementation provided exclusively during breastfeeding. A suggested 1 mg per kg per day ingestion for iron-fortified formula.
Term infants: 4 to 6 months to 12 months	One milligram per kilogram per day supplementation for exclusively breastfed children. It's unnecessary to take supplements if using iron-fortified formula.
Toddlers 1 to 3 years	Take 7 mg daily; modify your diet and/or supplement if anemic.
Children 4 to 8 years	Require 10 mg daily; Modify diet and/or supplement if anemic.

Table 2. Oral iron formulations and doses[20]

Formulation	Doses (element iron)
Ferrous fumarate	Tablet: 90 (29.5) mg, 324 (106) mg, 325 (106) mg, 456 (150) mg
Ferrous gluconate	Tablet: 240 (27) mg, 256 (28) mg, 325 (36) mg
Ferrous sulfate	Drops and solution: 75 (15) mg per mL Elixir and liquid: 220 (44) mg per 5 mL Syrup: 300 (60) mg per 5 mL Tablet: 300 (60) mg, 324 (65) mg, 325 (65) mg Extended-release tablets: 140 (45) mg, 160 (50) mg, 325 (65) mg
Polysaccharide-iron complex and ferrous bisglycinate chelate	Capsule: elemental iron (150 mg, 150 mg with or without 50 mg vitamin C) Elixir: elemental iron (100 mg per 5 mL)

Table 3. Iron content in common foods[20]

Food (serving size)	Amount of elemental iron (mg)
Soybean: cooked (1/2 cup)	4.4
Lentils: cooked (1/2 cup)	3.3
Spinach: cooked/ boiled, drained (1/2)	3.2
Beef, cooked (3 oz)	2.5
Beans (lima, navy, kidney, pinto): cooked (1/2 cup)	1.8 to 2.2
Baby food brown rice cereal: dry (1 tbsp)	1.8
Baby food green beans (6 oz)	1.8
Baby food oatmeal cereal: dry (1 tbsp)	1.6
Turkey and chicken: dark meat (3 oz)	1.1 to 2.0
Baby food lamb or chicken (2.5 oz)	1.0 to 1.2
Baby food peas (3.4 oz)	0.9

Table 4. Elemental iron supplementation dosage and duration of supplementation[21]

Age	Iron supplementation dosage or requirement	Duration of supplementation
Baby*:LBW (Low Birth Weight)	3 mg/kg/day	Age 1 month – 2 years old
Term infants	2 mg/kg/day	Age 4 months – 2 years old
Toddlers 2 – 5 years	1 mg/kg/day	Twice a week for 3 months per year
Children 5 – 12 years	1 mg/kg/day	Twice a week for 3 months per year
Adolescents 12 – 18 years	60 mg/day#	Twice a week for 3 months per year

Notes: * Maximum dose for a baby: 15 mg/day, a single dose
Add 400 µg folic acid for girls

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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