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Pros and Cons of Iron Deficiency and Iron Deficiency Anaemia

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1. Short Communication

Iron deficiency anaemia (IDA) and iron deficiency (AD) are very common specially in low-income countries [1]. People can suffer from symptoms of anaemia in the absence of anaemia itself if they have decreased iron stores as red blood cells and tissue will not receive enough iron from the plasma when iron stores are low. During inflammation, the hepcidin level increases and ferroprotein transcription decreases which results in decreased recycling of iron to the plasma and iron absorption from the duodenum [2]. Iron is essential for physiological and cellular functions including formation and repair of DNA, enzymatic activity, mitochondrial function and neurotransmission [3]. Iron deficiency should be recognised early, investigated, and treated to improve quality of life in many patient groups including patients with chronic heart failure, chronic kidney disease, inflammatory bowel disease, and pregnant women in the second and third trimester [3]. Common debilitating symptoms due to ID include fatigue, tiredness, lethargy, dizziness, tinnitus, headache, pallor, difficulty concentrating and restless leg syndrome which can be treated by iron supplementation even in the absence of anaemia [4]. Preoperative anaemia is a predictor of high mortality and morbidity even in the absence of symptoms due to IDA [5].

Body iron in red cells is 2.5 grams, 130 mg in myoglobulin and 150 mg in enzymes [4]. Average iron stores in men are 9.7 mg/kg, 5.7 mg/kg in premenopausal women and 7.8 mg/kg in post-menopausal women in high income countries [5].

One per cent of the total body iron is bound in the plasma to transferrin which can bind to the tissue receptor called soluble transferrin receptor. Plasma iron is rapidly recycled from aged red blood cells by macrophages [6]. 1-2 mg of daily iron is absorbed from the duodenum.

Hepcidin is a liver enzyme which is essential for regulation of systemic iron hemostasis. Iron is regularly exported to the plasma from macrophages, the duodenum and the liver [6]. During iron deficiency, the level of hepcidin drops leading to increased iron absorption and increased recycling. During inflammation, increased levels of hepcidin lead to decreased iron absorption from the duodenum and decreased recycling of iron leading to a functional deficiency, as iron stores are not affected. In iron deficiency, hepcidin reduces absorption of iron, which subsequently renders oral iron ineffective. As such, patients should be treated with a parenteral infusion [7, 8].

One millilitre of blood contains 0.5 mg of iron. For each donation of blood, a person loses 250mg of iron. As such, frequent donors should receive iron transfusions after donating blood [9].

The average daily intake of iron is 8 mg in adult males, 18 mg in premenopausal women and 27 mg in pregnant women [10]. Haem iron is more efficient than non-haem iron [10]. Vitamin C increases the absorption of the non-haem iron, and tanic acid (in tea and coffee) decreases absorption of iron.

Gastric acidity increases the need for iron absorption. Proton pump inhibitors and H2 blockers adversely affect oral absorption of iron. *Helicobacter pylori* decreases absorption of iron and causes iron deficiency anemia. Eradication of *H Pylori* subsequently cures iron deficiency and iron deficiency anemia [10-11].

Bariatric surgery, whether gastric bypass or gastric sleeve, is a common cause of ID and IDA [12]. Obese people develop functional iron deficiency due to inflammation, leading to nonalcoholic steatohepatitis, subsequently increasing the ferritin. This increases the hepcidin, leading to impaired iron absorption and recycling. Premenopausal women should not be offered endoscopy unless they do not improve after iron supplementation, or if they have a family history

of colorectal cancer in the first degree relative and investigations for coeliac disease are negative.

Patients can develop iron deficiency in coeliac disease even with normal endoscopy, and usually histology shows villous atrophy and crypt hyperplasia. Transglutaminase serum IgA antibody and serum IgA are the standard of care serology. Endomysial antibodies are very specific but less sensitive for diagnosing coeliac disease. Males over fifty years and postmenopausal women should have upper and lower endoscopy to exclude gastric ulceration, autoimmune gastritis, polyp, colorectal cancer, diverticulosis, and angiodysplasia. People from areas endemic for *Plasmodium falciparum* should receive prophylaxis treatment for malaria if they develop ID or IDA [11-12].

Declining cord clamping for three minutes will prevent iron deficiency in the newborn as it maximizes restoration of red blood cells [13]. Pregnant women develop functional iron deficiency in the second trimester due to expansion of the plasma and red cell mass [14]. Treating iron deficiency in pregnancy improve the quality of life and prevents low birth weight [15]. Functional iron deficiency develops in athletes due to increased hepcidin. Patients with chronic diseases and inflammation can develop functional iron deficiency which is obscured by a normal to high ferritin as it is a positive inflammatory marker. Transferrin saturation of less than 20% and ferritin less than 30 mg is consistent with iron deficiency anemia. Other supporting features include increased soluble transferrin receptor, low hemoglobulin, increased mean cell volume width and hypochromia, transferrin saturation of less than 20% with normal or increased ferritin, normal hemoglobulin, normal soluble transferrin receptor and detectable stained iron in the bone marrow is consistent with functional iron deficiency, transferrin saturation of less than 20% with ferritin less than 70ug/l, reduced MCV, normal or increased soluble transferrin receptor, reticulocytopenia and absent stainable iron in the marrow exclusion of Parvovirus B19 infection, drug induced reticulopenia, red cell aplasia, hypo-prolefrative bone marrow (in consultation with Haematology) [16].

ID is characterised by normal hemoglobulin, mean corpuscular volume, mean cell haemoglobulin concentration, normal reticulocyte number and function, and normal soluble transferrin receptor. Reduced MCV, ferritin, transferrin saturation, reticulocytes, increased soluble transferrin receptor, elevated hepcidin and absent bone marrow stainable iron [17] are consistent with iron deficiency anaemia and functional iron deficiency. Percentage of hypochromic blood cells are equivalent to HbA1c in diabetic patients as it reflects restricted erythropoiesis in the preceding 2-3 months [18]. The number of reticulocytes reflects the iron availability for erythropoiesis in the preceding four days.

Oral iron causes few side effects and makes adherence to medication difficult. Ferrous sulphate causes constipation, diarrhoea, gastritis and black stools. An isotope study has shown frequent doses of iron during the day impairs absorption in the subsequent days and confirms that on alternate days there are higher rates of absorption (19). Parenteral iron is safe and has become the standard of care.

Iron should not be given during active sepsis as it can promote bacterial growth. Ferric carboxymaltose is very popular in Australia and is well-tolerated. A common dose is 15-20 mg/kg diluted in 250ml of saline via a fifteen minute infusion. An uncommon side effect is hypophosphatemia due to increased FGF23 which acts on the renal tubules, causing phosphaturia and hypophosphatemia. This does not cause problems and does not need phosphate replacement, except in frequent transfusion as it can cause osteomalacia and fractures [20, 21].

Patients with iron deficiency should be investigated for their cause in order for it to be treated. If blood loss has been ruled out via endoscopy, capsule endoscopy, push endoscopy, and coeliac disease serology is negative, the patient should be referred to haematologist.

In summary, iron deficiency and iron deficiency anemia can cause impaired quality of life and an increased disease burden across the globe. The safety of parenteral iron transfusion has transformed the treatment of iron deficiency, functional iron deficiency and iron deficiency anemia, and has been proven to be safe and efficient.

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