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Role of Taurine in Children with Anaemia

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Iron deficiency (ID) is the most common health problem noted in paediatric population. The prevalence of anaemia in India among paediatric group is 23.5% in 5-7 years and 58.7% in children below 5 years. The major cause of ID in children is low intake of iron from the actual requirement. ID results in iron deficiency anaemia (IDA) which impacts energy production resulting in fatigue, and depletion of muscle stores. Iron is cofactor for energy production enzyme in the tricarboxylic acid cycle and synthesis of carnitine (which carries fatty acids across the mitochondrial membrane). Iron also plays a crucial role in enzyme rate-limiting step for gluconeogenesis, and plays a role in the function of certain neurotransmitter amines. Fatigue is the cardinal symptom of anaemia due to increased ID. Taurine is an amino acid present in mammalian tissue, most abundantly found in skeletal muscle. Muscle senescence and atrophy may decline the taurine concentrations, alters iron metabolism and increases oxidative injury. Therefore, a causal relationship may exist between taurine and iron metabolism in muscle health and disease. Iron preparations are major stand-by for the treatment of IDA; however, these preparations are associated with gastric side-effects. In anaemic patients, taurine along with iron supplementation is reported to: Enhance red blood cells (RBC) membrane stabilization, osmoregulation, and detoxification, Decrease GI related side effects of iron salts (anti-oxidant and anti-inflammatory effect), By building up energy, can give symptomatic relief from lethargy and weakness, Enhance light chain ferritin isoform (FTL) involved in cellular iron storage. Therefore, combination of taurine with iron may result in improved lethargy and increased iron stores in skeletal muscles resulting in treatment of IDA and associated cardinal symptom, fatigue.

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1. INTRODUCTION

Iron deficiency (ID) is a common problem in the paediatric population. Two populations at greatest risk for iron deficiency are toddlers transitioning from infant formula to table foods, and adolescent females [1]. World Health Organization (WHO), a decade ago in 2008, estimated that globally 1.62 billion people were anaemic, with the highest prevalence of anaemia (47.4%) among preschool-aged children; of these 293 million children, 89 million live in India. After a decade, the scenario has not improved, and still, India has a significant burden of anaemia among paediatric population. The prevalence of anaemia in India among children is 23.5% in 5-7 years and 58.7% in children below 5 years [2,3]. The primary cause of all types of anaemia in the world is due to iron deficiency, and young children are more vulnerable to this disease because of their rapid growth and need of high iron. The major cause of iron deficiency anaemia (IDA) in children is low intake of iron then the actual requirement. However, in developing countries, iron deficiency may not always be the only or primary cause of anaemia; in fact, it can also result from other nutritional deficiencies, such as folate and vitamin B12, malaria, other infectious and parasitic diseases. The prevalence of anaemia in the developing countries is very high and is multi-factorial that often coincides. The factors involve socioeconomic, nutritional, biological, environmental, and cultural characteristics [2]. To effectively address the situation, health providers would require to comprehensively understand the root causes of anaemia [4].

2. CLINICAL PRESENTATION OF ANAEMIA

Patients with ID anaemia can present with symptoms that are associated with all anaemia, which are sometimes associated with specific signs due to iron deficiency (Fig. 1) [5].

3. AETIOLOGY OF ANAEMIA

There are multiple physiologic, environmental, pathologic and genetic causes of ID that lead to IDA (Fig. 2). More importantly, aetiologies may vary considerably or tend to coexist in different patient populations (children, women and elderly), geographies (developing and developed countries) and specific clinical conditions. There is also a considerable complexity and a large repository of terminology for various subtypes of ID which are commonly used interchangeably or in contradiction in the literature [6].

Very frequent	Frequent	Rare
• Paleness (45–50%) • **Fatigue (44%)** • Dyspnoea • Headache (63%)	• Diffuse and moderate alopecia (30%) • Atrophic glossitis (27%) • Restless legs syndrome (24%) • Dry and rough skin • Dry and damaged hair • Cardiac murmur (10%) • Tachycardia (9%) • Neurocognitive dysfunction • Angina pectoris • Vertigo	• Haemodynamic instability (2%) • Syncope (0·3%) • Koilonychia • Plummer-Vinson syndrome (<0·1%)

Fig. 1. Clinical presentation of anaemia in children [5]

