METABOLISM OF IRON IN HUMAN BODY: A REVIEW

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ABSTRACT:- Iron is essential nutrients, excesses or deficiencies of which cause impaired cellular functions and eventually cell death. Systemic iron deficiency generates cellular iron deficiency, which in human results in diminished work capacity, reduced intellectual capacity, diminished growth, alterations in bone mineralization, and diminished immune response. Iron is similarly required in numerous essential proteins, such as the hemecontaining proteins, electron transport chain and microsomal electron transport proteins, and iron-sulfur proteins and enzymes such as ribonucleotide reductase, prolyl hydroxylase phenylalanine hydroxylase, tyrosine hydroxylase and aconitase. The essentiality of iron resides in their capacity to participate in one electron exchange reactions. Iron metabolism is very fine tuned. The free molecule is very toxic; there¬fore, complex regulatory mechanisms have been developed in mammalian to insure adequate intestinal absorption, transportation, utilization, and elimination.

KEYWORDS:- Iron, Proteins and Human body.

INTRODUCTION:-
Human iron metabolism is the set of chemical reactions that maintain human homeostasis of iron at the systemic and cellular level. Iron is both necessary to the body and potentially toxic. Controlling iron levels in the body is a critically important part of many aspects of human health and disease. Hematologists have been especially interested in systemic iron metabolism because iron is essential for red blood cells, where most of the human body's iron is contained. Understanding iron metabolism is also important for understanding diseases of iron overload, such as hereditary hemochromatosis, and iron deficiency, such as iron deficiency anemia. Iron is an essential bioelement for most forms of life, from bacteria to mammals. Its importance lies in its ability to mediate electron transfer. In the ferrous state, iron acts as an electron donor, while in the ferric state it acts as an acceptor. Thus, iron plays a vital role in the catalysis of enzymatic reactions that involve electron transfer (reduction and oxidation, redox). Proteins can contain iron as part of different cofactors, such as iron-sulfur clusters (Fe-S) and heme groups, both of which are assembled in mitochondria.

Transition metal iron is the most abundant metal on the earth. Its capacity to swiftly change between different valences, mainly Fe (II) and Fe (III), makes it an excellent electron transporter and it is found in a large number of essential enzymes and other macromolecules [Kurzt Eaton J & Brunk U, 2010]. Iron is, however, also associated with harmful processes, many of which take place inside the lysosomal compartment where iron occurs in low mass redox-active form, creating Fenton-type reactions with hydrogen peroxide that may diffuse from the cytosol (vide infra) [Terman A et al. 2010]. Most metabolically active iron exists within hemoglobin, myoglobin and cytochromes [Double L et al., 2008]. In mitochondria, iron is a vital part of the electron-transporting complexes and in the cytoplasm it is a prosthetic group of a number of enzymes that drive redox reactions [Double L et al., 2008]. Iron cycles easily between ferric (oxidized; Fe (III)) and ferrous (reduced; Fe (II) and readily forms complexes with oxygen, making this metal a central player in respiration and related redox processes [Tino Kurz et al., 2011]. Its facile interconversion from Fe (II) to Fe (III) makes it hazardous if present in free form. Fe (II) can react with oxygen (O_2) to form superoxide $(O_2^{\bullet -})$. More importantly, Fe (II) can also homolytically cleave hydrogen peroxide (H_2O_2) yielding hydroxyl radicals $(HO^{\bullet})$ and hydroxyl ions (OH^-) [Mandel S et al., 2006]. Therefore, antioxidants that are supposed to react with and detoxify $HO^{\bullet}$ must be present in tissues in enormous and non-physiological concentrations to be able to significantly protect against this radical [Mandel S et al., 2006]. Iron is an essential bio-metal required for normal physiological functioning of the cell. However, the levels of iron in the cell need to be tightly balanced, as

an excess of iron can have damaging effects due to the generation of iron-catalyzed reactive oxygen species (ROS) [Hamacher-Brady A 2012]. Unbalanced iron levels always affect the physiology of organisms. For instance, excess intracellular iron may result in the generation of reactive oxygen species (ROS), which can damage lipids, proteins, DNA; these adverse effects may eventually lead to genome instability and cell death in almost all organisms [Orrenius S et al., 2011, Romero A et al., 2014 & Turrens JF 2003]. On the other hand, iron deficiency is extremely common in different species. Iron deficiency caused anemia is one of the major public health problems, particularly in children and pregnant women [Denic S & Agarwal M. 2007, Miller JL. 2013]. In plants, the photosynthesis process is highly dependent on iron. Iron deficiency often reduces the amount of electron transferring complexes, increases proteins involved in carbon fixation, and causes chlorosis [Lopez-Millan F et al., 2013, Solti A 2008]. In budding yeast Saccharomyces cerevisiae, iron deficiency leads to the dysfunction of iron-dependent enzymes, hemoproteins and Fe-S proteins, thereby altering glucose metabolism and biosynthesis of amino acid and lipid [Philpott CC et al., 2012].

