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Review Paper

Iron fortification of milk and its effect to cure anemia and other human diseases

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Abstract

Milk is considered to be a complete food in itself with appropriate amounts of proteins, carbohydrates, fats, and other micronutrients. The amount of iron is very low in milk which eventually leads to anemia. Consuming excessive amounts of milk and especially whole milk inhibits the absorption of iron in the human gut. Iron fortification in cow's milk has proved to be a great approach to prevent iron deficiency. Infant formula must include an appropriate amount of proteins, carbohydrates, vitamins, and minerals. Cow milk is the basis of infant formula. Anemia is a disease that arises due to a lack of red blood cells and also due to poor ab of iron in the human body. Cow's milk contains more protein while human milk contains more fat such as docosahexaenoic acid, an omega-3 fatty acid. But in both cases iron content is very low (0.2mg/liter), this can be cured via a "Iron Fortification of milk". The cow milk's main proteins are casein, which binds to cation, including Fe, by clusters of phosphoserines. Infant bodies require more iron to be absorbed per unit of energy. Higher bioavailability of the dietary iron can be accomplished by increasing the content of food components promoting iron absorption (ascorbic acid, meat/fish) or by lowering the content of inhibitors (e.g., phytates, tannins). In the present study, iron-fortified milk still holds an upper hand over iron supplements, because it causes digestive intolerance, vomiting, morning sickness, and other minor side effects including black stools Ferrous sulfate is the most common salt used as an oral therapeutic drug but it results in various gastrointestinal side effects. Without affecting the quality and quantity of iron-fortified milk, consumers can consume the iron-fortified milk for more than 8 months in aerobic at room temperature. Overall study shows that iron-fortified milk is a realistic option and produces a positive effect on the iron status of humans. It gives a probable blueprint for achieving Millennium Development Goals focusing on mortality, morbidity, and malnutrition among children. Fortified milk provides essential micronutrients such as iron, zinc. These micronutrients improve iron content for growth and reduce the chances of anemia. This method could be adapted for the production of stable iron-enriched protein, an organic source of iron. As fortified milk contains more vitamin A that leads to 1.8 times more increment in iron absorption.

Keywords: Fe, Milk, Iron Fortification, Anemia, Bioavailability.

Introduction

Red blood cells have the ability to carry oxygen to the body tissue. Iron deficiency i.e., anemia occurs when your body does not have enough iron to produce hemoglobin. Hemoglobin is the part of red blood cells that gives blood its red color and enables the red blood cells to carry oxygenated blood throughout the body. If iron consumption is not enough or if losing too much iron from the body, and the body can't produce enough hemoglobin, iron deficiency anemia will eventually develop. But this condition is very severe in infants because of the high consumption of milk as cow milk interferes with the body's ability to absorb iron from food and supplements[1].

Excessive milk intake can lead children to consume less food because on the fill up to liquid so the infants do not take adequate iron but consumption of iron in the body is too fast as the baby body is growing fast and it takes time to red blood cell production to catch up. This is how the hemoglobin level decreased from its normal range which is 11-13.5 ctHB g/l. The addition of supplementary iron to milk or dairy products might increase the bioavailability of the iron. Loss of iron from demised with age and crease after the age of 5 years. Calcium and Casein both are present in higher in high amounts in cow milk that inhibits the non-heme iron absorption. Symptoms of iron include pale skin, lack of energy or tiring easily, Fast heartbeat, Sore or swollen tongue, Irritability, or fussiness.

Anemia is diagnosed by hemoglobin and hematocrit measures the amount of hemoglobin and red blood cell in the blood. Complete blood count CBC a complete blood count checks the red and white blood cells, platelets, and sometimes reticulocytes[2]. Peripheral smear, a small sample of blood is examined under the microscope and check whether the blood cells are normal or not. A blood test is also done to measure the amount of iron in the body[3].