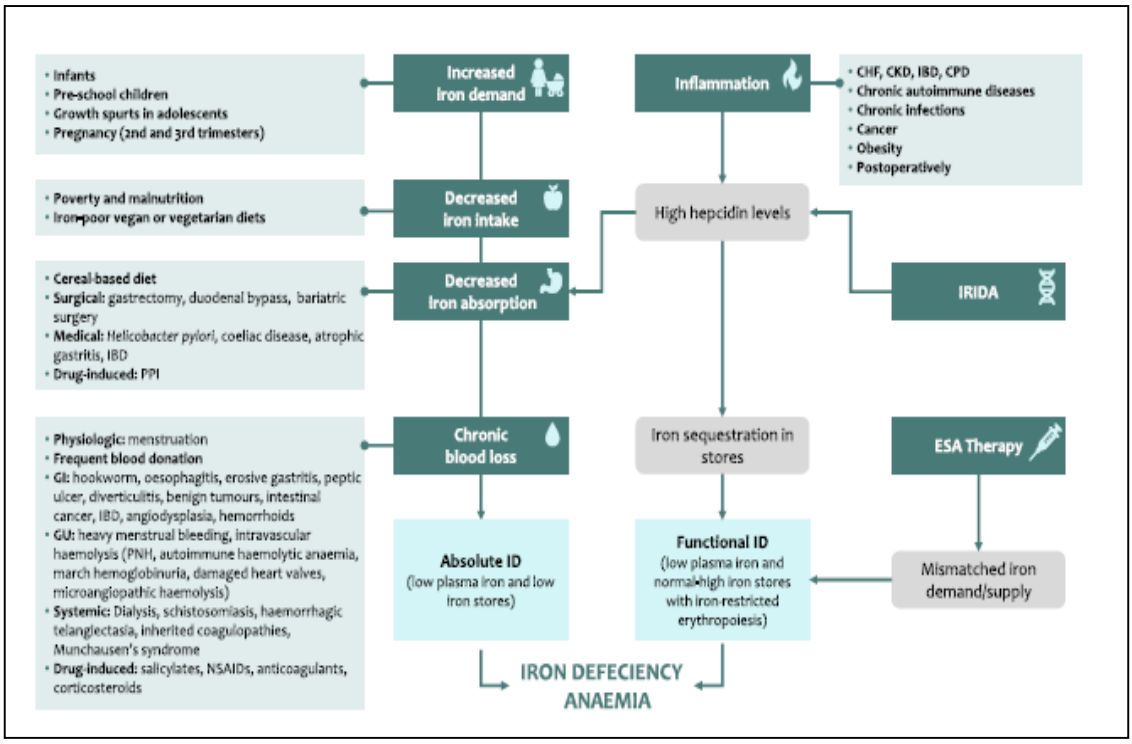

Fig. 2. Various aetiologies of iron deficiency anaemia [6]

CHF: Chronic heart failure; CKD: Chronic kidney disease; CPD: Chronic pulmonary disease; ESA: Erythropoiesis-stimulating agents; IBD: Inflammatory bowel disease; ID: Iron deficiency; IRIDA: iron-refractory iron deficiency anaemia; NSAIDs: Nonsteroidal anti-inflammatory drugs; PNH: Paroxysmal nocturnal haemoglobinuria; PPI: Proton-pump inhibitors

4. CLINICAL IMPLICATIONS OF ANAEMIA

IDA usually develops slowly from the progression of ID. Certain clinical consequences associated with anaemia are described in Fig. 3. IDA is associated with decreased cognitive performance and delayed motor and cognitive development in children. IDA impacts energy production resulting in fatigue, and depletion of muscle stores. Additional effects of ID attributed to the impact of low iron levels on DNA replication and cell cycle (oral lesions, hair loss, nail abnormalities), immune response (increased susceptibility to infections), myelogenesis and neurotransmission (restless leg syndrome) and inhibition of cytochrome P450 production (altered drug metabolism) [6].

5. IRON AND ENERGY

Iron sufficiency is major factor responsible for normal energy of the body. Iron plays crucial role for formation of hemoglobin and myoglobin which are oxygen carriers in red blood cells and muscles, respectively. Iron also plays an important role in several mitochondrial and electron transport proteins warranted for oxidative phosphorylation of ADP to ATP. Iron may also take part in energy production based on the following 4 ways [7,8]:

- Iron is co-factor of enzyme in the tricarboxylic acid cycle
- Iron is cofactor for the synthesis of carnitine, which is responsible for carrying fatty acids across the mitochondrial membrane.
- Iron provides power to an enzyme rate-limiting step for gluconeogenesis.
- Iron also plays a significant role in the function of certain neurotransmitter amines.

