Risks of iron supplements
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INTRODUCTION
Iron is a metallic element which is present in most of soils, mineral waters, and certain minerals. Iron is an essential mineral that is compulsory for life. Every living species, stating as of bacteria to humans, contain iron. It is found mainly in blood as the main component, and it is a fundamental component of hemoglobin, cytochrome, and other components of respiratory enzyme systems. The most important function of iron is to transport oxygen to tissues (hemoglobin) and in cellular oxidation mechanisms. Reduction of iron stores may lead to iron deficiency anemia. Iron is used as a building block to make up the blood in anemia. Iron is important to regulate our metabolic pathways such as rofecoxib pathway, magnesium salicylate action pathway, etodolac pathway, and diclofenac pathway. Iron is also involved in several metabolic disorders, some of which include adenine phosphoribosyltransferase deficiency, porphyria variegata, adenyllosuccinate lyase deficiency, and AICA-ribosiduria. To cure or prevent iron deficiency, anemia iron supplements are used, iron will enhance immunity, and it provides anticarcinogenic and cognition-enhancing activities.[1]

The majority of the iron that is required for the body is obtained during food items such as meat, fish, vegetables, fruits, and whole grains. However, from time to time, this is not sufficient for pregnant women, they may need additional iron, as people who have lost their blood or comprise of low hemoglobin levels for other reasons. Patients with kidney disease, they require a high dose of iron to bind phosphates into the bloodstream.[2]

Two types of iron, such as ferric and ferrous form are normally prescribed. However, ferrous iron is absorbed better than ferric iron. Accordingly, most iron supplements contain ferrous iron. Three types of ferrous iron are usually given, ferrous sulfate, ferrous fumarate, and ferrous gluconate. These supplements are existing in different forms, which includes tablets, capsules, liquids, drops, and extended-release.[3,4]

Ferric iron is not well absorbed like ferrous iron; hence, ferric iron is not prescribed as regularly like ferrous. In total, reports recommend that ferrous iron is tolerated better in patients than ferric iron. Since the gastrointestinal tract has a reduced amount of ability to decrease ferric iron to its ferrous form, there is a

ABSTRACT
Iron is a vital mineral that is included in many over the counter multivitamin and mineral supplements and is used therapeutically in higher doses to treat or prevent iron deficiency anemia. When taken at the usual recommended daily doses or in replacement doses, iron has little or no adverse effect on the liver. However, in high doses or accidental overdoses, iron causes severe toxicities. Today different types of iron supplements are available in the market without mentioning the individual compound. These supplements are based on at least 20 different iron compounds and sold under a wide range of brands. Iron supplements are good for women and children, but when we focus on individual compound, not all supplements are created equal potency, as some compounds may actually do more harm than good. From the recent research, it was found that two iron compounds, ferric citrate and ferric ethylenediaminetetraacetic acid are often used in dietary supplements and as a food additive, respectively, in worldwide markets can increase the biomarkers for colon cancer, suggesting a link to the death toll. This review reports the cautious of iron supplements and serious disorders of an overdose of ionic compounds.

KEY WORDS: Amphiregulin, Ferric citrate, Ferric ethylenediaminetetraacetic acid, Ferritin, Iron overload
condensed chance of iron poisoning with iron citrate, which is the most commonly used form of ferric iron.\textsuperscript{[5]}

The World Health Organization estimates that more than 25\% of population (1.62 billion) have iron deficiency anemia.\textsuperscript{[6]} Persons from developing countries are affected by this problem.\textsuperscript{[7]}

**DIETARY SUPPLEMENTS**

Iron is existing in various dietary enhancements such as multivitamin/multimineral supplements extraordinarily those are considered for ladies, kids, and seniors. By and large utilized types of iron in the enhancements incorporate of ferrous and ferric iron salts, for example, ferrous sulfate, ferrous gluconate, ferric citrate, and ferric sulfate. Because its higher dissolvability, ferrous iron in dietary enhancements is included bioavailable than ferric iron.\textsuperscript{[3,4]} High portions of advantageous iron cause gastrointestinal reactions, for example, sickness and constipation.\textsuperscript{[9]} Other types of supplemental iron, for example, heme iron polypeptides, carbonyl iron, iron amino-corrosive chelates, and polysaccharide–iron buildings, may have little sum gastrointestinal symptoms than the ferrous or ferric salts.\textsuperscript{[4]}

Each iron enhancement contains a diverse measure of natural particle. For instance, ferrous fumarate is 33\% natural iron by weight, while ferrous sulfate is 20\% and ferrous gluconate is 12\% basic iron.\textsuperscript{[4]} However, as a rule convergences of extraordinary type of iron is planned for the Supplement Facts plate, while the clients are not obligatory to gauge the amount of iron provided by different types of iron enhancements.