Iron Metabolism

Several research works are performed to generalize iron metabolism. "Iron ore" was the term used for iron metabolism, which comprises the study of pathways inside cells and organelles. This review paper addresses some important physiological pathways involved in iron metabolism. Reading iron metabolism is that we will know at which particular level of a metabolic pathway, iron fortification can be performed. Iron metabolic pathways also give adequate information of those substrates which combines well with Fe^{2+} and Fe^{3+}, with the help of these substrates or molecules we can later do iron fortification of milk. The physiology of Iron metabolism starts with the absorption of Fe in the small intestine from available food sources[4]. Then there are several proteins and peptides which play a prominent role in regulating iron absorption in infants and children. During Absorption, iron can be picked up in three different ways: i. Divalent metal transporter takes up the iron to the small intestine. ii. Mucosa have ferritin that stores iron inside cell iii. Ferroprotein transport iron in the blood.[5] Further, based on taking part in erythropoiesis, there are two ways for iron metabolism: Heme iron and Non Heme iron. The absorption of heme iron is more efficient due to Heme Carrier Protein-1. Heme iron generates a sufficient amount of functional and matured RBC. Some parts of heme iron were stored in erythrocytes within ferritin molecules. Some parts of heme iron were circulated in the bloodstream[6]. This work is exported by ferroprotein and transported into the blood by transferring. Senescent RBCs are catabolized and iron obtained from hemoglobinis recycled again. Nonheme ferric Fe must be reduced to ferrous Fe. This can be done by duodenal cytochrome b (DCYTB) or by other cell surface ferric reductases. After reduction ferrous iron is carried to erythrocytes by divalent metal transporter-1 (DMT-1), it is a proton symporter and requires low pH for functioning. Hepcidin is the queen of iron metabolism. It is a small peptide synthesized by hepatocytes in the liver; it inhibits iron absorption from the duodenum by blocking ferroproteins. So that more iron can be recycled from senescent RBCs[7].

Bioavailability

Bioavailability term has very significant importance in the fortification of milk. It is noted that lactoferrin is the most superior whey protein found in human milk as well as present in large quantities in colostrum, which gradually declines over time. Lactoferrin is a very good iron-binding protein that makes human milk easily available to the infant's body system[8]. But as the infant grows older, proteolytic activity increases whereas the lactoferrin level in human milk decreases which makes it essential to have infant formula. Although iron absorption in infants gets doubled in comparison to that of the adult's problem lies with cow milk. Cow milk contains caseins (almost 10 times more than human milk) which have a very strong affinity towards Fe. Hence it impairs Fe absorption in humans[9]. Caseintends to form curds in the stomach of infants and it passes through the gastrointestinal tract without complete digestion[10]. Casein in cow milk is present in the form of clusters of phosphoserines that have a high affinity with iron. This decreases the bioavailability of the iron in duodenal mucosa but solubilizes in alkaline pH. At physiological pH, a major proportion of iron exists in an oxidized state but to get absorbed, iron must be in the ferrous state in a complex with a protein such as heme. Even though casein inhibits iron absorption but protein hydrolysis lessens its effect and improves the absorption process. Now, casein phosphopeptides (CPP) released by alkaline phosphatase play a key role in this metabolism. There are different types of caseins that give different conflicting results. The results vary due to their structural and conformational features. There are two main cow milk caseins: alpha S casein and Beta casein. Beta casein improves iron absorption whereas alpha S hinders iron absorption. Here, in the graph, the dark bar represents alpha S casein whereas the light-colored bar represents beta S casein. Under both uptake and net absorption, we can see that alpha S caseins have comparatively lower values than beta S casein[11].

Milk Fortification

Fortification is the process of adding essential nutrients lost during the fat removal process back to the milk. The nutrient added to the mix is water-soluble bile that can easily distribute into milk. Milk fortified with vitamins such as A and D that helps with night blindness, rickets, and nervous system maintenance in children and adult[12]. The fortification of milk depends on the place you live and the nutrient lacking in the diet. The milk can also be fortified the nutrients such as iron, zinc, folic acid. Milk The milked for the Fortification can be fermented milk products, Cow milk, infant formula, pasteurized milk, etc. Consuming iron-fortified milk shows a drastic decrease in anemia (Ranging from 40%-13.7%) almost 55 million people of India consume the fortified milk[12].

Infant formula

Infant formula is intended as a complete or partial replacement of breast milk that can mimic the nutrition composite ion human breast milk in every possible way for normal infant growth[12].

An ideal Infant formal should include a proper amount of carbohydrate, vitamins, amino acid, proteins, fats, Water, and Minerals. The components added to the formula should estimate a safer side. Like in amino acids only L- form is allowed, D-form, and fructose are not allowed D will cause the D-lactic acidosis and fructose intolerance due to fructose[13]. Hydrogenated fats and oil are also not recommended but a few supplemental ingredients are added to attain health benefits, including compositions of fat, nucleotide, and iron and some of the fatty acids like Docosahexaenoic acid (DHA) arachidonic acid (AA), Probiotics that are generated by genetic engineering, are added[14]. The age up to which infant can receive the fortified milk is 6-1 yrs. with iron content. To prevent the infant from

iron deficiency during the 1yr of life it should consume 0.5-0.8 mg/day. The third result is based on the fact that an infant born with iron inherited of 75mg/kg body weight and should ensure that 140-200mg must be absorbed during 1yr. An infant consuming 1mg/kg/day has found a higher level of hemoglobin[13].

