IRON AND THE ATHLETE

AN UPDATE

– Written by Yorck Olaf Schumacher, Qatar

INTRODUCTION

Iron plays a key role in many physiological processes and its deficiency, resulting in anaemia, is the most common medical condition in the world[1]. In sports, it is estimated that 20% of all female and 5-10% of all male athletes suffer of iron deficiency anaemia.

Deficiency in athletes is usually caused by insufficient nutritional intake due to restrictive diets in combination with impaired intestinal resorption and increased loss. While these facts have been known for decades, there have been significant recent discoveries in both the regulation of the iron metabolism and the importance of iron for endurance performance. The present article aims at summarizing these new developments for a broader audience and highlight its implications for the daily care of athletes.

HORMONAL REGULATION

Iron, transferrin and ferritin are the widely known key variables to describe the metabolism of iron and its journey from the resorption in the upper part of the small intestine to the organs. The general conception is that iron is actively resorbed in the intestine through the divalent metal transporter 1 (DMT1). It is then exported from the intestinal cell via ferroportin and binds to transferrin to be transported. The cells in need of iron express the soluble transferrin receptor (sTfR), which harvests the transferrin molecules from the circulation and make them available in the cell through endocytosis. Ferritin represents the storage form, and its level provides an indication of the iron reserves of the body (Figure 1).

The vast majority of the 3-5 g of iron in the human body are contained in red blood cells or their precursors in the bone marrow. A smaller portion is part of the enzymes of the respiratory chain powering the energy metabolism or contained in reticuloendothelial cells such as macrophages. Any hormonal regulation of iron, similar to blood sugar and its insulin cascade, was unknown until recently. In this context, two new molecules were discovered in the years 2000-2014 that have a major role in the described regulation of iron and its resorption: hepcidine and erythroferrone.

Hepcidin

Hepcidin, first described in 2000[2], is a protein produced by the liver; its main function is to block ferroportin, the transmembrane protein that mediates the export of iron from intestinal cells or macrophages to the circulation. Increases in hepcidin will thus heavily impair iron availability as the iron will be unable to leave the intestinal cells or the macrophages.

Hepcidin levels are influenced by various factors, namely hypoxia (decrease), the body's general iron status (decrease or increase) and most importantly inflammation, which increases hepcidin levels through Interleukin 6. This explains the anaemia, which is observed in many chronic diseases. Haemochromatosis, a genetic disease
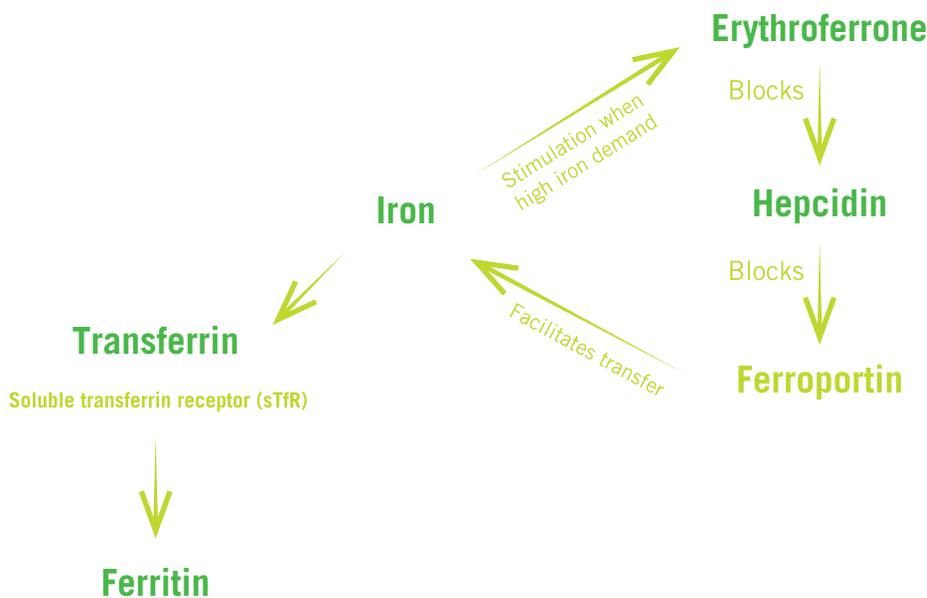
Figure 1: Schematic representation of the regualtory pathway of iron metabolism in the human body.

where iron storage is excessive, is linked to mutations in proteins related to hepcidin, downregulating its function.