Since the literature survey, it was discovered that 14–18\% of Americans are with iron enhancement. 12–19 years children are in a scope of 6\% use, lactating ladies are 60\% utilization extend and pregnant ladies are in 72\% usage.\textsuperscript{[9,11]}

**COMMONLY USED IRONIC COMPOUND IN IRON SUPPLEMENTS**

Ferrous sulfate is also famous as green vitriol. This is used to treat or prevent the iron deficiency throughout pregnancy and anemia. While ferrous gluconate or ferrous fumarate tablets are complete double, the quantity is compulsory to meet the demand of elemental iron in ferrous sulfate tablets. However, if any unabsorbed dietary iron is present in our body, it may increase free radical production in the colon to concentrations which would lead to mucosal cell damage or increased construction of carcinogens.

Ferrous gluconate is a type of mineral iron used in oral iron supplement, and ferrous gluconate is absorbed in the stomach and small intestine. It forms ferritin when united with apoferrin. Ferritin is stored in the liver, spleen, red bone marrow, and intestinal mucosa as a storage form of iron. This transport oxygen to the tissues by hemoglobin and this iron is also found in myoglobin, transferrin, and ferritin and is component of a number of enzymes such as catalase, peroxidase, and cytochromes. Ferrous gluconate is also used as food additives, color retention agent, and nutrient supplement.

Ferrous fumarate is an alternate salt type of the mineral iron utilized in dietary expansion to treat iron insufficiency related disorder. Ferrous fumarate increases serum ion concentration, which is then assimilated into hemoglobin that is required for the transport of oxygen. The overabundance iron is put away in reticuloendothelial cells. It is utilized as a source of dietary iron in uncommon dietary sustenances.

Ferric citrate is another compound which is normally utilized in iron enhancement. It is an acknowledged option in contrast to ferrous sulfate since it is gentler on the stomach and is all the more effectively consumed by the body.\textsuperscript{[12]} Ferric citrate is promoted in a brand name Auryxia and is a usually realistic iron enhancement used to delight pallor in individuals with unending kidney malady.\textsuperscript{[2]}

Ferric ethylenediaminetetraacetic acid (EDTA) is beneficial into different nourishment things, for example, grains, flour, and powdered beverages, as a sustaining operator. As a dietary enhancement, ferric EDTA included numerous nations, as the U.S., China, Mexico, the Philippines, and a few European states. To overcome iron inadequacy, it is added to kids’ drug in the U.K. what is more, France. The Food and Drug Administration endorsed the utilization of ferric EDTA, as a sustenance added substance to an assortment of sauces, including soy sauce, sweet and sharp sauces, and fish sauce in the United States.\textsuperscript{[2,13]}

Ferrous succinate as supplemental iron is in the anticipation and treatment of iron insufficiency frailty. Iron has putative invulnerable improving, anticarcinogenic, and discernment upgrading exercises.

Iron dextran is a dark colored, somewhat viscous fluid complex of ferric hydroxide and dextran for intravenous or intramuscular use. Iron dextran is utilized for the treatment of patients with reported iron inadequacy in which oral organization is unsuitable or incredible.\textsuperscript{[13]}

Ferric pyrophosphate is an iron substitution item. The presence of free iron causes various reactions as it can catalyze free extreme course of action and lipid peroxidation just as the event of associations of iron
in plasma. The ferric particle is firmly complexed by pyrophosphate. It shows a developing interest as this insoluble structure can be milder in the gastrointestinal tract and present higher bioavailability. Ferric pyrophosphate is utilized for the treatment of iron misfortune or iron inadequacy as detailing with a milder gastrointestinal impact. This is affirmed by the Food and Drug Administration as sustenance added substance and utilized in fortifier.

Iron (II) sulfate heptahydrate is a hydrate that is heptahydrate type of iron (2+) sulfate. It is utilized as a wellspring of iron in the treatment of iron insufficiency sickness, utilized in nutraceutical, and diminishing operator. This is normally utilized in fluid measurement medicines. In any case, for strong measurement medications, the monohydrate is regularly utilized. It contains an iron (2+) sulfate (anhydrous).

