NON HAEMATOLOGICAL EFFECTS OF IRON DEFICIENCY – A PERSPECTIVE
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ABSTRACT
Iron deficiency is a continuum beginning from lowering of tissue stores to the phase of exhausted tissue stores, interference with iron driven biochemical reactions in the body, microcytosis, hypochromia, increasing severity of anaemia with all its attendant consequences. Iron deficiency anaemia is a very well known concept but what is often not appreciated is the effect of broad canvas of iron deficiency on various tissues, organs and systems in our body in addition to iron deficiency anaemia leading to concept of “Iron deficiency disease”. In this condition not only tissue delivery of oxygen is compromised but proliferation, growth, differentiation, myelogenescis, immunofunction, energy metabolism, absorption and biotransformation are compromised leading to abnormal growth and behaviour, mental retardation, reduced cardiac performance and work efficiency, infection etc which ultimately leads to the concept that “iron deficiency not only breaks the machine but also wrecks the machinery.”

Key words: Biochemical Basis, Development, Myelogenesis, Infection, Pica.

INTRODUCTION
Iron is an essential element for the growth and development. It is a constituent of major oxygen carrying protein haemoglobin in the red cells. It is also a common knowledge that with the deficiency of iron in the body the red cells contain lesser amount of haemoglobin and results in anaemia. It is very well known that iron deficiency causes thrombocytosis. Almost three decades back Oski[1] introduced the concept of “non haematological effects” of iron deficiency. We did know that several non haematological consequences of iron deficiency like glossitis, koilonychia dysphagia etc are associated with iron deficiency anemia, long before biochemical assays of various parameters were generally available to clinicians. The merit of Oski’s paper and several articles subsequently
written by him\textsuperscript{[2,4]} and others pointed that in an iron deficient state even in the absence of anaemia several clinical signs and symptoms are seen and these signs and symptoms are the result of iron deficiency per se and not due to the consequences of anaemia.

Biochemical basis of causation of non haematological signs and symptoms in iron deficiency.

Oxygen transport and cellular respiration: Iron is an important component of several respiratory proteins and respiratory enzymes. Hence deficiencies of iron in these molecules cause defective electron transport and cellular respiration. The red coloured protein, haemoglobin in red cells carries oxygen. Similarly muscles which constitute a major bulk of our body as well as heart which is almost synonymous with life contains iron containing protein myoglobin. This myoglobin is present in a very high quantity in postural muscles, where it behaves as an important oxygen trapping proteins.

Several mitochondrial proteins within the cells including cytochromes contain iron and these are both haem proteins and non haem iron-sulphur complexes.\textsuperscript{[5]} Several of the citric acid cycle enzymes like aconitase, succinate dehydrogenase, isocitrate dehydrogenase require iron as the essential cofactor for the enzyme activity.

Bactericidal activity and oxidant damage

Several enzymes which are involved in bactericidal action and those involved in production and break down of \( \text{H}_2\text{O}_2 \) are iron containing enzymes. Catalase is such an enzyme; hereditary deficiency of this enzyme can cause recurrent mouth ulcer and oral infection.\textsuperscript{[6]} Myeloperoxidase in neutrophils also requires iron for its optimum bactericidal activity.

Porphyrin metabolism

Certain porphyrin metabolizing enzymes are also under feed back control of iron. Haem synthase, Uroporphyrinogen decarboxylase are the two examples. Thus it is clearly seen that in the absence of iron even if haemoglobin levels are maintained artificially, cellular respiration in each and every cell is affected and the cells are metabolically compromised. When a cell is metabolically compromised several consequences occur. (i) cells may not be in a position to carry out their assigned function. (ii) cells may not be able to reproduce or divide, as these need energy and the energy is derived from cellular respiration and oxidative phosphorylation (iii) finally cells may die by apoptosis.

Pigment metabolism

Iron is intimately concerned with melanin metabolism. The enzyme phenylalanine hydroxylase,\textsuperscript{[7]} homogentisic oxidase requires iron for formation of homogentisic acid and melanin quinones. Hence iron deficiency can affect the formation of melanin pigments. Phenylalanine metabolism is also intimately concerned with catecholamine and thyroxin generation in the respective tissues.

DNA and RNA metabolism\textsuperscript{[8-10]}

DNA synthesis is an extremely important step before a cell can divide. In fact most of these syntheses take place during the “S” (synthetic) phase of cell division. One of the most important enzymes involved in DNA synthesis is ribonucleotide reductase. This enzyme requires iron for its optimum action and the enzyme is responsible for converting ribonucleotides to deoxyribonucleotides. In the absence of iron this reaction cannot proceed satisfactorily and building blocks of DNA synthesis i.e. deoxy ribonucleotides cannot be produced. Xanthine oxidase, which is involved in oxidation of purines also requires iron as one of the cofactors.

