THE PUPPET MASTER OF IRON ABSORPTION

HEPCIDIN

This fact sheet is about hepcidin, its effect on iron absorption and potential groups that are at risk of iron deficiency. Although hepcidin's mechanism of action is well established, this is still an emerging area of research and a direct link between risk factors of iron deficiency and hepcidin's role in the process, are still being investigated.

IRON ABSORPTION

Iron is a vital element for the body to carry out normal function, yet it is the most common nutrient deficiency in the world[1]. Iron is absorbed in the first part of the small intestine, the duodenum. After entering the enterocytes that line the duodenal intestinal wall, iron is then stored within the liver (bound to the major iron storage protein ferritin), bone marrow or white blood cells or alternatively is utilised[2]. When iron is required it leaves the cell via the only known iron exporter, ferroportin[2]. It is then transported via the blood to be utilised for processes such as red blood cell production (erythropoiesis)[2]. Iron status must be tightly regulated within the body, as both **iron overload** and **iron deficiency** result in adverse outcomes[3].

Iron deficiency

The most common symptoms associated with iron deficiency include: fatigue, shortness of breath, pallor and headaches[4]. If iron deficiency remains untreated it can progress into anaemia, where iron stores are insufficient to support normal red blood cell production and subsequently compromises oxygen transport to tissues[5].

Iron overload

Iron overload (haemochromatosis) is a genetic condition that affects 1 in 200 New Zealanders, and is thought to be the most common genetic disorder in the world[6]. In this condition, too much iron is toxic and can damage major organs and weaken the body's immune system making it more susceptible to infections and illnesses[6]. Common symptoms associated with haemochromatosis include joint and/or belly pain, extreme tiredness, weakness, general poor health, weight loss, loss of sex drive, skin may look slate-grey or bronze[6].

Since the body has no dedicated iron excretion pathway, iron status is primarily regulated through its absorption at duodenal enterocytes, the release of recycled iron from white blood cells and release from iron stores (ferritin in the liver). All of which are subject to the influence of the hormone, hepcidin[7].

WHAT IS HEPCIDIN?

Hepcidin is the body's hormonal regulator of iron absorption. It is a 25 amino acid peptide hormone that is primarily made in the liver[7]. It elicits its effects by binding to ferroportin, the body's only known iron exporter[8]. Once hepcidin is bound to ferroportin it causes degradation and disintegration of the ferroportin cell wall, leading to iron being trapped in the cell. As a result, high hepcidin levels mean iron is unavailable for normal physiological function[8]. This means dietary iron may not be well absorbed in times when hepcidin levels are high[8].

REGULATORS OF HEPCIDIN EXPRESSION

Hepcidin levels are controlled by 3 main factors: **oxygen supply to tissues (hypoxia), inflammation and current iron status[9].**

HYPOXIA

Hepcidin expression is down-regulated in periods of low blood oxygen concentrations, hypoxia[9]. During hypoxia, iron requirements increase due to the increased red blood cell production (erythropoiesis)[9]. An increase in erythropoiesis results in an up-regulation in an erythroid regulator, erythroferrone, which supresses hepcidin production, allowing for increased iron absorption and utilisation[9]. This means those that ascend high altitudes generally have low hepcidin levels to maximise their iron availability for red blood cell formation[10].

INFLAMMATION

Inflammation up-regulates hepcidin production, in particular, the secretion of the inflammatory cytokine interleukin-6 (IL-6) has been shown to stimulate transcription (the first step in gene expression) of the hepcidin gene[11,17]. High inflammation is common in periods of chronic disease (such as inflammatory bowel disease or chronic kidney disease), and in those with a body mass index over 30kg/m^2 and potentially in certain ethnicities[24,25].

CURRENT IRON STATUS

Current iron status is a known 'evolutionary' feedback mechanism for hepcidin production. Hepcidin levels increase when iron status is high to prevent iron overload, and conversely is down-regulated when iron status is low to aid absorption and limit progression to iron deficiency[11,12].