Chemistry of Iron:
Iron, element 26 in the periodic table, is the second most abundant metal (after aluminum) and the fourth most abundant element of the earth's crust. Its position in the middle of the elements of the first transition series (so designated because their ions have incompletely filled d orbitals) implies that iron has the possibility of various oxidation states (from −II to +VI), the principal ones being II (d6) and III (d5), although a number of irondependent monooxygenases generate high valent Fe (IV) or Fe (V) reactive intermediates during their catalytic cycle. Whereas Fe^{2+} is extremely water soluble, Fe^{3+} is quite insoluble in water (Ksp = 10^{-39} M and at pH 7.0, $[Fe^{3+}]$ = 10^{-18} M) and significant concentrations of water-soluble Fe^{3+} species can be attained only by strong complex formation. Iron (III) is a hard acid that prefers hard oxygen ligands while iron (II) is on the borderline between hard and soft, favouring nitrogen and sulfur ligands. The interaction between Fe^{2+} and Fe^{3+} and ligand donor atoms will depend on the strength of the chemical bond formed between them [Robert C. 2001].

Chemical Properties of Iron:-
Iron (Fe) belongs to the sub-family of transition elements that also includes Cr, Mn, Co, Ni and Zn. In living matter, iron exists in two stable oxidative states: ferrous (Fe^{2+} and ferric (Fe^{3+}). In aqueous media, Fe^{2+} is spontaneously oxidized by molecular oxygen to Fe^{3+} to form $Fe(OH)_3$. Consequently, the maximal solubility of Fe in an oxidative environment such as extracellular fluids is limited by the product solubility constant of $Fe(OH)_3$. At pH 7.0 the maximal solubility of Fe^{3+} is very low at 10^{-17M}, whereas Fe^{2+} solubility is much greater at 10^{-1M}. Because of the low solubility of Fe in the presence of oxygen, over time organisms have been forced to evolve proteins that are able to bind Fe^{3+} and keep it thermodynamically stable but, at the same time, make it kinetically available for biological processes. In vertebrates, the function of extracellular Fe^{3+} binding and transport is fulfilled by the plasma protein transferrin (Tf), which has two Fe^{3+} binding sites with affinity constants on the order of $1–6\times10^{22}$ M^{-1} for Fe^{3+} [Miguel A & Marco TN 2005].

Iron Metabolism:-
Iron metabolism is a set of chemical reactions maintaining human homeostasis of iron at both systematic and cellular level [Sahni S et al., 2014]. Many proteins have been identified playing roles in iron metabolism. Some proteins such as ferritin or Tf are the main cargos of blood iron, whereas peptides such as iron regulatory proteins (IRPs), hepcidin, and matriptase (Mt2) are key determinants of iron regulation at different physiological levels [Munoz P & Humeres A. 2012]. A set of different proteins, notably divalent metal transporter-1 (DMT1), ferroportin (FPN1), and transferrin receptors (Tfrs) in association with ferroxidases such as duodenal cytochrome B, ceruloplasmin (Cp) and heme carrier protein (HCP1), are involved in the cellular membrane transportation of iron (Weiss G 2009). Others proteins such as myoglobin (Mb), Hb and many different enzymes are the 'end' products of iron metabolism, because they require iron for their functions [Weiss G 2009].

Regulation of Iron:
Iron is present in many different types of cells, having specific functions such as iron supply or iron storage. Iron-exporting cells include enterocytes, which absorb iron from the digested food, macrophages and

hepatocytes, which both recycle iron according to demand. In addition, placental syncytiotrophoblast cells transport iron into the fetal circulation. Cellular iron homeostasis is maintained by IRP1 and IRP2 [Anderson P et al., 2012]. IRPs bind to iron-responsive elements (IREs) located in the untranslated regions of genes and mRNAs encoding proteins involved in iron uptake, storage, utilization, and export. The IRP/IRE system is thus effectively involved in the fine-tuning of the synthesis as well as suppression of the many proteins involved in the multiple 'ironomics' pathways [Sophie W et al., 2014]. Role of Iron as Cofactor of Enzymes Eukaryotic cells contain numerous iron-requiring proteins such as iron-sulfur (Fe-S) cluster proteins, hemoproteins and ribonucleotide reductases (RNRs). These proteins utilize iron as a cofactor and perform key roles in DNA replication, DNA repair, metabolic catalysis, iron regulation and cell cycle progression [Zhang C et al., 2014]. In most eukaryotic cells, iron is necessary to facilitate the assembly of functional Fe-S cluster proteins, hemebinding proteins, and ribonucleotide reductases (RNRs) [Dlouhy AC & Outten CE. 2013, Heath JL et al., 2013]. These iron-requiring proteins are abundantly present in mitochondria, cytosol, and nucleus; such proteins diversely function in electron transfer, ribosome maturation, DNA replication and repair, and cell cycle control [Kaplan J et al., 2013, Ye H &Rouault TA., 2010, White M et al., 2012]. Iron is a requisite metal in almost all biological systems [Khan MI et al., 2012]. RNRs are enzymes that require iron to reduce ribonucleotides to synthesize deoxyribonucleotides (dNTPs), there by generating the necessary precursors of DNA replication and repair [Zhang C et al., 2014]. Imbalanced dNTP pools usually lead to increased DNA mutations, DNA breaks and cell death by enhancing misincorporation and by inhibiting the proof freading function of DNA polymerases [Kumar D et al., 2010]. The disruption of hemoproteins, such as cytochromes b5 and nitric oxide synthase, possibly increases ROS production. Cytochromes b5 is a membrane bound hemoprotein and generally serves as an electron carrier in several oxidative reactions of reductases, such as NADH-cytochrome b5 reductase [Reid E et al., 2013], NADPH-cytochrome P450 reductase [Gan L et al., 2009, Pyrih J et al., 2014]. Fatty acid desaturases involved in lipid and cholesterol biosynthesis [Laradeet K et al., 2008]. Role of Iron in Heme Biosynthesis Iron is required in the synthesis of

