Kaunia : Integration and Interconnection of Islam and Science Journal
Vol.20, No.1, April 2024, pp. 1-10
ISSN 1829-5266 (paper), E-ISSN 2962-2085 (online)
Available online at http://ejournal.uin-suka.ac.id/saintek/kaunia

Significance of Dietary Iron for Human Biological System and Brain Development

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Submitted: 3th June 2024 ; **Accepted**: 2nd July 2024 ; **Published**: 16th July 2024

Abstract
The need for iron in the human biological system is enormous and lack of iron is dangerous especially for children, youngsters, and women due to the role of iron in growth and development among other things. It is important to state that iron is very critical in the functioning of nervous system as well. The aim of this paper is to conduct a review pertaining the significance of iron in humans, and specifically on brain development (cognition, learning and relations). The paper utilized review and conceptual methods to elucidate, advantages of iron chemistry (eg in hemoglobin, myoglobin, cytochromes, iron-sulfur proteinous entities, etc), the effects of iron deficiency or deficits in schooling children and the rest, sources of dietary iron, iron inhibitors or blockers, iron deficiency anemia, iron in the fetal developments and some methods for intervening in iron deficiency.
Keywords: *Brain, Iron, Cognition, Deficiency, Supplementation*

INTRODUCTION

Humans can get iron from dietary sources such as nuts, molasses, legumes, liver, fish, kidney, dark leafy vegetables, red meat, spleen, egg, etc; but, other dietary constituents could depreciate iron usage or uptake such as in the case of soft drinks, antinutrients, etc. Iron is an essential element in the biological system with a diverse array of functions and applications. Iron function principally in the transport of oxygen in the hemoglobin protein. It is a component in cytochromes enzymes, succinate dehydrogenase, myoglobin, catalases (Iqbal et al., 2015). Iron is needed importantly for synthesis of myelin, neurotransmitters synthesis, neurotransmitters packaging, and neurotransmitters degradation; therewith, affecting brain and neurological functions. Iron exists as in hemoglobin, transferrin (transport form, and ferritin (storage form) (Soetan et al., 2010). Other enzymes such as peroxidases, require iron for functioning (Duruibe et al., 2007);(Soetan et al., 2010). Thus, the lack or shortage of iron is of great concern. Iron deficiency has been a nightmare for human biological system, especially in case of children because it affects neurotransmitters, brain functions, proteins synthesis, and organogenesis (Soetan et al., 2010);(Gupta, 2014).

Effects of iron deficiency anemia are vast because Fe metal is for many critical functions in the human body. Scarcity of Fe can lead to disease, for example the prominent pernicious anemia. In anemia, insufficiency of oxygen occurs due to decreased hemoglobin (the major residence of Fe). Resultantly, many complications such as reduced immunity, impaired cognition, poor development, poor growth, heart problem, children mortality, liver problem, and other morbidities are due to Fe-deficiency anemia (Siamisang et al., 2023). Fe insufficiency in the body could mostly occur due to dietary insufficiency, because plants been taken by animals or humans are from deficient environments. The aim of this paper is to conduct a review pertaining the significance of iron in humans, and specifically on brain development (cognition, learning and relations).

IRON CHEMISTRY ADVANTAGES

Iron successfully become ubiquitous, as well as abundant element of the geosphere and biosphere, while playing a central role during the diverse array of biological events. The suitable properties of iron that relates to its diverse uses are as follows:

- Iron possess the ability to easily transform from one oxidation state to the other, that is $^{+}$II and $^{+}$III (or $^{+}$IV, and $^{+}$V)
- Iron has very tendency to make oligomers and polymers through condensation process

• Iron transform between high-spin and low-spin states in ligands
• Iron display flexibility by donating ligand function
• Iron has the temerity to make hexaaqua in water.