Athletes have increased Hepcidin levels and thus impaired iron release from the intestinal cells for up to 72h after exercise, impairing their iron resorption during this time.

Erythroferrone

Erythroferrone is produced by erythroblasts (red blood cell precursors) in the bone marrow and is one of the regulators of Hepcidine. In fact, high levels of erythroferrone inhibit hepcidine production, and thereby allow more iron to be released into the circulation. The erythroferrone production in the erythroblasts is impacted by erythropoietin, which itself is linked in its level to the stabilization of the Hypoxia Induced Factor (HIF) 1 alpha in situations of hypoxia[3] suppression of the iron-regulatory hormone hepcidin allows increased iron absorption and mobilization from stores. We identified a new hormone, erythroferrone (ERFE).

Thus, the discovery of hepcidin and erythroferrone now completes a full pathway for iron resorption and metabolism with feedback loop which is closely related to the erythropoietic chain. In its structure, it is similar to many other endocrine systems in the organism.

In practice, hepcidine and erythroferrone have helped explaining many pathologies such as the anaemia of chronic diseases or haemochromatosis but have also shed light on certain conditions frequently seen in the athlete, for example the high prevalence of anaemia, which is, based on these new findings, not only caused by poor nutrition and increased iron loss associated to exercise, but also amplified by the increased expression of hepcidin and its negative effect on iron resorption in the training athlete.

IRON AND PERFORMANCE

Although the body only contains a rather small amount of iron, the impact of a shortage of iron can be significant. If assuming a total iron content of 3 g, 2.5 g will be contained in red blood cells, 300 mg in enzymes of the respiratory chain and 200 mg will be involved in other metabolic processes. Both red blood cells and the respiratory chain are key determinants of aerobic physical performance, as they mediate transport and metabolism of oxygen.

Obviously, iron deficiency will, from a certain severity onwards, cause anaemia (lack of red blood cells through the reduced amount of available haemoglobin, of which iron is the most important component). From a theoretical perspective, every gram of haemoglobin can bind and transport 1.36 ml of oxygen. Thus, reduced haemoglobin content will impair oxygen carrying capacity, the key determinant of aerobic endurance performance, which is described through the maximal oxygen uptake (VO2max). Conversely, a loss of 1 g of haemoglobin will reduce oxygen uptake by about 4 ml[4]. A healthy, iron repleted endurance athlete has about 10-14 g/kg of haemoglobin, an anaemic patient as little as 3-7 g/kg. (Note that these are absolute numbers of haemoglobin mass in relation to bodyweight (g/kg), not haemoglobin concentration (g/dl) which is the variable commonly measured in routine blood tests). It is clear that such a difference in total haemoglobin content and thus oxygen transport capacity will have significant impact on endurance performance. In the 1970s, numerous studies involving blood withdrawal and subsequent re-infusion have confirmed the theoretical numbers: Lacking 75 g of haemoglobin (which corresponds to about 500 ml of blood) will impair oxygen uptake by about 300 ml. From a performance perspective this translates to a performance loss of about 1 min in a 10 km race.

Non-anaemic iron deficiency

There has been a long-lasting debate on whether non-anaemic iron deficiency, i.e. iron deficiency (low iron or ferritin) with haemoglobin concentration and red cell markers within the normal range, will impair physical performance. A multitude of studies exist on this topic and a number of investigations have linked non-anaemic iron deficiency to conditions such as fatigue, altered mood state or reduced performance in military exercises (see for example[5]). Many of these studies were done on very large collectives, containing thousands of subjects, often in military settings, where diet and physical activity was well controlled. Nevertheless, the influence of methodical and socio-economic confounders was raised and outcomes in view of individual athletic performance have been controversial. In 1997, a review on the topic[6] focusing on performance, concluded that "Although oral iron supplementation is effective in raising ferritin levels, there is no evidence supporting iron supplementation for increasing endurance performance in athletes who have isolated low ferritin levels but normal haemoglobin levels".