In conclusion, iron plays a crucial role as it delivers oxygen to cells, facilitates the use of oxygen by cells, and spurs other metabolic pathways; moreover, iron is crucial for energy. Iron is as important as oxygen in converting chemical energy from diet to useful metabolic energy required for life [7,8].

6. FATIGUE AND ANAEMIA

Fatigue is defined as a persistent feeling of tiredness, weakness or exhaustion that limits the capacity of physical and/or mental work of an individual [9]. Fatigue is mostly described as a multi-causal, multi-dimensional and complex concept in which psychological, biochemical and physiological mechanisms play a role [9].

Iron deficiency is generally associated with increased fatigue reduced exercise intolerance, diminished quality of life, increased hospitalization rates and reduced survival as compared with patients without ID [6]. This is supported by animal studies which show that ID in heart muscles, irrespective of systemic iron levels, is associated with decreased heart contraction, ventricle dilation and heart failure, which can be attributed to the decrease in iron-sulphur cluster synthesis and mitochondrial electron transport in response to stress [6]. IDA results in low delivery of oxygen to body tissues due to reduced iron levels in muscle or brain tissue, and impact on energy production, myoglobin synthesis and brain development [6].

7. TAURINE AND IRON METABOLISM IN MUSCLE: THE LINK

Iron plays an important part in many physiological and pathophysiological biochemical processes. The iron pool in the body comprises of:

- Heme proteins: Hemoglobin, myoglobin and heme enzymes
- Transport and storage proteins: Transferrin and ferritin
- Functional iron-sulfur cluster proteins: e.g., complexes I, II and III of the respiratory chain

Iron proteins are important for cellular growth and proliferation. It also plays an important role in muscle energy metabolism. The most part of iron in cells is bound with protein, and only about 1-2% of iron is free [10].

Taurine (2-aminoethanesulfonic acid) is a small, sulfur-containing [3-amino acid with a sulfonic acid group] rather than the more common carboxylic acid group [11]. Taurine, a non-proteinogenic amino sulfonic acid, is degraded product of endogenous methionine and cysteine or it is derived from dietary sources of animal origin [10]. Taurine is intracellular free amino acid present in abundance in most mammalian tissues. Taurine is also involved in few biochemical reactions [11]. High concentrations of taurine are present in excitatory tissues such as, retina, brain, heart and skeletal muscle. These excitatory tisssues are reported to have high metabolic rate and are highly vulnerable to oxidative damage [10].

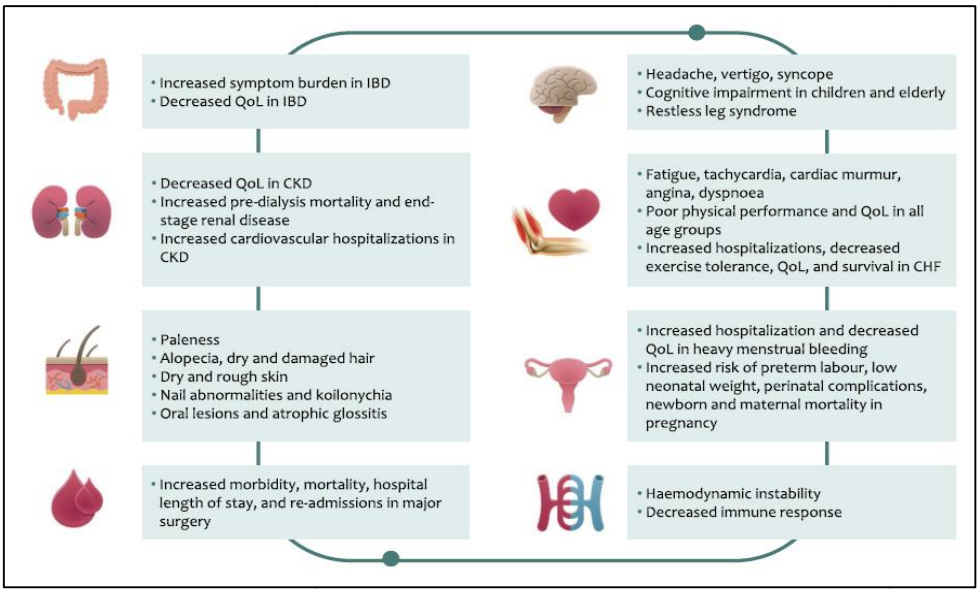

Fig. 3. Clinical implications of iron deficiency anaemia [6]

CHF: Chronic heart failure; CKD: Chronic kidney disease; IBD: Inflammatory bowel disease; QoL, quality of life

Skeletal muscle is major storage of taurine in mammalian body. In humans and other species, taurine is substantially in higher concentration in oxidative type I compared to glycolytic type II muscles. Muscle senescence and atrophy results in decline of cellular taurine concentrations, altered iron metabolism, and increased oxidative injury. Moreover, aging and diseased state results in altered iron metabolism, particularly when the labile iron concentration is higher. Therefore, a clinically significant link exists between taurine and iron metabolism in muscle health and disease [10].