Accordingly, hard metal centres (eg Fe^{3+}) prefer hard ligands (oxygen-based donors) to make coordinations. Iron form coordination compounds consisting of central atom (metal) which is bonded to ligands forming a defined geometrical structure. The iron forms coordination compounds in the heme entities of cytochrome, and hemoglobin; iron-sulfur proteinous entities of Ferrodoxins, as well as Rieske proteins; and two-iron centres (such as ribonucleotide reductase) (Gupta, 2014). However, iron is affected by chelate effect, that is, stabilization of a complex using multidentate ligands, eg Fe^{3+} form a complex with enterobactin (Halterman et al., 2001);(Erdem et al., 2021);(Gutema et al., 2023). Nevertheless, upon intake of iron mostly Fe^{3+}, prior to intestinal absorption it transforms to Fe^{2+}, after absorption it returns to Fe^{3+} in the blood. The oxidation of Fe is dealt with by copper ceruloplasmin. The Fe^{3+} is consumed by apotransferrin, and simultaneous carbonate coordination occurs. The responsibility of transferrin is to conduct a delivery of iron to tissues for utilization. For example, sites of hemoglobin making, and protoporphyrin IX. Transferrin is regarded as glycoprotein having 80kDa as molecular weight, possessing two binding sites for Fe^{3+} of the N-terminal lobe, and C-terminal lobe. Transferrin transfer other anions because it only engulfs about 40% of iron. Ferritin is another form of iron that is advantageous to human biology. Ferritin is a form of stored iron, containing a hollow protein sphere (apo-ferritin, M=450kDa, 24 units of 163 amino acids each) and have an outside diameter of 130 and inner diameter of 70 A. The internal surface contains layer of carboxylate functions that coordinate Fe^{3+} (Felek, 2023).

Verily, iron occur as heme form where it performs sufficient role in useful products of the biological system such as hemoglobin (for oxygen transport) and: myoglobin (for oxygen storage). In heme present in hemoglobin there is reversible binding of oxygen required by the human biological system. When humans breath, oxygen finds it ways into the partition of the hemoglobin to make a bond, thereby turning the blood to bright red color. This blood when passing through the cells and tissues release oxygen and bind carbon dioxide that will in turn be shuttled out of the body through the lungs (Gupta, 2014). Moreso, the heme containing cytochromes carry out distinct biological functions; for example, cytochrome P450 is related as a vast family that facilitates detoxification of toxic materials, as well as drugs in the human body. While, cytochrome c is an essential enzyme responsible for discharging the process of scavenging reactive oxygen species (ROS); whereas, additionally, carry out function in electron transport chain. Transferrin, a non-heme iron containing material is available to deal with Fe transfer for certain purposes such as transport to required tissues. Likewise, ferritin also store iron for human body consumption. Summarily, respiratory chain requires certain iron-Sulphur proteins. Ferredoxin is utilized in the first step of mitochondrial respiratory chain acting as reduction equivalents acceptor. Similarly, Rieske protein, another iron-Sulphur protein act as acceptor at step 3. At step 4 cytochrome b and c receive reduction equivalents, while, step 5 require cytochrome c (see Figure 1 and 2).

Transporting Oxygen Through Hemoglobin

Within the pulmonary alveoli, hemoglobin takes in oxygen, and degradation of carbonic acid occurs. On reaching the tissues, hemoglobin delivers oxygen to the myoglobin (because it has affinity to oxygen more than the hemoglobin) (Hamdule et al., 2023).

At the end, oxygen is reduced to water in the respiratory chain, carbon dioxide is transform to hydrogen carbonate that is divulged out of red cells while taking in chloride, then transported to the pulmonary alveoli where carbonic acid is made, and degraded.

Iron Deficiency Relationship with Cognitive Level of Schooling Children

Iron deficiency is a dominant hematologic problem among children. When the bone marrow content of iron is depleted, usually children develop dietary iron deficiency. Likewise, girls need iron for the changing physical development occurring. Iron deficiency in children is characterized with anemia, behavior change, low cognition, impaired motor ability, lower mental development. Parable, a study performed in America among children by (Halterman et al., 2001) demonstrated lower scores due to iron deficiency in children, and adolescents. Ideally, models and studies show that, effects of iron deficiency that manifest in effects of learning or cognition are due to change in centers or signals that are responsible for cognition in the brain. This implies change in hippocampus, may be due to hypoxia, anemia, stress, and direct effects (Fretham et al., 2011).