From a basic science perspective, the influence of non-anaemic iron deficiency is much less studied. The entity in question here is the performance of the

respiratory chain. The respiratory chain is the enzymatic cascade that produces the energy that is at the basis of any metabolic process in the human body. In this cascade, several enzymes contain iron molecules and a shortage will thus potentially impair the functioning of these enzymes and theoretically affect this pathway. While nature has, in the course of evolution, always established safeguards and alternative pathways for important biological systems, it is nevertheless important to assess the impact of iron deficiency on these systems in view of athletic performance.

Interesting experiments have been conducted to investigate the importance of iron in the functioning of the enzymatic energy cascade[7,8]: In animal studies, rats were progressively deprived of iron through repetitive bloodletting until they had no measurable iron reserves anymore and assessed in their performance without and with full re-establishment of the circulating blood volume (through transfusion). The results showed that despite the full availability of oxygen transport (i.e. the acute correction of the anaemia through blood transfusion), the number of mitochondria and the activity of the enzymes of the respiratory chain was reduced when the animals were iron depleted previously. Their treadmill performance was thus impaired. The authors of the study concluded that iron deficiency without anaemia affected oxidative capacity through negatively impacting the function of the enzymes, whereas anaemia affected mostly oxygen transport through reduction in the amount of haemoglobin.

These findings and the 1997 recommendations in mind, more recent studies have approached the question from a different, combined perspective. Both "iron deficiency" and "anaemia" are arbitrary definitions based on broad reference ranges. For example, according to the World Health Organisation (WHO), a haemoglobin level lower than 12 g/dl is considered as anaemia in non-pregnant women. Ferritin levels between 15 and 150 mg/dl are widely considered as normal. It is clear that there is a considerable range of what is normal for the individual athlete. In several recent studies, researchers investigated non-anaemic athletes with various levels of ferritin (within the normal range) and supplemented them with oral and intravenous iron. They could demonstrate that even in, by definition, non-anaemic, non-iron deficient athletes, supplementation with iron resulted in an increase of haemoglobin mass and thus improved oxygen carrying capacity, which potentially entails an increase in endurance performance[9,10].

This further emphasizes the importance of iron levels and its monitoring in the athlete and has led to modified practical recommendations.

PRACTICAL RECOMMENDATIONS

Based on the arguments highlighted above and the most recent findings, Ferritin levels of above 30 ng/ml should be aimed for in adult athletes to assure full supply for their erythropoietic system and the respiratory chain. The latest results have triggered a debate whether or not these recommendations should be increased to 50 ng/ml or higher, especially in situations where the athlete spends time at altitude to enhance his performance and the demand on the iron metabolism increased. In younger athletes (younger than 15 years) slightly lower levels (20 ng/ml) seem appropriate.

If education on the iron content of various foods and the increase of nutritional intake is not sufficient to cover potential deficits, supplementation should be initiated through oral, once-a-day of 50-100 mg of elemental iron (or alternate day intake of the double dose) for 8-12 weeks, depending on the degree of deficiency. Most preparations have different types of iron (iron fumarate, iron sulfate..), the "real" content of elemental iron does usually not correspond to the iron weighing on the label (which refers to the content, i.e. iron sulfate,- fumarate etc.). For example, ferrous sulfate usually contains about 20% of elemental iron. The athlete should also be educated on inhibitors/enhancers of iron intake such as tea or coffee (which impair iron resorption) or Vitamin C

and orange juice (which improve it). Twice daily dosing has been shown to impair iron resorption and to be inferior to once a day intake, likely through downregulation in the hepcidin pathway explained above. The same applies for chronic supplementation, where iron is supplemented continuously over many months.

Iron monitoring

It is recommended to monitor iron levels once a year and after completion of any supplementation therapy in elite athletes competing at national or international level. A cost-effective test to be included in periodic health evaluation for this purpose in addition to a full blood count is the ferritin level (Caveat: ferritin is impacted by inflammation and should be interpreted with this confounder in mind).

Altitude

Most athletes competing at international level in endurance sports nowadays spend considerable time at altitude training camps. One of the main goals of this type of training is to increase the amount of circulating red cells to improve oxygen transport and thus endurance performance. Given that iron is the main component of haemoglobin, the oxygen transporting protein of the red blood cells, shortage of iron can thus negate any positive effect of altitude training on the red blood cell system. It is thus recommended that ferritin levels of 50 ng/ml or more are achieved before starting an altitude training camp. Interestingly, the response in red cell production to altitude is further improved when iron is supplemented during the stay at altitude, independent of the ferritin level, i.e. even athletes with high ferritin show a better increase in haemoglobin mass when they supplement iron while at altitude[11].