Monoamine Metabolism

Catecholamine is one of the most important monoamines involved in adrenergic neurotransmission and is the glandular secretion of adrenal medulla with potent action on blood pressure, cardiac rhythm, carbohydrate and lipid metabolism. In the central and peripheral nervous system it is the harmonious function and interaction of cholinergic and adrenergic nervous system that control our innumerable viscero vegetative functions, e.g. sleep, wakefulness, moods and so on. Iron has also been found to be an important component of neuronal monoamine oxidase.\textsuperscript{[10,11,12]} Tryptophan hydroxylase, another enzyme involved in production of serotonin also uses iron as an essential cofactor.\textsuperscript{[13]} Dopamine receptors are downregulated during iron deficiency\textsuperscript{[14]} and there is an altered GABA metabolism in this condition.\textsuperscript{[14]}

Cytochrome P-450 and drug metabolizing enzyme\textsuperscript{[15]}

There are a large number of drug metabolising enzymes of this class which contains haeme iron as essential component of the enzyme. These enzymes are involved in phase I reaction in biotransformation of drugs and other xenobiotics. These enzymes are present in ample quantities in liver. Hence it is expected that iron deficiency may alter metabolism of some of the drugs. The clinical consequences of this is uncertain.

Myelinogenesis

Oligodendroglia in central nervous system contains large amount of iron. Studies have shown increased transferrin receptors in vascular endothelium of choroid plexuses in the brain. Knowing the essential role of oligodendroglia in myelinogenesis, it is but natural to explore the possibility that iron deficiency in experimental animals may cause abnormal myelination during immediate postpartum development phase corresponding to 4-20 month age of human infants. Biochemically oligodendroglia contains a protohaem oxygenase, which is involved in cholesterol biosynthesis and may influence myelination through this process.

Hence to summarise, the biochemical function of iron points to cell proliferation, differentiation, \( \text{O}_2 \) transport, electron transport, cholesterol biosynthesis, neurotransmitter modulation, xenobiotic metabolism, biotransformation, fuel homeostasis through modulation of various glycolytic and citric acid cycle enzymes, specific and non specific immune function by involving T cell activation, mitosis, macrophage NRAMP 1 and 2 production and neutrophil myeloperoxidase activity in microbial killing. These functions are so pervasive and so basic for survival that iron deficiency is likely to interfere with function of every organ system in the body.
In the succeeding paragraph we will see apart from anaemia and its consequences how iron deficiency perse present in its heterogenous clinical form.

**Clinical presentation of iron deficiency gastrointestinal tract**
Angular stomatitis, Glossitis, Koilonychia, sideropenic dysphagia with postcricoid oesophageal web [16] in iron deficiency can easily be explained by the necessity of iron for cellular proliferation and differentiation. Whether iron deficiency can cause atrophic gastritis and malabsorption syndrome is a question, which is more difficult to answer. Weight of evidences seems to indicate that iron deficiency can be caused by these pathologies rather than they themselves be caused by iron deficiency except under rare circumstances. Several studies from India have shown that iron deficiency anaemia which is resistant to iron therapy is caused by symptomatic celiac disease [17,18] which was considered to be rare in India. One of the clinical presentations of iron deficiency with or without anaemia is abnormal eating behavior or pica which can be in the form of eating clay (geophagia), ice (pagophagia) and similar things. A study conducted by Mehta et al [19] also showed malabsorption of D-xylose in 7/25 patients of iron deficiency which was reversed by parenteral iron therapy and significant rise of hemoglobin, proving thereby that iron deficiency per se can cause malabsorption. [20] In certain patients eating beetroots can cause red colored urine (beturia) if underlying iron deficiency is present.

**Skin and its appendages**
Premature loss of hair, alopecia areata, greying of hair, folliculitis, acne and reduced growth of nails [20] have been reported with iron deficiency with or without anaemia. Koilonychia is one of the best known clinical features of iron deficiency.

**Cardiovascular physiology**
Several non invasive studies like systolic time intervals [21] have shown myocardial dysfunction during iron deficiency without anaemia as evidenced by reduced PEP / LVET ratio. This ratio was normalized within days of iron replacement before haemoglobin started to rise significantly. Similarly abnormal ST segment depression on treadmill test has been demonstrated in iron deficiency anaemia and this test reversed on parenteral iron therapy. [22]

**Effect on cerebral function**
Poor cortical arousal, diminished attention span, reduced scholastic performance in schools have been reported in iron deficiency anaemia [23-25] and these abnormalities partly reverse on iron replacement. Depression, disturbances of sleep rhythm and reduced mental alertness also occur in this condition. [20] It is believed that in infants with iron deficiency not all parameters of cognitive development can be totally reversed; neither the various domains of higher cerebral function show recovery at the same rate. Hence the degree of reversal often depends on time of measurement of these parameters. [24,27] It has been demonstrated that iron is concentrated in different parts of central nervous system like globus pallidus, substantia niagra, nucleus accumbens in an adult but the pattern changes in different age groups. [10] However, most of these areas are associated with dopaminergic and GABA minergic pathways and several receptors of dopamine D1 & D2 are down regulated in iron deficiency anaemia. [12-14] Peripheral nerve conduction velocity also improves in a study following iron replacement. [28]

