Review Article

Anaemia & Fatigue: Role of taurine

Abstract

Anaemia is a condition in which the number of red blood cells and consequently their oxygen-carrying capacity is insufficient to meet the body's physiologic needs. Iron deficiency is thought to be the most common cause of anaemia globally, but other nutritional deficiencies, acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect haemoglobin synthesis, red blood cell production or red blood cell survival, can all cause anaemia. Anaemia affects roughly a third of the world's population; half the cases are due to iron deficiency. It is a major and global public health problem that affects maternal and child mortality, physical performance, and referral to health-care professionals. Oral iron is readily available, inexpensive, and convenient treatment option for anaemia management. Fatigue is considered as the cardinal symptom of anaemia which needs to be addressed along with increasing haemoglobin. This article highlights the roles played by taurine in increasing the effectiveness of oral iron for increasing hemoglobin in iron deficiency anaemia treatment.

Key words: Anaemia; iron deficiency; haemoglobin; oral iron; fatigue; taurine

1. Introduction

Iron status can be considered as a continuum from iron deficiency with anaemia, to iron deficiency with no anaemia, to normal iron status with varying amounts of stored iron, and finally to iron overload - which can cause organ damage when severe. Iron deficiency, and specifically iron deficiency anaemia (IDA), remains one of the most severe and important nutritional deficiencies in the world today. Every age group is vulnerable. Iron deficiency impairs the cognitive development of children from infancy through to adolescence. It damages immune mechanisms, and is associated with increased morbidity rates. During pregnancy, iron deficiency is associated with multiple adverse outcomes for both mother and infant, including an increased risk of haemorrhage, sepsis, maternal mortality, perinatal mortality, and low birth weight [1]. WHO cut-offs for defining anaemia and its severity is presented in Table 1 [2].

Table 1: Haemoglobin levels to diagnose anaemia at sea level (g/l) [2]

Population	Non-Anaemia	Anaemia [a]		
		Mild [b]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

[a] Haemoglobin in grams per litre

[b] "Mild" is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent.

2. Prevalence

It is estimated that in developing countries nearly all women are to some degree iron deficient, and that more than half of the pregnant women suffer from anaemia. Even in industrialized countries, the iron stores of most pregnant women are considered to be deficient. Moreover, as much as 30% impairment of physical work capacity and performance is reported in iron-deficient men and women [1].

2.1. Global anaemia prevalence

Globally, anaemia affects 1.62 billion people, which corresponds to 24.8% of the population. The highest prevalence is in preschool-age children and the lowest prevalence is in men. However, the population group with the greatest number of individuals affected is non-pregnant women (Table 2) [3].

Table 2: Global anaemia prevalence and number of individual's affected [3]

Population group	Prevalence of anaemia		Population affected	
	Percent	95% CI	Number (millions)	95% CI
Preschool-age children	47.4	45.7-49.1	293	283-303
School-age children	25.4	19.9-30.9	305	238-371
Pregnant women	41.8	39.9-43.8	56	54-59
Non-pregnant women	30.2	28.7-31.6	468	446-491
Men	12.7	8.6-16.9	260	175-345
Elderly	23.9	18.3-29.4	164	126-202
Total population	**24.8**	**22.9-26.7**	**1620**	**1500-1740**

2.2. Indian Scenario

India is one of the countries with very high prevalence of anaemia in the world. Almost 58% of pregnant women in India are anaemic and it is estimated that anaemia is the underlying cause for 20–40% of maternal deaths in India. India contributes to about 80% of the maternal deaths due to anaemia in South Asia. Nutritional anaemia is a major public health problem in India and is primarily due to iron deficiency. The National Family Health Survey-3 (NFHS-3) data suggests that anaemia is widely prevalent among all age groups (Table 3) [4].

Table 3: Prevalence of anaemia among different age groups [4]

Age groups	Prevalence of anaemia (%)
Children (6‑35 months)	79
Children (6‑59 months)	69.5
All women (15‑49 years)	55.3
Ever married women (15‑49 years)	56
Pregnant women (15‑49 years)	58.7
Lactating women (15‑49 years)	63.2
Adolescent Girls	
12–14 years	68.6
15‑17 years	69.7
15‑19 years	55.8

3. Pathophysiology

Iron deficiency is defined as a condition in which there are no mobilizable iron stores and in which signs of a compromised supply of iron to tissues, including the erythron, are noted. The more severe stages of iron deficiency are associated with anaemia [1].