Noteworthy, infants at the ages of 0-3 months, 4-6 months, 7-12 months, everyday need 1.7mg/-day, 4.3mg/day, and 7.8mg/day amount of iron respectively; children of 1-3 years, 4-6 years, and 7-10 years, need 6.9mg/day, 6.1mg/day, and 8.7mg/day Fe respectively. While, adolescents (11-18 years old)

need 14.8mg/day Fe for girls, and 11.3mg/day for boys respectively (The Association of UK Dieticians, 2020).

Better Source of Iron for Intake

Source of iron from animal is determined as "heme iron" and iron from plants is determined as "non-heme iron." "Heme iron" improves iron availability (status), while the plant-based iron may be affected by inhibitors or relations. Some animal-based iron sources are enumerated: beef, lamb leg, lover pate, back bacon, eggs (fried), salmon, prawns, mackerel, chicken, shrimp, clams, tuna, etc. Some plant-based iron sources are enumerated this way: Kidney beans, Brazil nuts, peanuts, walnuts, potato (baked), Tofu, butter beans, dates, lettuce, green peas, spinach, tomato, broccoli, sesame seeds, figs, cereals, sunflower seeds, apple, orange, avocado, banana, watermelon, cashews, strawberries etc (Inuwa et al., 2011);(Mahendran et al., 2015).

Iron Blockers in Animals

There are some compounds or food materials that act as iron blockers; therefore, reducing iron availability. Some of which are consumed in natural foods, and others are found in food prepared by humans. Some of the iron blockers are as follows:

• Beverage drinks such as coffee, soda, tea, cocoa, red wine,
• Calcium has the ability to block all types of iron absorption
• Phytate has the ability to bind Fe, and it is found in plants such as legumes, and grains. However, it can be minimized through processing methods
• Tannins possess binding ability to adhere to iron, and can be reduce through processing (Dasa & Abera, 2018);(Matondo et al., 2020).

Phenolic Groups- Found in beverages or plants can adhere to iron and render it unavailable for absorption in the biological system.

Facilitators or Helpers of Iron Absorption in animals

There are certain substances that facilitate iron intake as follows:

• Meat enhances iron absorption through chelation, and gastric acid effect (that enhances iron solubility in the stomach)
• Fish, poultry act as enhancers of iron absorption by bringing in the heme-iron components
• Vitamin C and other organic acids like the lactic acid, malic acid, beta-carotene, vitamin A, erythorbic acid (Saunders et al., 2012);(Narwal et al., 2017);(Dasa & Abera, 2018);(Umar et al., 2023).

Iron is Needed by Plants Too

All organisms need iron, that is why the element is common on earth. Soils contain iron, likewise, rocks, and minerals have iron contents. Mostly, iron is sourced to plants in soils through secondary oxide minerals; but availability for plants uptake is low (Samson et al., 2022);(Sarkingobir et al., 2023). Plants absorb iron from soil as Fe(II) ions, and in few cases Fe(III). It is useful for respiration, redox reactions, enzyme reactions, and photosynthesis. If there is low level of iron (for example below 50 ppm) deficiency occurs. Signs of iron deficiency include, stunting, yellowing of leaves; whereas, toxicity symptoms include bronzed striped leaves. Addition of iron fertilizers is a good strategy to correct iron deficiency in soils for better plant uptake (example addition of Fe-EDTA) (Shabbir et al., 2019).

Signs of Iron Deficiency in Humans

Iron deficiency manifest in signs such as impaired cognitive function, delayed psychomotor development, heart palpitations, weakness, swollen and red tongue, difficulty in maintaining body temperature, mouth sores, brittle nails, itchy skin, decreased school performance, decreased work performance, irritability, decreased immunity, sensitivity to cold, premature birth, higher infant mortality, fatigue, impaired cognition (Adewoyin, 2015);(Alhazmi et al., 2022); (Siamisang et al., 2023).