Infant formula can be of three types: Cow Milk-based formula: - Most infant formula is made up of cow milk because of its very close resemblance to human breast milk[13]. The formula contains iron, vitamin, minerals, added vegetable oil[13].

Soya-based formula: Formulas that are produced from soy protein are found to be more effective for infants suffering from galactosemia and congenital lactose deficiency[14].

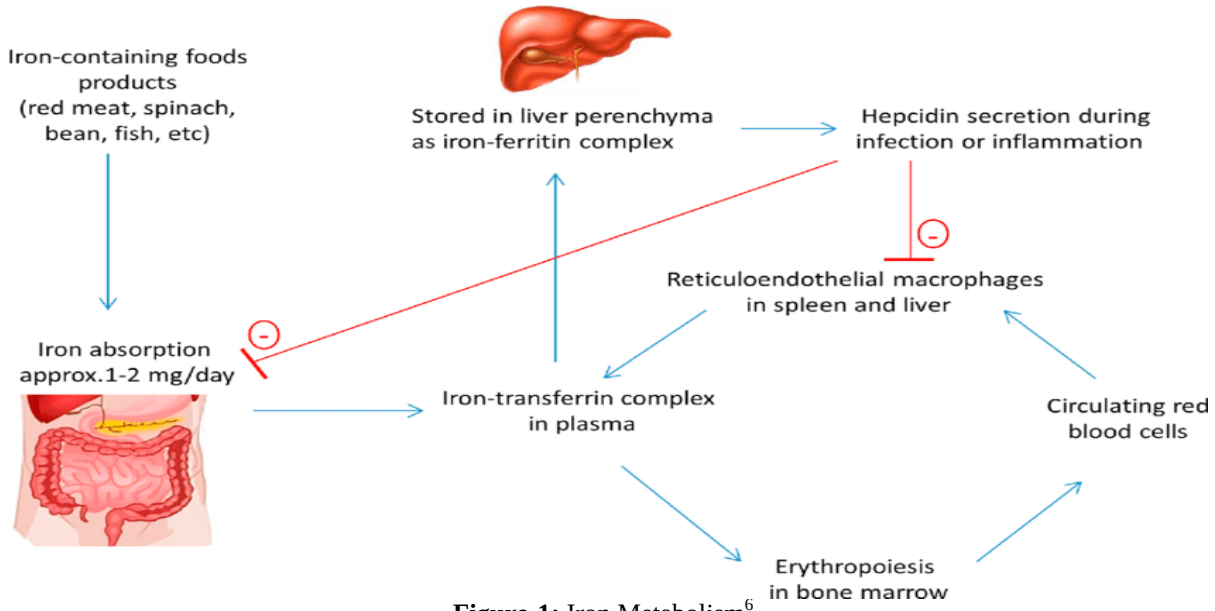

Figure-1: Iron Metabolism[6].

Table-1: Composition difference between Fortified milk and unfortified[12].

	Fortified 2% milk	Unfortified 2%milk
Calories	122	123
Protein	8 grams	8 grams
Fat	5 grams	5 grams
Carbohydrates	12 grams	12 grams
Vitamins A	15% of the Daily value (DV)	8% of the DV
Vitamin B12	54% of the DV	54% of the DV
Vitamin D	15% of the DV	15% of the DV
Riboflavin	35% of the DV	35% of the DV
Calcium	23% of the DV	23% of the DV
Phosphorus	18% of the DV	18% of the DV
Selenium	11% of the DV	11% of the DV
Zinc	11% of the DV	11% of the DV