8. DIAGNOSIS OF ANAEMIA IN CHILDREN

The basic action for diagnosis of anaemia is ordering complete blood count and peripheral blood smear test. When complete blood count is evaluated well, it provides major clues for condition present in childhood. If anaemia is present, the complete blood count should be checked for hemoglobin and hematocrit values based on the normal values for age and gender. The lower limits of normal by age and gender specified by the World Health Organization should be used for distinguishing patients with anaemia (Table 1). For infants less than 6 months, due to physiological anaemia, lower values are observed; however, these values should not be less than 9g/dL in physiologic anaemia in term infants [12].

9. TREATMENT OF ANAEMIA IN CHILDREN

The important principles in treatment of IDA include diagnosis, detection of cause that results in ID and elimination of this cause, replacement of deficiency, improvement in nutrition and educating patients and families about anaemia [12].

After 6 months of breastfeeding, children need an additional source of iron to maintain adequate iron nutrition. WHO recommends micronutrient powders in children aged 6–23 months if the prevalence of anaemia is 20% or higher, with the aim of providing 12·5 mg elemental iron daily, preferably as ferrous fumarate. Thereafter, iron is added to children's daily food. In a 2013 meta-analysis,83 food fortification with micronutrient powder reduced anaemia by 31% and iron deficiency by 51% compared with placebo in children younger than 2 years [5].

9.1 Iron Supplementation

In 2011, WHO recommended daily iron supplementation with 60 mg of elemental iron to prevent iron deficiency in menstruating adolescent girls. Similar recommendations were made for children aged 0–5 years (2 mg/kg daily) and children aged 5–12 years (30 mg daily) [5].

For therapeutic iron supplementation, four common iron preparations are available: ferrous sulphate, ferrous sulphate exsiccated, ferrous gluconate, and ferrous fumarate. Iron absorption by enterocytes seems saturable; thus a dose of iron could prevent absorption of subsequent doses. Ascorbic acid addition to iron formulation can improve the bioavailability of dietary iron [5].

Parenteral iron treatment is recommended when oral iron treatment fails, particularly in cases where rapid correction of anaemia is warranted and in patients suffering from gastrointestinal absorption disorders such as, celiac disease or inflammatory bowel disease [12].

9.2 Iron Therapy and its Side-effects

Iron preparations available in market, are associated with side-effects which may be severe when they develop.

Iron absorption with ascorbic acid increases which results in increased side-effects associated with oral iron supplements as it increases the amount of ferrous iron downstream. These side-effects include epigastric discomfort, nausea, diarrhoea, and constipation [5].

Table 1. Limits for hemoglobin and hematoctrit values by the World Health Organization [11]

Groups by age and gender	Hemoglobin g/dL	Hematocrit (%)
6-59 months	11	33
5-11 years	11.5	34
12-14 years	12	36
Females age >15 years	12	36
Males age>15 years	13	39

In patients on iron infusion, particularly rapid infusion, may develop side-effects such as, allergy, anaphylaxis, hypotension, nausea, vomiting and abdominal pain [12].

10. ROLE OF TAURINE SUPPLEMENTATION IN CHILDREN WITH ANAEMIA

It has been known for several decades that taurine concentrations in brain are high, and many researchers reasoned intuitively that it should have some specific function or functions.[10] Taurine supplementation in premature infants may have significant effects on growth and development of these infants. Taurine is an amino acid that helps infants absorb fat from the gastrointestinal tract and ensures that the liver deals with waste products efficiently. Taurine may also have important roles in protecting nerves from damage, especially in the eyes and ears [13].

In anaemic patients, taurine along with iron supplementation is reported to enhance 4 parameters:

- Enhances red blood cells (RBC) membrane stabilization, osmoregulation, and detoxification [14].
- Anti-oxidant and anti-inflammatory effect helps ion reduction of gastrointestinal side effects [15].
- Provides symptomatic relief from lethargy and weakness by building up energy [16].
- Enhances light chain ferritin isoform (FTL) involved in cellular iron storage [10].