**Renal function and drug metabolism**
The important role of P-450 cytochrome oxidase group of enzymes in drug metabolism is very well known. Thus it is but natural that some of the drug metabolism may be altered in iron deficiency. However in iron deficiency with anaemia there could be several reasons for altered drug handling by the body in addition to its effect on metabolism. The absorption of drug from GI tract may be delayed or may be incomplete. Increased cardiac output and redistribution of blood flow to various organs particularly to liver may alter the drug available to biotransformation site and may alter the volume of distribution of the drug as evidenced by prolonged half life and its correction by iron therapy on antipyrene half life. [29] Finally the abnormal creatinine clearance due to iron deficiency may also alter the drug excretion. Hence there are theoretical reasons that every phase of drug handling i.e. absorption, distribution metabolism and excretion is likely to be altered by iron deficiency but in practice no adverse reaction or interaction due to drug administration specially caused by iron deficiency has been reported.

**Musculoskeletal function**
Easy fatigability and decreased work performance in iron deficiency and its improvement following iron therapy have been reported in various case control studies. This finding has enormous consequences in national economy. Studies show that anaemia due to iron deficiency tends to affect fast acting muscle function (sprint function) whereas cellular deficiency of iron tends to affect endurance exercise. [10,31-33]

**Iron deficiency and immune function**
A lot of studies have been done on the effect of iron deficiency in immune function starting with the seminal paper by Chandra et al. [34] Clinically increased incidence of furunculosis, candidiasis, upper respiratory infection was noted in association with iron deficiency. Studies of cell mediated immunity [35,36] phagocytosis [37,38] humoral immunity [39] showed some changes in iron deficiency. However iron is also required for growth of various microorganisms, hence in this way iron deficiency anaemia in a community where certain infections are rampant may also offer some protection against these infections as was evidenced by increasing incidence of malaria in an African population when iron supplement was given. [40]

**Miscellaneous**
Iron deficiency has been linked to abnormalities in implantation and growth of embryos in animals particularly with reference to the development of lungs, heart and brain [41] how its implication in human fetal growth and development needs to be
assessed. Several other clinical conditions like restless leg syndrome, hyperventilation in infants and febrile seizures in children have been linked to iron deficiency. The role of iron was also found to interfere with certain areas of blood coagulation notably platelet function and fuel economy leading to hyperglycemia and insulin sensitivity. Thyroid hormone production may also be compromised with iron deficiency.

**DISCUSSION**

In this brief overview it has been amply demonstrated that iron deficiency in some way or other interferes with many vital functions in the body; however iron excess is equally dangerous as evidenced in cases of transfusional siderosis and haemochromatosis. Over the course of evolution our body has developed a tight iron absorption mechanism as there is no full proof mechanism of substantially altering the iron excretion from the body. As a result the tightness of iron absorption from the gut is often tilted towards iron deficiency rather than iron excess. A recent study by Mehta et al showed almost 40% of the clinically asymptomatic nursing staff had either anaemia or biochemical evidence of iron deficiency or both. Other studies conducted in India also showed similar picture.

Critical requirement of iron in O2 transfer in intermediary metabolism, in electron transport, in oxidative phosphorylation and in neurotransmission makes it an extremely important nutritional element in human economy. In our undergraduate physiology curriculum we used to read a famous line by JBS Haldane on the chapter on anoxia “anoxia not only breaks the machine but also wrecks the machinery”. Iron deficiency not only produces “anaemic anoxia” while producing anaemia; stagnant anoxia while producing myocardial dysfunction and heart failure in almost all tissues it produces a condition allin to “Histotoxic anoxia” by depressing the electron transport in the mitochondria and interfering with some of the key enzymes of Tricarboxylic acid cycle. Only difference in the anoxia caused by iron deficiency in the cellular level compared to that of caused by cyanides is the rapidity of the action of cyanide. The effect of anoxia (better called hypoxia) due to deficiency of iron is insidious and takes months and years, and allows the body to undergo some of the readjustments, which ultimately translates into decreased growth, mental ability, work performance and immune function.

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This first set of children' heating in 2000. And while Canadian and continued to burn biomass for cooking and persisting violation and reporting major monitors’ population as 18% of the country. Mortality, as 18% of the country’s largest challenges. Contributed to a decline in diarrheic diseases contributed to a decline in diarrheic diseases. It finds that Nor’s environmental indicators in Nor contributed to a decline in diarrheic diseases. That data shows a rising number of childhood medical and biological quality in Nor. The adverse effect of iron repletion on the course of certain infections. Br Med J 1978;2:1113–5. The adverse effect of iron repletion on the course of certain infections. Br Med J 1978;2:1113–5.