Group of People at Risk of Iron Deficiency

Infants at the ages of 0-3 months, 4-6 months, 7-12 months, everyday need 1.7mg/day, 4.3mg/day, and 7.8mg/day amount of iron respectively; children of 1-3 years, 4-6 years, and 7-10 years, need 6.9mg/day, 6.1mg/day, and 8.7mg/day Fe respectively. While, adolescents(11-18 years old) need 14.8mg/day Fe for girls, and 11.3mg/day for boys respectively (The Association of UK Dieticians, 2020). Because of one reason or the other, some people that are at risk of iron deficiency are as mentioned below:

• Children and adolescents- these groups of people are growing, therefore the blood volume, and neurons level (nervous system) have to be increased to support the growing needs and raising energy requirements for the body
• Pregnant, and Menstruating Women

• Fetal growth, and raising blood demands require iron during pregnancy. Likewise, losses of blood through menstruation require iron
• Athletes- People doing exercises need much energy that may spur more utilization and needs
• Older adults- Older people may have poor diet, and diseases, that in turns lead to increased iron needs in the body (Clifford et al., 2015); (Umar et al., 2022); (Shehu et al., 2023)

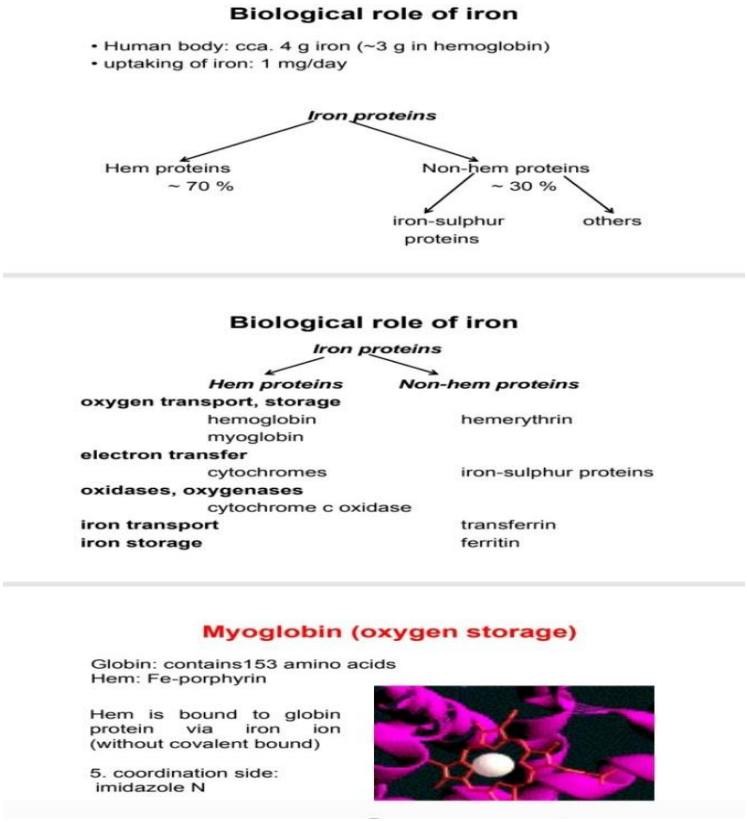

Figure 1: Some Specific Roles of Iron (Dieter, 2008)

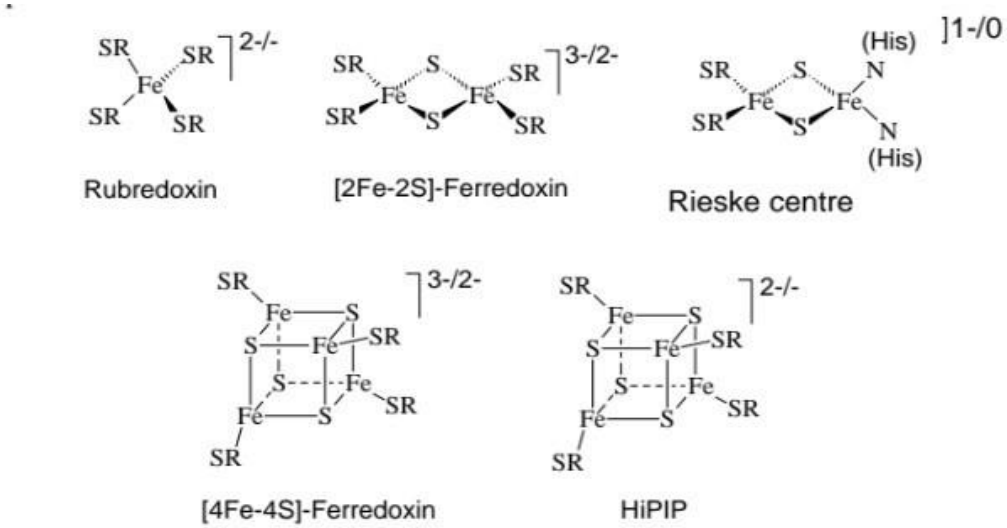

Figure 2: Iron- sulfur Proteins (Dieter, 2008)