When iron-deficient erythropoiesis occurs, haemoglobin concentrations are reduced to below-optimal levels. When individual haemoglobin levels are below two standard deviations (-2SD) of the distribution mean for haemoglobin in an otherwise normal population of the same gender

and age who are living at the same altitude, iron deficiency anaemia is considered to be present [1].

Iron deficiency is the result of long-term negative iron balance. Iron stores in the form of haemosiderin and ferritin are progressively diminished and no longer meet the needs of normal iron turnover. From this critical point onward, the supply of iron to the transport protein apotransferrin is compromised. This condition results in a decrease in transferrin saturation and an increase in transferrin receptors in the circulation and on the surface of cells, including the erythron [1].

All tissues express their need for iron in exactly the same way, i.e. by the same type of transferrin receptors on cell surfaces in proportion to actual iron need. Accordingly, a compromised supply of iron to the erythron is associated with a similarly insufficient supply of iron to all other tissues [1].

Functionally, the lack of mobilizable iron stores will eventually cause a detectable change in classical laboratory tests, including measurement of haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, total iron-binding capacity, transferrin saturation, and zinc-erythrocyte protoporphyrin [1].

4. Consequences of Anaemia

Anaemia can cause a range of symptoms including fatigue, weakness, dizziness and drowsiness. Children and pregnant women are especially vulnerable, with an increased risk of maternal and child mortality. The prevalence of anaemia remains high globally, particularly in low-income settings, where a significant proportion of young children and women of childbearing age can be assumed to be anaemic. Iron deficiency anaemia has also been shown to affect cognitive and physical development in children and reduce productivity in adults [5].

Anaemia is an indicator of both poor nutrition and poor health. It is problematic on its own, but it can also impact other global nutritional concerns such as stunting and wasting, low birth weight and childhood overweight and obesity due to lack of energy to exercise. School performance in children and reduced work productivity in adults due to anaemia can have further social and economic impacts for the individual and family [5].

The consequences of anaemia in women are enormous as the condition adversely affects both their productive and reproductive capabilities. Among women, iron deficiency prevalence is higher than among men due to menstrual iron losses and the extreme iron demands of a growing foetus during pregnancies, which are approximately two times the demands in the non-pregnant state. Worldwide, it is estimated that about 20% of maternal deaths are caused by anaemia; in addition, anaemia contributes partly to 50% of all maternal deaths. First, anaemia reduces women's energy and capacity for work and can therefore threaten household food security and income. Second, severe anaemia in pregnancy impairs oxygen delivery to the foetus and interferes with normal intra-uterine growth, resulting in intrauterine growth retardation, stillbirth, LBW and neonatal deaths. Therefore, anaemia is a major contributor to poor pregnancy and birth outcomes in developing countries as it predisposes to premature

delivery, increased perinatal mortality and increased risk of death during delivery and postpartum [4].

5. Anaemia and Fatigue

Sufficient iron is key for normal energy. Iron is necessary for forming haemoglobin and myoglobin, the oxygen carriers in red blood cells and muscles, respectively. Iron is also part of several mitochondrial electron transport proteins required for the oxidative phosphorylation of ADP to ATP. Iron may also influence energy in four other ways. It is a cofactor for an enzyme in the tricarboxylic acid cycle. It is a cofactor in the synthesis of carnitine, which carries fatty acids across the mitochondrial membrane. It powers an enzyme rate-limiting step for gluconeogenesis. And it plays a role in the function of certain neurotransmitter amines. In short, because it delivers oxygen to cells, facilitates the use of oxygen by cells, and spurs other metabolic pathways, iron is essential for energy. Iron is as vital as oxygen in converting chemical energy from food into metabolic energy for life [6].