Reinforcing of nourishment with iron is one progressively elective strategy to support the fundamental mineral like iron. For instance, fortress of flour with iron is the act of purposely expanding the substance of a basic mineral in nourishment, to recuperate the healthful nature of the sustenance. This is the perform dependent on general well-being to profit them with negligible hazard to well-being. Fortress of nourishments with folic corrosive has been commanded in numerous nations solely to advance the folate status of pregnant ladies to forestall neural tube defect.[12]

RESULTS

Iron deficiency occurs either due to chronic blood loss or intake of food which is not sufficient to meet our body’s requirement. Normally ferritin which is an iron store that is sufficient for accelerated erythropoiesis and restoration of iron homeostasis. If homeostasis remains for a long period in weeks to months, then the iron supplement is required to treat this disorder. Iron deficiency may be due to ectoparasitism, endoparasitism, hematuria, epistaxis, hemorrhagic skin, coagulopathy, thrombocytopathy, and gastrointestinal hemorrhage.

Heme iron from supplements or red meat may increase the formation of cancer-causing N-nitroso compounds in the digestive tract which was revealed in clinical trials in humans.[14,15]

Added reports suggest that taking iron supplements is well and good, especially for women. However, some of the iron supplements be causing more harmful. Researchers from Chalmers University of Technology in Sweden and collaboration with the UK Medical Research Council and Cambridge University found two iron compounds, ferric citrate and ferric EDTA, are often used in dietary supplements and as a food additive correspondingly, in worldwide markets can increase the biomarkers for colon cancer, signifying a link to the deadly disease.[16-19] They have identified two iron compounds such as ferric citrate and ferric EDTA could increase the production of amphiregulin, a biomarker for colon cancer. American Cancer Society estimated 50,630 deaths are due to colon cancer in the previous year in the U.S. alone.

As of the literature survey, ferric citrate and ferric EDTA have been ever-increasing tumor formation in mice by developing colon cancer. The learning was carried out only in the animal model, and the possible effects on human cells were not earlier investigated.

Recently, the study was carried out in two types of cultured human colon cancer cells to come across the effect of normal supplemental doses. The effect of ferric citrate and ferric EDTA was compared with ferrous sulfate, which is normally used ion dietary supplement on two types of cultured human colon cancer cells by cell proliferation assays and Western blot analysis. Ferrous sulfate exhibited no effect whatsoever, whereas both ferric citrate and ferric EDTA led to increases in cellular levels of amphiregulin, a biomarker used for cancer and its receptors. The effect is noted even at very low doses of the two compounds.[12,20]

The total quantity of 3–4 g of body iron in ordinary adults is in hemoglobin. The excess iron is stored in the form of ferritin or hemosiderin in the liver, spleen, and bone marrow or is located in myoglobin in muscle tissue.[21] Just the little measures of iron are discharged in urine, feces, the gastrointestinal tract, and skin. Misfortunes are more noteworthy in discharging ladies as a result of blood misfortune.[22-24] Hepcidin, a coursing peptide hormone, is the key controller of both iron retention notwithstanding the dissemination of iron all through the body, incorporating into plasma.[25-27]

Hence, intense admissions of in excess of 20 mg/kg iron from enhancements or drugs can prompt gastric bombshell, clogging, queasiness, stomach agony, heaving, and faintness, particularly if sustenance is not taken in the meantime.[8,28,29] Taking enhancements containing 25 mg natural iron or more can likewise decrease zinc ingestion and plasma zinc fixations.[3,30,31] Overdoses of iron, once ingestions of 60 mg/kg, can prompt multisystem organ disappointment, trance-like state, seizures, and even death.[9,32]

Iron over-burden happens in certain grown-ups who have ingested iron enhancements for delayed interims.[33] Iron over-burden issue is genetic hemochromatosis, which bit by bit construct iron
in tissues and organs. Ultimately, untreated hemochromatosis makes the danger of joint inflammation, malignancy, diabetes, and heart failure. Still in little overabundance measure of iron may expand the hazard for a liver ailment, for example, cirrhosis and disease, heart assault or heart disappointment, diabetes mellitus, osteoarthritis, osteoporosis, metabolic disorders, hypothyroidism, hypogonadism, and inexhaustible indications. Once in a while, it prompts sudden passing. Neurodegenerative illnesses, for example, Alzheimer’s, early-beginning Parkinson’s, Huntington’s, epilepsy and numerous sclerosis are quickened by abundance iron.