Table 1: Some types of UK foods and contents; Source: (The Association of UK Dieticians, 2020)

Type of Food	Iron per 100gr	Type of Food	Iron per 100gr
Animal-based sources		**Fruit,nuts and seeds**	
Beef (Rump steak)	3.6mg	Figs (partially dried)	3.9mg
Beef mince(stewed)	2.7mg	Apricots (partially dried)	3.4mg
Pork chop(grilled)	0.7mg	Dates (dried)	1.3mg
Lamb leg (roasted)	1.8mg	Almonds	3mg
Chicken (roasted, light meat)	0.7mg	Brazil nuts	2.5mg
Liver Pate	5.9mg	Peanut butter(smooth)	2.1mg
Sausages (pork)	1.1mg	Hazelnuts	3.2mg
Back Bacon (grilled)	0.6mg	Sesame seeds	10.4mg
Eggs(fried)	2.2mg	Sunflower seeds	6.4mg
Fish-based Sources		**Vegetables**	
Cod/Haddock (baked)	0.1mg	Brococoli (boiled)	1mg
Salmon (steamed)	0.4mg	Spinach(boiled)	1.6mg
Mackerel (grilled)	0.8mg		
Prawns(boiled)	1.1mg		
Tuna (canned in brine)	1.0mg		
Plant-based sources			
Baked beans (in tomato sauce)	1.4mg		
Butter beans (canned)	1.5mg		
Chickpeas (boiled)	2mg		
Kidney beans (canned)	2mg		
Tofu (steamed)	1.2mg		

Table 2: Specific iron needs by specific groups; Source: (The Association of UK Dieticians, 2020).

Group	Age(years)	Iron (mg)per day
Infants	0-3months	1.7
	4-6months	4.3
	7-12months	7.8
Children	1-3 years	6.9
	4-6 years	6.1
	7-10 years	8.7
Adolescents	11-18 years	14.8 (girls)
		11.3 (boys)
Adults	19-50 years	8.7 (males)
	19-50 years	14.8 (females)
	50+ years	8.7

IRON DEFICIENCY AFFECTS EDUCATIONAL PERFORMANCE OR COGNITIVE DOMAIN

Several empirical studies in the literatures had reiterated that, students (especially youngsters) suffer in learning, cognitive, and academic achievement due to iron deficiency. Parable, (Soleimani & abbaszadeh, 2011) explore the relationship between iron deficiency, and academic achievement of female students in secondary schools in Iran. The results depicted positive link between iron and academic achievement of the students investigated. (Iqbal et al., 2015) assessed the iron deficiency on intellectual performance of primary schooling children of Islamabad, and iron deficiency is linked with intellectual scores among the children. (Abd Elrazik et al., 2019) conducted iron deficiency effect assessment on primary school students school achievement; therewith, a result showing that iron deficiency suffering students show low school achievement, and low physical activity.

Iron Relates with Fetal Development

Fe is an essentially needed element for brain development. Brain stores iron in the extrapyramidal tracts that are laid down in the first months of life. Once the closing of blood brain bilayer takes place, little iron is allowed into the brain comparatively. Thus, enough intake of iron is more crucial during this time. Iron is a parcel of synthesis, degradation, and uptake of neurotransmitter "Dopamine." Iron is involved in lipid biosynthesis (myelination in turns). Brain cells responsible for myelination or myelin making contains iron (transferrin and ferritin). Thus, low iron affects myelination as well as transmission (Abbaspour et al., 2014);(Yiannikourides & Latunde-Dada, 2019);(Tebbi, 2022).