Fatigue is considered the cardinal symptom of anaemia. Pathogenesis of anaemia-related fatigue remains unclear, but some suggest that abnormalities in energy metabolism play a role in inducing fatigue. At the clinical level, the relationship between anaemia and fatigue is universally accepted. Use of validated instruments has shown a direct effect of haemoglobin levels on fatigue and other quality of life parameters. Thus, amelioration of anemia and fatigue should be considered simultaneously (Table 4) [7].

Table 4: Relationship between haemoglobin levels above or below 12 g/dL and several parameters of clinical benefit [7]

Correlations Between Anemia and Fatigue: Hb > 12 g/dl versus Hb ≤ 12 g/dl	
QOL Parameter	**P values**
Higher QOL scores	0.003
Less fatigue	0.01
Fewer non-fatigue anaemia symptoms	0.02
Better physical well-being	0.003
Better functional well-being	0.001

Abbreviations: Hb, hemoglobin; QOL, quality of life

6. Management of Iron Deficiency Anemia

Iron deficiency is the predominant cause of anaemia across countries and in both sexes, with women more commonly afflicted. There is clear evidence to support prompt treatment in all patients with iron deficiency anaemia because it is known that treatment improves quality of life and physical condition as well as alleviates fatigue and cognitive deficits [8].

Oral iron supplementation is effective when intestinal uptake is intact. However, its use should be limited to patients with mild anaemia (Hb, 11.0-11.9 g/dL in non-pregnant women and 11.0-12.9 g/dL in men) because repletion occurs slowly. When faster repletion is desired, intravenous administration is the preferred route. The pros and cons of oral and intravenous iron is highlighted in table 5 [8].

Table 5: Oral vs. Intravenous Iron [8]

Oral Iron	
Pros	**Cons**
• Over the counter availability • Convenient • Cost-effective • Effective in patients without impairment of intestinal absorption	• Slower iron repletion due to limited daily intestinal absorption • Limited patient compliance due to dose-dependent gastrointestinal side-effects • In disease setting the uptake of iron is impaired • May result in mucosal injury or potential disease exacerbation in patients with inflammatory bowel disease
Intravenous iron	
Pros	**Cons**
• Rapid repletion of iron stores • Safe, particularly when formulations with dextran are avoided • Effective in patients with impaired intestinal absorption	• Administration requires healthcare professionals which increases the costs. • Can result in iron overload and transient increase in oxidative stress • May result in anaphylactic reaction when administered with dextran-containing formulations

6.1. Oral iron

Oral iron is readily available, inexpensive, and convenient, making it a viable treatment option. However, intestinal iron absorption is limited. The maximum rate of absorption of 100 mg of oral iron is 20% to 25% and is reached only in the late stage of iron deficiency. Latent iron deficiency and iron deficiency anaemia correspond to mean absorption rates of 10% and 13%, respectively, whereas healthy males absorb 5% and healthy females 5.6%. Iron that remains in the intestinal lumen may cause mucosal injury, and studies in animal models suggest an exacerbation of disease activity and the induction of carcinogenesis in IBD. Furthermore, dose-dependent gastrointestinal side effects hinder compliance and result in non-adherence in up to 50% of patients. Thus, it is reasonable to adjust the dosage to improve tolerability. Although doses typically range from 100 to 200 mg of elemental iron per day, successful repletion can be achieved with doses as low as 15 to 30 mg of elemental iron daily [8].

6.2. Iron salts

Several formulations are available over the counter and are typically composed of ferrous iron salts (e.g., ferrous sulfate, ferrous gluconate, and ferrous fumarate) [8]. There are many oral iron preparations, but no one compound appears to be superior to another. If ferrous sulfate has unacceptable side effects, ferrous gluconate at a daily dose of 325 mg (35 mg of elemental iron) can be tried [9].

6.3. Gastrointestinal side-effects associated with oral iron treatment

First-line treatment is oral therapy with ferrous iron [Fe(II)] salts. Gastrointestinal side-effects are the most commonly reported adverse effects associated with oral iron treatment and include nausea, flatulence, abdominal pain, diarrhoea, constipation, and black or tarry stools. GI side-effects result in non-adherence in up to 50% of patients leading to significant treatment failures and unnecessary follow-up investigations [10].