Fortress of flour with iron was cultivated before in created nations to fight iron deficiency. Some of these nations gloat been repressed iron braced flour since of conceivable antagonistic impacts of abundance iron. Various increasingly broad surveys are reachable with arranging of potential dangers in private nations with weight control plans contain an assortment of iron-rich foods.

People with genetic or secure clutters may influence iron retention. Iron fortress will give to press load anyway the extra addition in body iron load in many people would be minor. To maintain a strategic distance from neural cylinder deserts in pregnant ladies, a stronghold of sustenances with folic corrosive has been commanded in numerous nations to show signs of improvement, the folate status of pregnant ladies. Neural tube defect—a birth deformity which influenced 0.5% (1 out of 200) US births before fortress began

In general, the admission of folic corrosive in pregnancy to challenge neural tube forms. Along these lines in all people, this fortress prompts raised blood convergences of true to form happening folates and of unmetabolized folic corrosive. High blood centralizations of folic corrosive may diminish common killer cell cytotoxicity, and high folate status may decrease the reaction to drugs used to treat intestinal sickness, rheumatoid joint pain, psoriasis, and malignant growth. High folate may lessen nutrient B-12 status, which prompts expanded danger of intellectual weakness and iron deficiency in the older and, in pregnant ladies, through an expanded danger of insulin obstruction and stoutness in their youngsters. This way, a high folic corrosive admission because of stronghold likely could be hurtful for a larger number of individuals than the arrangement is intended to help.

DISCUSSION

Iron supplements are used medically by pregnant women, breastfeeding mothers, people who have lost blood, and patients with chronic kidney disease and cancer. The researchers inform that these groups of people might be at a higher risk of overwhelming harmful levels of the carcinogenic chemical. Ferric citrate and ferric EDTA increase the formation of amphiregulin, that is known cancer marker. Hence, people use these two supplements might often be connected with long-term cancer with poor prognosis. However, consumers do not know the type of compounds present in the supplement; it can repeatedly be complex to identify what accurately they are buying. Many stores and suppliers, even pharmacies, do not point toward what kind of iron compound is current. Prescribed label contain iron, or iron mineral to facilitate is not easy for consumers to recognize if their iron supplement is safe for them. However, this study has its limitations; the outcome is completed based on lab-cultured cancer cells. However, the clinical trial in human being reveals the exact mechanisms in the human body, which is yet to study.

However, iron is an essential mineral for our body, but particularly toxic when excess amount is consumed. Numerous blood transfusions due to blood loss or anemia, getting iron shots or injections, or consuming high levels of supplemental may overload iron compound. As the body has no active excretion pathways for iron, a continuous load of iron exceeding 1–2 mg/day will result in iron overload, and organ failures counting liver and heart. Therefore, iron supplement and a high folic acid intake due to to fortification may be harmful to more people than the policy is calculated to help.

A different way of eliminating excess iron is blood loss. As a result, menstruating women and those who donate blood frequently be at lower risk of iron overload. Measures to abolish iron toxicity are by accepting individual body iron metabolism. Development of patients’ outcome is suitable promising if a right early diagnosis is made, and suitable management of these inflexible conditions by means of iron chelation with high compliance is conducted.

Although iron deficiency is able to occur to anyone, women are at major risk gender and as such, are in greater danger from the effects of these carcinogenic iron compounds. Recurrently during menstruation and pregnancy women will lose more iron, as a result, they have to depend on iron supplements to attain the minerals they cannot get from presently their diet. Food is a natural source of iron than any type of iron supplement.

CONCLUSION

To finish up as of our perceptions, just patients among reported iron lack, iron consumption, or endless blood
misfortune ought to ingest iron enhancements. Still nourishing iron over-burden can be created behind the long periods of supplementation. Patients could assume control over the counter arrangements of iron enhancements for an alleged medical advantage and be uninformed that it conveys potential dangers as taken for an extensive stretch of time. Doctors ought to manage the impacts and term of supplemental iron treatment and sever it if there is no therapeutic sign. People among hemochromatosis-related changes or specific sorts of sickness may have expanded hazard to create iron over-load with ingestion of iron enhancements. Since overabundance body iron in any structure is to be required to be hurtful and can manual for organ harm, patients with iron over-burden from iron enhancements ought to likewise be blessed to receive dispose of the over-burden iron.

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