iron-porphyrin (heme) proteins such as hemoglobin, myoglobin, cytochrome, cytochrome oxidase and nitric oxide synthase [Brown KR et al., 2004]. Heme commonly serves as the prosthetic group for hemoproteins [Pamplona A et al., 2007]. These hemoproteins are involved in oxygen transport, oxidative catalysis and electron transport [Girvan HM &Munro AW., 2013]. In addition, heme is important for systemic iron homeostasis in mammals, as it is present in many normal dietary sources [Pamplona A et al., 2007]. Many hemes are enzymatically degraded by their degradation systems, such as heme oxygenases (HO, including HO-1, 2, and 3) and microsomal cytochrome P450 reductase. A considerable amount of hydrogen peroxide (H_2O_2) is produced during heme degradation, which may cause cellular toxicity and DNA damage [Quincozes-Santos A et al., 2013, Wagener A et al., 2003]. Iron Deficiency Iron deficiency anemia is characterized by a defect in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic) [Sophie W et al., 2014]. The capacity of the blood to deliver oxygen to body cells and tissues is thus reduced [Stang J, Story M. 2005]. Iron deficiency anemia increases nuclear DNA damage in adults, as demonstrated by an increased DNA damage in anemic subjects [Aslan M et al., 2006]. Conversely, the results of iron nutritional deficiency in rats do not affect DNA stability or lipid peroxidation [Diaz-Castro J et al., 2008]. The deficiency of several ribosomal proteins (RP) can cause diamond black fan anemia (DBA), which is a genetic syndrome characterized by red blood cell aplasia [Danilova N et al., 2014]. Moreover, fanconi anemia, a genetic disorder, is caused by defects in a cluster of proteins responsible for DNA repair [Deans, J & West C., 2009]. Studies have also indicated that dietary iron-deficient anemia induces various metabolic changes and even apoptosis in rat liver [Kamei A et al., 2010]. Functions of Iron Functions of iron include but not limited to the followings: energy metabolism, cell growth and differentiation, oxygen binding and transport, muscle oxygen use and storage, enzyme reactions and Protein synthesis [Beard L, 2001].

Toxicity:-
Iron is also potentially toxic. Its ability to donate and accept electrons means that it can catalyze the conversion of hydrogen peroxide into free radicals. Free

radicals can cause damage to a wide variety of cellular structures, and ultimately kill the cell. Iron bound to proteins or cofactors such as heme is safe. Also, there are virtually no truly free iron ions in the cell, since they readily form complexes with organic molecules. However, some of the intracellular iron is bound to low-affinity complexes, and is termed labile iron or "free" iron. Iron in such complexes can cause damage as described above.

To prevent that kind of damage, all life forms that use iron bind the iron atoms to proteins. This binding allows cells to benefit from iron while also limiting its ability to do harm. Typical intracellular labile iron concentrations in bacteria are 10-20 micromolar, though they can be 10-fold higher in anaerobic environment, where free radicals and reactive oxygen species are scarcer. In mammalian cells, intracellular labile iron concentrations are typically smaller than 1 micromolar, less than 5 percent of total cellular iron.

CONCLUSION:-

Iron is an essential element in the body but its effect in the body is like a two-edged sword. At one end it is essential for maintaining most of the body functions and at the other end it becomes potentially toxic if in excess. Iron is an essential transition metal utilized in an extensive range of electron-transport mechanisms. Mitochondrial oxidative phosphorylation and many cytosolic oxidative processes depend on the capacity of iron to alternate between valences. The needed iron-sulphur and heme complexes are mainly manufactured in the mitochondria, while cellular uptake of iron-transferrin and release of iron from its store in ferritin involves participation of the lysosomal compartment.

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