Gastrointestinal symptoms most probably result from a combination of two factors:

(i) Free radical generation through iron-induced redox cycling in the gut lumen and at the mucosal surface which can promote inflammation and

(ii) Changes to the microbiota composition or metabolism [10].

7. Taurine

Taurine (2-aminoethane-sulfonic acid) is a sulfur-containing amino acid which is not used for protein synthesis and is therefore the most abundant free amino acid in mammalian tissues. The intracellular concentration of taurine ranges between 5 and 20 µmol/g wet weight in many tissues, especially in excitable ones, such as brain, heart and skeletal muscle. Endogenous synthesis occurs in the liver via the cysteine sulfinic acid pathway. Precursors of taurine biosynthesis are methionine and cysteine which occurs mainly in liver. The endogenous synthesis of taurine is highly variable between individuals also in relation to nutritional state, to the amount of protein intake and to cysteine availability [11].

8. Role of Taurine in Anaemia Management

Taurine supplementation can enhance 3 important parameters when given along with iron supplementation in IDA:

- Enhances red blood cell (RBC) membrane stabilization [12]
- Decreases GI related side effects of iron salts (anti-oxidant and anti-inflammatory effect) [11,12]
- By building up energy, can give symptomatic relief from lethargy and weakness.[11]

8.1 Taurine enhances red blood cells membrane stabilization

Taurine is known to function as direct or indirect antioxidant. It stabilizes biomembrane structures and function by inhibiting lipid peroxidation and preventing increased membrane permeability caused due to effects of oxidants. Taurine is also maintains intracellular ion homeostasis, and inhibits membrane protein phosphorylation. Taurine stabilizes RBC membrane by similar antioxidative effect (Figure 1) [12].

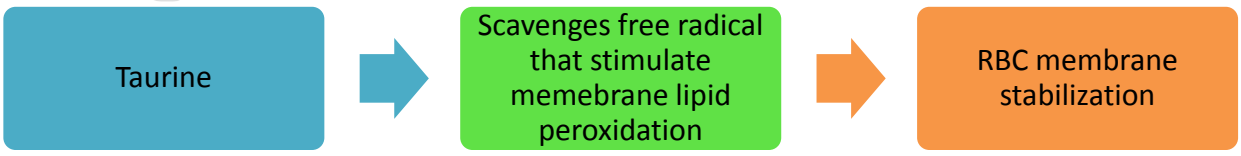

Figure 1: Red blood cell membrane stabilization by taurine [12]

8.2 Anti-oxidant and anti-inflammatory effect

Taurine is known to induce anti-oxidant and anti-inflammatory effects in various tissues [11]. Commercial iron supplements are associated significant gastrointestinal (GI) side-effects. These GI side-effects induced by iron are due to increased oxidative stress in gut. Studies suggest that taurine being an excellent antioxidant may exert its anti-oxidative effect and ameliorate the oxidative stress induced by iron [13].

The oxidative stress induced by iron is associated with increased inflammatory effects [13]. Taurine plays a key role in alleviating inflammation associated with oxidative stress [14]. At the site of inflammation taurine reacts with inflammatory components and forms less toxic taurine conjugate which exerts anti-inflammatory and antioxidant properties of taurine [15].

Moreover, Taurine when administered in combination with oral iron is reported to increase effectiveness of iron in IDA treatment [13].

8.3 Taurine provides symptomatic relief from lethargy and weakness

Skeletal muscle is one of the tissues able to concentrate the largest amount of body's taurine, via the taurine transporter (TauT) activity. Taurine supplementation significantly increases the amino acid content in skeletal muscle, without any adaptive change in TauT activity; in parallel an increase in force and a greater resistance and recovery after fatigue have been observed. These changes were paralleled by an increase in calsequestrin1, the calcium binding protein that works to maintain high amounts of calcium in the cysterna of sarcoplasmic reticulum. This suggests that taurine supplemented muscle can store a greater quantity of calcium with consequent greater calcium availability for contraction [11].