Factor	Effect on Hepcidin	Effect on Iron	Associated Populations
Hypoxia (low blood oxygen levels)	↓ Hepcidin production	↑ Iron absorption	Those at high altitudes (travelling and living)
Inflammation, particularly IL-6	↑ Hepcidin production	↓ Iron absorption	• Athletes • Those with chronic diseases • BMI > 30kg/m^2 • Certain ethnicities
Current Iron status	Low iron stores ↓ hepcidin High iron stores ↑ hepcidin	Feedback loop: Those with low iron stores will absorb more iron, those with adequate iron stores will absorb less iron.	Adolescent females, pregnant women and children are all at risk of poor iron stores, likely due to dietary intake patterns and menstrual cycles.

RISK FACTORS FOR HIGH HEPCIDIN LEVELS

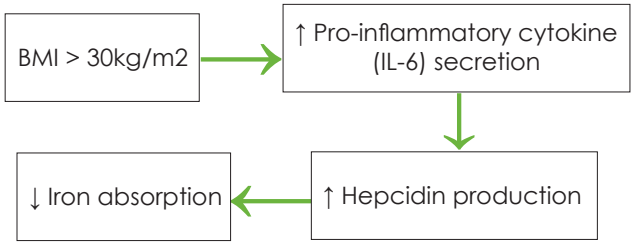
ETHNICITY

In New Zealand, the ethnicities at highest risk of iron deficiency include Māori, Pacifica and Asian[13,14]. Within New Zealand, Asians were reported to be five times more likely to be iron deficient than non-Asians[15]. African-Americans, Hispanics and South Asians have been shown to have high levels of inflammation and this is thought to be a possible contributor to the development of iron deficiency in these ethnicities[16].

Possible explanations for certain ethnicities having higher inflammation include a genetic link to increased expression of inflammatory cytokines such as IL-6[22,23] and stress associated with immigration[16]. The inflammatory link with high prevalence to iron deficiency, may be due to increases in inflammatory cytokines (IL-6) up-regulating hepcidin production, impairing iron's absorption and utilisation[8,17].

HIGHER BODY MASS INDEX

Interestingly, individuals with a body mass index (BMI) greater than 30kg/m^2 or greater than 25 kg/m^2 for Asians, have a higher risk of iron deficiency, despite consuming more iron in their diet[18]. Having a higher body mass index is shown to be associated with a pro-inflammatory state in which there is increased secretion of inflammatory cytokines[19]. This persistent pro-inflammatory state may up-regulate hepcidin levels and impair iron absorption and utilisation[18]. Research has shown that participants that went on a weight loss programme had lower levels of hepcidin and a correlating increase in iron absorption, indicating weight loss may aid in improving iron status in those with higher body mass index[20].



Proposed mechanism underpinning the link between higher BMI and iron deficiency[18]

ATHLETES

Another population group who are at higher risk of developing iron deficiency are athletes, particularly naturally menstruating females. Athletes are subject to increased iron losses via the cumulative processes of sweating, gastrointestinal bleeding, haematuria (blood loss in urine) and haemolysis (destruction of red blood cells)[21]. In addition to these increased losses, athletes may also be susceptible to iron deficiency due to decreased absorption secondary to inflammation. Inflammatory cytokines increase by 2-3 fold after strenuous or continuous exercise[21]. This acute inflammatory response causes an increase in hepcidin, peaking around 3 hours post exercise. This means iron absorption may be impaired 3-6 hours post training[21]. Timing iron-rich meals to avoid this peak in hepcidin could be helpful to maximise iron's absorption.

WHAT DOES THIS MEAN FOR HEALTH PROFESSIONALS?

- All population groups who are likely to have high hepcidin levels should have their iron levels regularly checked.
- Those of Māori, Pacific and/or Asian ethnicity may absorb iron poorly compared to other ethnicities related to variations in hepcidin concentration. These ethnicities should be regularly monitored for iron status, and may not respond as well to dietary increases in iron.
- Weight loss in individuals with a BMI over 30kg/m^2 may help to increase iron absorption, however should be done in a sustainable manner under the guidance of a health professional.
- Athletes should avoid consuming iron-rich meals 3-6 hours after exercise, and instead plan these meals after this time or before exercising to maximise absorption.

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