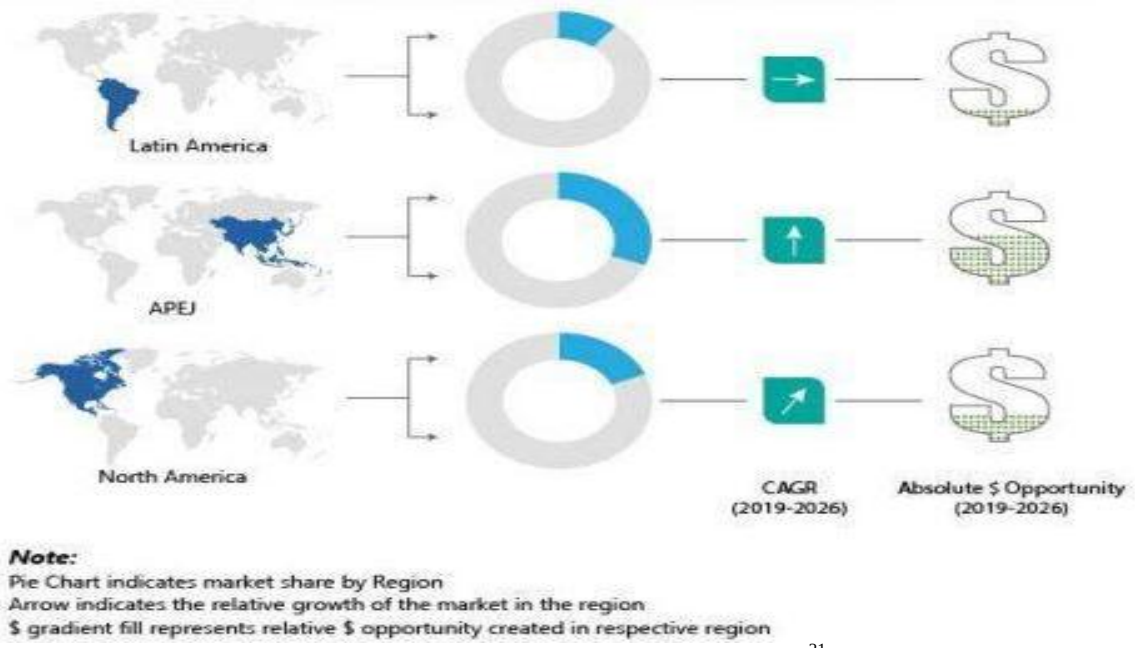

Figure-2: Global Fortified Dairy Product Market[21].

Iron Fortification

There are many methods by which we can fortify the milk. To increase the bioavailability of iron in the milk we can add various salts like ferric pyrophosphate also known as sodium-Citro-ferric pyrophosphate which is made up of ferric pyrophosphate and sodium citrate. Whether the salt helped in increasing the bioavailability of milk, animals were fed with different compositions of the diet. Animal treated with iron-fortified milk lyophilizes on another hand these animals are also treated with normal diet having no iron lyophilates. After 21 days of this experiment, the blood sample and urine sample shows the best results having a low anemic rate in this group of animals.

Factors Influencing the Choice of iron fortification compounds: A large number of ionic compounds have been used for the fortification of milk. Many factors can help us to choose the method for fortification of milk I.e., the relative bioavailability of the addition of iron salts may not interfere with any other nutrients absorbents, stability of the salt. The compounds which can use for the fortification in milk are ferrous sulfate, ferrous gluconate, ferrous fumarate ferric pyrophosphate, ferrous bio glycinate, and elemental iron powders[15].

Relative bioavailability: The iron absorption or relative absorption of any compounds can be defined by which two compounds can dissolve in the stomach with the help of gastric juices like ferrous for sulfate and ferrous gluconate readily dissolved in aqueous solution i.e., it can easily dissolve in gastric juices likewise ferrous fumarate is poorly dissolved in the aqua solution but dissolved in the gastric HCl.[18] FPP and elemental iron powder as only partially dissolved in the gastric fluid and their relative absorption is governed by dissolution Defined milk typically goes through several changes before reaching the consumers which may include storage packaging distribution and cooking[16].

Liberty of iron compounds: We have to choose that compound that does not give a necessary change when soluble in gastric juices like ferrous sulfate gives brown coloration and unwanted changes when dissolved in an aqueous solution but ferrous fumarate does not do such type of changes. Relative check of solubility in gastric juices Iron powders and FPP are the least expensive and commonly used iron compounds there are many iron powders supplements used worldwide that have relative solubility in gastric juices like reduced iron powder[17].

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Adjustable fortification

There is always an intriguing question of whether the adjustable iron fortification creates some difference in the babies or not. It has been analyzed that infants with high iron intake have more ferritin levels i.e., children consuming 1.2mg/100ml iron have more ferritin than those consuming 0.4mg/100ml iron. Apart from that, there is no difference in the neural development the infants[19].

Mothers usually fret about iron causing constipation but the amount of iron present in infant formula does not contribute to constipation. Rather infants and children are given fortified food and dairy products with 1.2mg/100ml iron, showed lower chances of anemia, compared with 0.4mg/100ml of iron[20].

Conclusion

The main motto of the fortification of iron is to deliver a meaningful level of bioavailability without compromising taste, color, texture, and stability. But primitive fortification procedures were only associated with unsatisfactory taste, color, and bioavailability. Advanced fortification technology has been shown to solve all the problems by administering encapsulation principles along with chelation and electrochemical chemistry (redoxmodulation) which leads to more market acceptance. Iron sources stabilized either with chelation–redox modulation or vesicle-based encapsulation approaches can be a boon towards the eradication of iron deficiency anemia. The global fortified dairy product market has shown a tremendous rise within a few years.

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