

## Sports anaemia: facts or fiction?

Cosimo Ottomano<sup>1</sup>, Massimo Franchini<sup>2</sup>

<sup>1</sup>*Division of Haematochemical Diagnostic, Department of Pathology and Laboratory Medicine, University Hospital of Parma, Parma;* <sup>2</sup>*Department of Transfusion Medicine and Haematology, Mantua, Italy*

There is an ongoing, unsolved debate as to whether iron supplementation, often used by elite athletes, is really necessary or not. A preliminary question that needs an answer is whether the existence of sports anaemia is supported by facts or whether it is fiction. Whether iron should be prescribed to athletes depends on the answer to this preliminary question.

The human body contains approximately 3-5 g of iron. The daily loss of 1-2 mg is replaced by dietary iron (8 mg/day for adult men, and 18 mg/day for adult women) absorbed within the small intestine<sup>1</sup> by duodenal enterocytes. Since iron is transported around the body in a redox inactive form, it must be bound to a monomeric glycoprotein known as transferrin, which maintains the iron in a soluble, non-toxic form<sup>2</sup>. Bound to transferrin, iron is transported in the bloodstream to be released into a variety of cells through specific, cell surface receptors: transferrin receptor 1 (TfR1), commonly found on red blood cells, other erythroid-lineage cells, hepatocytes, monocytes and the blood-brain barrier, or transferrin receptor 2 (TfR2), expressed predominately on liver cells<sup>3</sup>. The transferrin-transferrin receptor (Tf-TfR) complex undergoes endocytosis, allowing iron to be released from transferrin and transported across the endosomal membrane by protein divalent metal transporter 1 (DMT1)<sup>4</sup>. Once inside the cell, iron is incorporated into iron-containing proteins, and excess intracellular iron is converted into ferritin, a stored form of iron.

Iron performs many important roles that are directly relevant to an athlete's performance. It is not surprising that a significant loss of this metal commonly occurs with exercise. Despite this, the body has no innate mechanism to replace the iron losses due to physical activity; thus, a sufficient dietary intake is essential for athletes in periods of heavy training. The mechanisms involved in exercise-induced iron loss are mainly gastrointestinal bleeding, haematuria, sweating and haemolysis<sup>5-7</sup>, with inflammation and hormone activity also being

relevant, according to the more recent research in this field<sup>8</sup>. During exercise visceral blood flow can be reduced by more than 50%, due to increased sympathetic nervous system activity, in function of exercise intensity<sup>9</sup>, with possible necrosis and mucosal bleeding of the gastrointestinal tract<sup>10,11</sup>. Repeated episodes of training and competition induced blood loss through the gastrointestinal tract may, therefore, contribute to iron deficiency and anaemia within athletes<sup>1</sup>. Sweating, which is mainly a mechanism of thermoregulation and thus essential during exercise, is also a mechanism by which the body may lose iron and athletes exercising for prolonged periods in multiple training sessions in the heat may incur a cumulative debt, which could ultimately affect body iron status<sup>12</sup>. Haematuria may be the consequence of mechanical trauma in the glomerulus or of haemolysis<sup>6</sup>. Furthermore, the movement of the bladder during running may cause bleeding due to microscopic lesions of the interior wall<sup>13</sup>. Interestingly, McInnis and colleagues<sup>6</sup> suggested that the intensity of exercise is the causal mechanism underlying haematuria, since renal blood flow is decreased proportionally to exercise intensity, resulting in an increased filtration fraction and glomerular filtration rate. Haemolysis has been reported during a range of exercise modalities such as swimming, cycling and resistance training<sup>14</sup>. During non-weight bearing activities, the haemolysis might result from the compression of the blood vessels caused by vigorous contraction of the muscles involved in the activity<sup>14</sup>. However, haemolysis is due primarily to impact forces resulting from foot-strike<sup>15</sup>. Haemolysis induces iron loss as a consequence of the destruction of the red blood cell membrane and consequent release of both haemoglobin (Hb) and iron into the surrounding plasma. Since free iron is a poison, its oxidative potential is limited by haptoglobin, a glycoprotein with strong affinity for free Hb which is able to "clean up" the lost contents of haemolysed red blood cells<sup>16</sup>. When the free Hb