Intravenous iron therapy

On rare occasions, the preferred form of iron supplementation, i.e. oral administration through tablet or liquid preparations, is inefficient. This can be due to malabsorption syndromes or other gastrointestinal pathologies or incompliance with the intake due to the frequent side effect of gastrointestinal discomfort. Also, rapid iron replenishment might be required in certain situations in athletes (e.g., prior to an altitude camp in view of a major competition); in such cases, intravenous iron therapy can be considered. While in the past, intravenous iron preparations were prone to side effects, newer products based on iron sucrose or -maltose are much safer and can be administered in out-patient settings.

It is of note that when considering intravenous iron therapy, the regulations of the World Anti Doping Agency in view of infusions must be respected ("Infusions or injections of 100 ml or less within a 12-hour period are permitted unless the infused/injected substance is on the Prohibited List.").

In summary, iron is a key element in many pathways contributing to athletic performance. New discoveries in the last decade have improved our knowledge about its role and its regulation and lead to a modification in the guidelines regarding its supplementation.

References

1. De Benoist B, World Health Organization, Centers for Disease Control and Prevention (U.S.). Worldwide prevalence of anaemia 1993-2005 of WHO Global Database of anaemia [Internet]. Geneva: World Health Organization; 2008 [cited 2013 May 3]. Available from: http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf

2. Ganz T, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. Am J Physiol-Gastrointest Liver Physiol. 2006;290(2):G199.

3. Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet. 2014 Jul;46(7):678–84.

4. Schmidt W, Prommer N. Impact of alterations in total hemoglobin mass on VO 2max. Exerc Sport Sci Rev. 2010 Apr;38(2):68–75.

5. McClung JP, Karl JP, Cable SJ, Williams KW, Nindl BC, Young AJ, et al. Randomized, double-blind, placebo-controlled trial of iron supplementation in female soldiers during military training: effects on iron status, physical performance, and mood. Am J Clin Nutr. 2009;90(1):124.

6. Garza D, Shrier I, Kohl HW 3rd, Ford P, Brown M, Matheson GO. The clinical value of serum ferritin tests in endurance athletes. Clin J Sport Med Off J Can Acad Sport Med. 1997 Jan;7(1):46–53.

7. Davies KJ, Donovan CM, Refino CJ, Brooks GA, Packer L, Dallman PR. Distinguishing effects of anemia and muscle iron deficiency on exercise bioenergetics in the rat. Am J Physiol. 1984 Jun;246(6 Pt 1):E535-543.

8. Davies KJ, Maguire JJ, Brooks GA, Dallman PR, Packer L. Muscle mitochondrial bioenergetics, oxygen supply, and work capacity during dietary iron deficiency and repletion. Am J Physiol. 1982 Jun;242(6):E418-427.

9. Garvican LA, Saunders PU, Cardoso T, Macdougall IC, Lobigs LM, Fazakerley R, et al. Intravenous Iron Supplementation in Distance Runners with Low or Suboptimal Ferritin. Med Sci Sports Exerc. 2013 Jul 18;

10. Dellavalle DM, Haas JD. Impact of iron depletion without anemia on performance in trained endurance athletes at the beginning of a training season: a study of female collegiate rowers in central NY state. Int J Sport Nutr Exerc Metab [Internet]. 2011 Oct 4 [cited 2011 Oct 12]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21974839

11. Sim M, Garvican-Lewis LA, Cox GR, Govus A, McKay AKA, Stellingwerff T, et al. Iron considerations for the athlete: a narrative review. Eur J Appl Physiol [Internet]. 2019 May 4 [cited 2019 May 6]; Available from: http://link.springer.com/10.1007/s00421-019-04157-y

Yorck Olaf Schumacher M.D., Ph.D.
Head of Subspecialty Medicine
Aspetar – Orthopaedic and Sports Medicine Hospital
Doha, Qatar

Contact: Yo.Schumacher@aspetar.com