Iron deficiency is very prevalent in the world especially in developing countries and the likes, among children, pregnant women and youngsters (Gambling & McArdle, 2004); (Cleghorn, 2007). When the hemoglobin level fall during pregnancy it is a condition dubbed as anemia in pregnancy and it is mostly regarded as dietary issue, that is why it is suggested that, a woman in pregnancy double its iron intake; because the deficiency exert serious consequences on the mother and the child due to morbidity and mortality risk. Some of the risks include, premature birth, low-birth weight, short-term and long-term consequences (Gambling & McArdle, 2004); (Cumurcu et al., 2009); (Castro & Viana, 2018); (Hamdule & Kirkham, 2023). On short-term basis, iron deficient mother give birth to baby with iron-depleted store, as well as iron-deficient child, low fetal weight, higher placenta weight. On long-term basis, high blood pressure of weaned child, glucose intolerance, neurological poor development, fine motor skills, change in behavior, irreversible cognitive change, low immunity, low social-emotional health (see Figure 3) (Pem, 2012).

Forms of Iron in Food Materials

Foods provide iron for healthy people, but people with disorders or health problems, and iron deficient food materials are bound to suffer iron deficiency. Meat provides heme form of iron to organisms. Iron exists in heme form within myoglobin, and hemoglobin and has highest bioavailability, albeit inhibitors may diminish iron release. The other form of iron is non-heme, from seeds, nuts, grains, dark-greenly vegetables; but this type of iron availability can be affected due to its chemical nature; for example, phytate, oxalate, hydroxide, phosphate, ferric citrate are chemical forms of compounds of iron available for humans. Other iron forms include, ferritin, lactoferrin, fortified iron (eg EDTA, ferric chloride, iron-dextran, ferrous gluconate, ferrous sulfate. Availability of iron could be inhibited by factors such as phytate, calcium, polyphenols, milk proteins, albumins, egg protein; while enhancers of iron could be ascorbic acid, and muscular tissue proteins (Soetan & Oyewole, 2009);(Zielinska-Dawidziak, 2015);(Moghaddam et al., 2016).

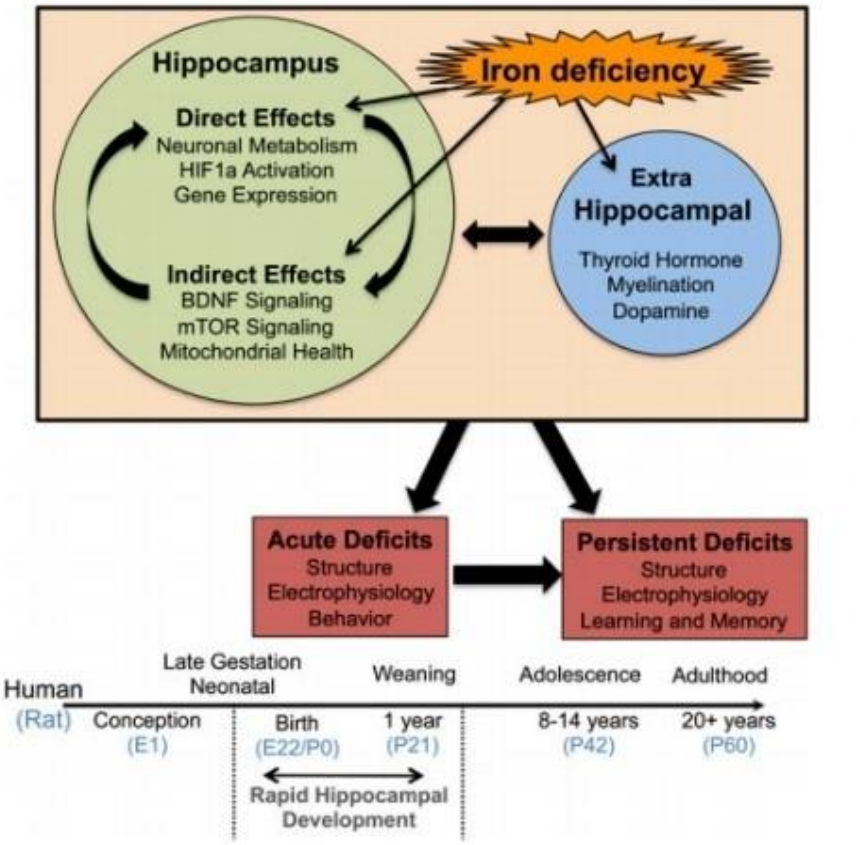

Figure 3: Concepts of role of iron in brain; Source: (Fretham et al., 2011)