concentration in plasma rises, there is a decline in serum haptoglobin levels: this blood profile is common in runners. Interestingly, Miller and colleagues<sup>17</sup> found a force-dependent relationship between heel-strike and the degree of haemolysis experienced during running. Indeed, significantly greater changes in serum haptoglobin and plasma free Hb levels were noted during downhill running when compared to an uphill run of equivalent duration and gradient. In accordance with these findings, Telford and colleagues<sup>15</sup> showed that an acute, 1 hour session of continuous running at 75% peak  $VO_{2max}$  was responsible for a four-fold increase in the levels of plasma free Hb when compared to a session of cycling of equivalent intensity and duration. After accounting for factors such as circulatory stress, the authors concluded that heel-strike was the major cause of haemolysis during running. Thus, it is possible that a force-dependent relationship between heel-strike and haemolysis may be directly affected by the type of ground surface that the athlete trains on, and the intensity at which the session is conducted since these variables affect the impact force upon heel-strike. However, research in this field is lacking. Furthermore, little is known about the effect of such a stimulus over the course of multiple training sessions, but it has been suggested that a chronic haemolytic stimulus (i.e. consecutive training sessions) might have a cumulative effect on haemolysis and iron deficiency<sup>15</sup>.

With respect to the many points mentioned above, it is very important to consider the research by Lippi and Guidi<sup>18</sup> published in this issue of *Blood Transfusion*. Indeed, their study is the first that demonstrates that an ultramarathon run is not associated with significant muscle injury, but also that it does not induce clinically significant variations in Hb, haematocrit, red blood cell count, as well as serum potassium. The research confirmed a significant and acute post-exercise decrease in serum haptoglobin, due to a certain degree of haemolysis during the long-distance run, although the concentration of the protein always remained below 0.5 g/L, suggesting that the degree of red blood cell injury might be considered very modest or even clinically negligible. Of note, they found a significant reduction of mean corpuscular volume, as previously observed by Banfi and colleagues in rugby players<sup>19</sup>, accompanied by an

increase of the mean corpuscular Hb concentration. It was suggested that there may be a compensatory mechanism involving a shift of intracellular water outside of the red blood cell to counterbalance the loss of fluid.

Before concluding, two more laboratory tests must be remembered, namely serum transferrin receptor (sTfR) and red blood cell protoporphyrin. The sTfR accurately reflects the demands of bone marrow for iron (i.e., high sTfR concentrations indicate iron-deficient erythropoiesis) and this parameter, especially the sTfR/log(ferritin) index, is less variable than the measurement of ferritin alone<sup>20</sup>. However, investigations on the influence of physical activity on sTfR expression are limited. In accordance with previous studies, Schumacher *et al.* found that ferritin concentrations declined after exercise tests in 39 individuals; in contrast, sTfR was unaffected by a 45-minute constant-speed running test at 70%  $VO_{2max}$  and decreased only during incremental exercise challenges to the point of exhaustion. Taking the different extracellular fluid shifts into account (haemoconcentration during the exhaustive test and haemodilution during the aerobic test), the investigators concluded that sTfR reflects exercise-induced changes in iron metabolism more reliably than does serum ferritin, which is also influenced by factors other than iron stores<sup>21</sup>. The hypothesis that iron availability is not limiting for red blood cell production despite reduced concentrations of serum ferritin during exercise is further supported by the observation that free red blood cell protoporphyrin concentrations remain unchanged during intensive training<sup>22</sup>. The final step of haem biosynthesis is the insertion of ferrous iron into protoporphyrin which depends critically on the availability of iron as a substrate; the first step of haem biosynthesis, the formation of 5-aminolaevulinate, is also subject to regulation by iron. No operational limitation of haem biosynthesis according to the availability of iron in erythrocytes has been demonstrated in athletes.

In conclusion, there is no evidence that iron supplementation increases athletic performance, except in individuals in whom iron deficiency is established. In athletes with low serum ferritin concentrations without anaemia, iron supplementation might be useful; moreover, determination of sTfR or red blood cell-free protoporphyrin concentrations

may identify those in whom iron administration is likely to be beneficial. Serum ferritin concentrations should be monitored in conditioned athletes, and physiological decreases in serum ferritin during the early stages of training should be taken into account when individuals are examined and before any decision to give iron is made. Important risk factors contributing to the development of an iron deficiency status are young-adolescent age, female sex, vegetarian diet and *Helicobacter pylori* infection. Because most studies have shown no beneficial effect of iron supplementation on performance, the uncontrolled use of iron should be avoided. Thus, our answer to the initial question is that we believe that sports anaemia does not exist. Some athletes are anaemic and consequently must be diagnosed and treated.