Taurine exerts an inhibitory control on channels that couple the metabolic state of the myofiber with membrane excitability, such as the ATP-dependent potassium (KATP) channels and calcium-activated potassium channels. Taurine blocks skeletal muscle KATP channel by binding the channel complex nearby the sulphonylurea receptor. During ischemia–reperfusion injury, the opening of KATP is involved in the cytoprotective effect of the preconditioning mechanisms, by preventing the influx of calcium ions and preserving the ATP content of the muscle. The efflux of taurine during exercise and/or ischemia may be required to relief a basal inhibitory effect and to enhance the potassium efflux and membrane repolarization via the specific channels activated by ATP depletion and/or intracellular calcium accumulation. This would exert a protective action against exercise-induced fatigue or impairment in muscle performance related to ischemia–reperfusion injury [11].

Taurine is also essential to maintain muscle performance and excitation–contraction coupling. It is commonly known for its claimed effects as energizer and anti-fatigue compound and it is present in many energy soft drinks as well as in supplement cocktails for athletes [11].

9. Conclusion

IDA is the most common and important nutritional deficiency across the globe. IDA is associated with range of symptoms such, as fatigue (cardinal symptom of anaemia), weakness, dizziness and drowsiness. Oral Iron supplementation being readily available and inexpensive remains the first-line treatment for IDA; however, it is associated with range of gastrointestinal side-effects such as, nausea, flatulence, abdominal pain, diarrhoea, constipation, and black or

tarry stools. Taurine being the most abundant free amino acid in mammalian tissues is reported to improve red blood cell (RBC) membrane stabilization, reduce GI related side effects of iron salts (by inducing anti-oxidant and anti-inflammatory effect), and by building up energy can provide symptomatic relief from lethargy and weakness when administered with oral iron supplementation.

10. References

1. Iron Deficiency Anaemia - Assessment, Prevention, and Control: A guide for programme managers by WHO. 2011. Accessed 17 August 2020. Available: https://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf.
2. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011. Accessed 17 August 2020. Available: https://www.who.int/vmnis/indicators/haemoglobin.pdf.
3. WHO Vitamin and Mineral Nutrition Information System (VMNIS). 2008. Accessed 17 August 2020. Available: https://www.who.int/vmnis/anaemia/prevalence/summary/anaemia_data_status_t2/en/.
4. Guidelines for Control of Iron Deficiency Anaemia. Ministry of Health and Family Welfare. 2013. Accessed 17 August 2020 Available: https://www.nhm.gov.in/images/pdf/programmes/child-health/guidelines/Control-of-Iron-Deficiency-Anaemia.pdf.
5. WHO Health Topics Anaemia. 2011. Accessed 17 August 2020 Available: https://www.who.int/health-topics/anaemia#tab=tab_2.
6. Eichner ER. Fatigue of anemia. Nutr Rev. 2001;59(1 Pt 2):S17-S19.
7. Sobrero A, Puglisi F, Guglielmi A. Fatigue: a main component of anemia symptomatology. Semin Oncol. 2001;28(2 Suppl 8):15-18.
8. Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of Iron Deficiency Anemia. Gastroenterol Hepatol (N Y). 2015 Apr;11(4):241-50.
9. DeLoughery TG. Microcytic anemia. N Engl J Med. 2014;371(14):1324-1331.
10. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383.
11. De Luca A, Pierno S, Camerino DC. Taurine: the appeal of a safe amino acid for skeletal muscle disorders. J Transl Med. 2015;13:243.

12. Higgins JP, Tuttle TD, Higgins CL. Energy beverages: content and safety. Mayo Clin Proc. 2010;85(11):1033-1041.

13. Sirdah MM, Abushahla AK, Al-Sarraj HA. Effect of the addition of the antioxidant taurine on the complete blood count of whole blood stored at room temperature and at 4ºC for up to 7 days. Rev Bras Hematol Hemoter. 2013;35(1):44-51.

14. Sirdah MM, El-Agouza IM, Abu Shahla AN. Possible ameliorative effect of taurine in the treatment of iron-deficiency anaemia in female university students of Gaza, Palestine. Eur J Haematol. 2002;69(4):236-242.

15. Marcinkiewicz J, Kontny E. Taurine and inflammatory diseases. Amino Acids. 2014;46(1):7-20.