IRON DEFICIENCY ANEMIA IS RISKY IRON PROBLEM

Anemia due to iron affects 1/3 of the world population. It is pertinent to state that, iron is needed in the body at least to make hemoglobin that is responsible for shuttling oxygen to various parts of the body. If there is no enough iron, enough hemoglobin cannot be manufactured, and along the line the physical, as well as mental capacity of the person involved is reduced. This state, where the red cells are reduced due to iron deficiency is linked to low-birth weight in babies, maternal death, perinatal death, fetal death. Particularly, in children iron deficiency causes impaired learning ability, impaired motion development, lower length, lower height, damaging body's defense mechanism, poor infection control, reduced productivity in later life (WHO/BASICS/UNICEF, 1999).

Mechanism of Development of Anemia

Children suffer from anemia, if there is depleted iron store during pregnancy, leading to giving birth of children with depleted iron (in the liver, bone marrow, spleen). Therefore, the iron stores have to be used up when there is no supplementation or replenishment. Other reasons for development of anemia could be deficiency of folic acid, vitamin C, vitamin A, vitamin B12, and some other minerals deficiencies (Yiannikourides & Latunde-Dada, 2019).

Measures for Iron Deficiency Anemia Prevention

The following measures could be utilized to prevent anemia: Dietary improvement, helminths control, better reproductive health (such as HIV/AIDS prevention, birth spacing, proper antenatal care), iron supplementation, fortification of food materials (such as flour), administration of folic acid (for pregnant women), eating more vegetables and foods (such as beans, groundnuts, green leaves, liver, fish, kidney), malaria control, proper breastfeeding, early and routine screening or diagnosis (WHO/BASICS/UNICEF, 1999);(Inuwa et al., 2011); (Zielinska-Dawidziak, 2015);(Shabbir et al., 2019);(Qureshi et al., 2020).

Rare Iron Toxicity

Fe toxicity has been regarded as rare condition that occur due to excess iron intake for reasons. Parable, people consuming alcohol are at the risk of developing excess Iron absorption, hemachromatosis causes excess iron absorption. Excess iron can cause cancer, heart disease (formation of free radicals that injure blood vessels), increased risk of type 2 diabetes (Clifford et al., 2015). Other effects are increased risk of infection to bacteria, cardiomyopathy, inborn metabolic problems (Dasa & Abera, 2018).

Strategic Methods to Address Fe Micronutrient Malnutrition in Humans

Some of the methods used to intervene in order to address the issue of iron malnutrition are as follows:

• Supplementation- During iron supplementation, a drug containing readily available iron is given to the person affected, for example ferrous sulfate drug is used for treatment of iron deficiency.

• Diversity in food intake-Since some food material do not contain iron or enough iron, it is better for a person to take various food materials from plants and animals sources using better nutritional guidance based on knowledge and research; therewith, natural food materials are better sources of iron indeed.

• Animal obtain food from plants through nutrition. Thus, a strategy of enriching plants using biofortication is helpful. Fortification- For example, crop biofortification, "which refers to the breeding of cultivars with higher levels of micronutrients, is increasingly being recognized as a cost-effective and sustainable approach. Fe biofortified crops have been released with higher ppm compared to normal varieties on wheat, sorghum, lentil, foxtail millet, little millet and pearl millet" (Ariraman, 2020).

• Many deficient soils cannot support the plants with micronutrients such as iron. Therefore, supplying plants with fertilizer laden with iron could invariably incorporate iron into the food chain. Fertilizer Addition- This involved applying iron or related compounds in the manure or fertilizer used for cultivation of food crops, so that the crops incorporate the element for upward shuttling in the food chain (Narwal et al., 2017).

CONCLUSION

This paper elucidated the significance of iron in diverse activities of human body, especially growth and development, learning (cognition or relations). It is pertinent to stress that, proper iron intake from foods is significant, the public have to be informed for better growth, learning, and development of youngsters and the entire society.

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