*The Authors declare no conflicts of interest.*

## References

- 1) Nielsen P, Nachtigall D. Iron supplementation in athletes. Current recommendations. *Sports Med* 1998; **26**: 207-16.
- 2) Andrews NC. Iron metabolism: iron deficiency and iron overload. *Annu Rev Genomics Hum Genet* 2000; **1**: 75-98.
- 3) Gomme PT, McCann KB, Bertolini J. Transferrin: structure, function and potential therapeutic actions. *Drug Discov Today* 2005; **10**: 267-73.
- 4) Papanikolaou G, Pantopoulos K. Iron metabolism and toxicity. *Toxicol Appl Pharmacol* 2005; **202**: 199-211.
- 5) DeRuisseau KC, Chevront SN, Haymes EM, et al. Sweat iron and zinc losses during prolonged exercise. *Int J Sport Nutr Exerc Metab* 2002; **12**: 428-37.
- 6) McInnis MD, Newhouse IJ, von Duvillard SP, et al. The effect of exercise intensity on hematuria in healthy male runners. *Eur J Appl Physiol Occup Physiol* 1998; **79**: 99-105.
- 7) Babic Z, Papa B, Sikirika-Bosnjakovic M, et al. Occult gastrointestinal bleeding in rugby players. *J Sports Med Phys Fitness* 2001; **41**: 399-402.
- 8) Roecker L, Meier-Buttermilch R, Brechtel L, et al. Ironregulatory protein hepcidin is increased in female athletes after a marathon. *Eur J Appl Physiol* 2005; **95**: 569-71.
- 9) Osada T, Katsumura T, Hamaoka T, et al. Reduced blood flow in abdominal viscera measured by Doppler ultrasound during one-legged knee extension. *J Appl Physiol* 1999; **86**: 709-19.
- 10) Gaudin C, Zerath E, Guezennec CY. Gastric lesions secondary to long-distance running. *Dig Dis Sci* 1990; **35**: 1239-43.
- 11) Peters HP, De Vries WR, Vanberge-Henegouwen GP, et al. Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. *Gut* 2001; **48**: 435-9.
- 12) Waller MF, Haymes EM. The effects of heat and exercise on sweat iron loss. *Med Sci Sport Ex* 1996; **28**: 197-203.
- 13) Blacklock NJ. Bladder trauma in the long-distance runner: "10,000 m haematuria". *Br J Urol* 1977; **49**: 129-32.
- 14) Selby GB, Eichner ER. Endurance swimming, intravascular hemolysis, anemia, and iron depletion, new perspective on athlete's anemia. *Am J Med* 1986; **81**: 792-4.
- 15) Telford R, Sly GJ, Hahn AG, et al. Footstrike is the major cause of hemolysis during running. *J Appl Physiol* 2003; **94**: 38-42.
- 16) Giblett ER. The haptoglobin system. *Ser Haematol* 1968; **1**: 3-20.
- 17) Miller B, Pate RR, Burgess W. Foot impact force and intravascular hemolysis during distance running. *Int J Sports Med* 1988; **9**: 56-60.
- 18) Lippi G, Schena F, Salvagno GL, et al. Foot-strike haemolysis after a 60-km ultramarathon. *Blood Transfus* 2012; **10**: 377-83.
- 19) Banfi G, Di Gaetano N, Lopez RS, Melegati G. Decreased mean sphered cell volume values in top-level rugby players are related to the intravascular hemolysis induced by exercise. *Lab Hematol* 2007; **13**: 103-7.
- 20) Malczewska J, Szczepanska B, Stupnicki R, et al. The assessment of frequency of iron deficiency in athletes from the transferrin receptor-ferritin index. *Int J Sport Nutr Exerc Metab* 2001; **11**: 42-52.
- 21) Schumacher YO, Schmid A, Konig D, et al. Effects of exercise on soluble transferrin receptor and other variables of the iron status. *Br J Sports Med* 2002; **36**: 195-9.
- 22) Spodaryk K. Haematological and iron-related parameters of male endurance and strength trained athletes. *Eur J Appl Physiol Occup Physiol* 1993; **67**: 66-70.

---

**Correspondence:** Cosimo Ottomano  
 U.O. Diagnostica Ematochimica  
 Dipartimento di Patologia e Medicina di Laboratorio  
 Azienda Ospedaliera-Universitaria di Parma  
 Via Gramsci 14  
 43126 Parma, Italy  
 e-mail: cosimo.ottomano@dgroup.it

---