10.1 Enhances Red Blood Cell Membrane Stabilization, Osmoregulation, and Detoxification

Taurine functions as direct or indirect antioxidant. Taurine is reported to stabilize biomembrane structures and function by blocking lipid peroxidation and reducing the membrane permeability which was increased due to effects of oxidants. Taurine inhibits homeostasis of intracellular ion and blocks the phosphorylation of protein membrane. The anti-oxidative effect of taurine stabilizes RBC membrane and scavenges free radicals that enhances membrane lipid peroxidation. Thus, taurine stabilizes RBC membrane [15].

10.2 Anti-oxidant and Anti-inflammatory Effect

In various tissues, taurine is known to induce anti-oxidant and anti-inflammatory effects [15]. Commercial iron supplements results in increased oxidative stress in gut which in turn causes gastrointestinal side-effects. Taurine is an excellent antioxidant which may exert anti-oxidative effect resulting in reduced iron induced oxidative stress [16].

The iron induced oxidative stress is associated with elevated inflammatory effects.[16] Taurine being an anti-oxidant plays a key role in alleviating inflammation caused due to increased oxidative stress [16]. Taurine reacts with inflammatory components forming a taurine conjugate which exerts anti-inflammatory and antioxidant properties [17].

Taurine when given along with oral iron increases the efficacy of iron in IDA treatment [16].

10.3 Symptomatic Relief from Lethargy and Weakness by Taurine

The largest amount of body's taurine is present in skeletal muscle, via the taurine transporter (TauT) activity. Supplementation of taurine enhances amino acid content in skeletal muscle, without any change in TauT activity. Taurine supplementation provides parallel an increase in force and a greater resistance and recovery after fatigue. These changes enhance calsequestrin, (the calcium binding protein) simultaneously. calsequestrin1 maintains high amounts of calcium in the cysterna of sarcoplasmic reticulum. This suggests that taurine supplemented muscle stores a higher quantity of calcium with higher calcium availability for contraction [15].

Taurine induces an inhibitory control over the channels that couple metabolic state of the myofiber with membrane excitability - ATP dependent potassium (KATP) channels and calcium-activated potassium channels. Taurine blocks KATP channel by binding the channel complex present near sulphonylurea receptor. During ischemia reperfusion injury, opening of KATP provides cytoprotective effect of the preconditioning mechanisms through prevention of calcium ions influx and preservation of muscle ATP content. Taurine efflux may be required during exercise and/or ischemia to relive a basal

inhibitory effect and to increase potassium membrane repolarization through specific channels stimulated by ATP depletion and/or intracellular calcium accumulation. This results in taurine's protective effect for exercise induced fatigue or impairment in muscle performance related to ischemic injury [15].

Taurine plays a crucial in energy metabolism by [18]:

- Reducing NADH/NAD+ ratio during glycolysis via activation of complex I and NADH sensitive enzymes
- Conjugating bile acids to facilitate lipid absorption via intestines
- Restoring fatty acid oxidation by increasing PPAR alpha levels

Restoration of taurine levels through supplementation leads to improved contractile function of muscles.

10.4 Enhances Light Chain Ferritin Isoform (FTL) Involved in Cellular Iron Storage

Taurine supplementation increases the light chain ferritin isoform (FTL) which is crucial for cellular iron storage and myoglobin protein levels. FTL-rich ferritin accumulates more iron ions comparewd to heavy chain ferritin isoform (FTH). Therefore the cellular iron storage capacity can be higher in the taurine containing cells, demonstrating the prevention of excess labile iron accumulation. After iron supplementation the levels of the heme proteins myoglobin and cytochrome c increases significantly. Most iron is present as heme protein, i.e. hemoglobin in red blood cells and in this process taurine plays a regulative role [10].

11. CONCLUSION

Iron deficiency is common in pediatric population. Fatigue being a cardinal symptom of anemia is associated with impaired quality of life. Available iron supplements may enhance iron content but the fatigue remains the unaddressed issue. Moreover, these iron supplements are associated with gastrointestinal side-effects. Taurine, an amino acid present in abundance in mammalian tissues is associated with various function and is known to enhance energy. When iron supplementation is provided with taurine, it may enhance lethargy and fatigue in anemic patients. Moreover, taurine being anti-inflammatory and anti-oxidative it may reduce the gastrointestinal side-effects caused by iron. In addition taurine is reported to enhance iron stores which may further contribute to fast increase in serum iron levels. Taurine along with iron may boost energy, reduces GI side-effects, stabilizes RBC membrane, enhances iron stores, and provides complete care to anaemic patients with significant rise in hemoglobin levels.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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