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Iron deficiency in endure athletes

Michał Rogulski

Independent Public Health Care Center in Garwolin ul. Lubelska 50, Garwolin

https://orcid.org/0009-0004-7328-5016

michal.rogulski97@gmail.com

Yauheniya Patarocha

Independent Public Health Care Center in Garwolin ul. Lubelska 50, Garwolin

https://orcid.org/0009-0007-0472-9789

eugeniapatarocha@gmail.com

Aleksandra Ślusarska

Public Oupatient Medical Center in Strzelin, ul. Mickiewicza 20 Strzelin

https://orcid.org/0009-0009-8208-1222

a.slusarska4@gmail.com

Jolanta Mędyk

Independent Researcher

https://orcid.org/0009-0008-3346-0827

lek.jolantamedyk@gmail.com

Paulina Błasiak

Independent Researcher

https://orcid.org/0000-0002-7967-1776

blasiak.paulina.alicja@gmail.com

Małgorzata Wirkijowska

Formmed Center for Treatment of Congenital Defects and Malformations, ul. Warszawska 197D, Babice Nowe

https://orcid.org/0009-0003-5857-965X

wirkijowskam@gmail.com

Patryk Mikołajec

Hospital Saint Anne in Miechow, ul. Szpitalna 3, Miechow

https://orcid.org/0009-0001-3300-0061

patrykmikolajec@gmail.com

Ruslan Huk

Independent Public Health Care Center in Garwolin ul. Lubelska 50, Garwolin

https://orcid.org/0009-0008-5756-9448

hukr1992@gmail.com

Barbara Bilecka

Jan Kochanowski University Collegium Medicum, aleja IX Wieków Kielc 19A, Kielce

basiabilecka@gmail.com

https://orcid.org/0009-0009-5611-2996

Jakub Wirkijowski

Independent Public Clinical Hospital of Prof. W. Orlowski, Czerniakowska 231, 00-401, Warsaw, Poland

https://orcid.org/0009-0007-9882-9341

k.wirkijowski0@gmail.com

Abstract

Iron deficiency, with or without anemia, is more prevalent in endurance athletes than in the general population. Especially in marathon and half-marathon runners - these groups of endurance athletes are at high risk for iron deficiency via several mechanisms, such as sweating, gastrointestinal bleeding, urinary-tract blood loss, hemolysis, and others.

Methods: Our study followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9]. A literature search was conducted using the online electronic databases such as PubMed and ScienceDirect. Keywords which were searched for in this study: "Hemoglobin", "Iron", "Iron Deficiencies", "Hepcidin", "Ferritin", Transferrin", "Hemoglobin", "Athletes" and "Athletic performance". This search included human and experimental studies. Randomized controlled trials (RCTs) were included as well. We prioritized articles published within the last 10 years; however, to assert more relevant information, the earlier articles were also included in our study. We eliminated duplicate articles, articles not in English, and not relevant for our research articles (for example, the RCTs in non-athletes or RCTs which don't reflect the correlation between iron status and sport performance). Summary information from these articles was synthesized together to create a narrative review of the literature.

Results: the correlation between physical performance in endurance athletes and their iron status turned out to be significant. Athlete's physical performance can be improved by improving their iron status. Our review revealed that iron supplementation has the most pronounced effect on physical performance in athletes, especially in those with lower ferritin levels.

Conclusions: Iron is playing a key role in numerous metabolic functions of the human body. The disruption of the balance of iron leads to decreased athletic performance. Iron deficiency has been widely described in many studies regarding athletes, especially in endurance ones. Intense exercise leads to iron deficiency due to foot strike hemolysis, iron loss in sweat, gastrointestinal bleeding, urinary-tract blood loss and decreased iron absorption. To prevent iron deficiency it is extremely important to introduce iron-rich foods to your diet. Iron-rich foods (such as meat, poultry, and seafood) contain the heme form, which has superior bioavailability compared to non-heme form contained mostly in plant-based foods. Therefore, athletes from a high-risk group of iron deficiency as vegans, vegetarians, and those who resign from meat because of personal, health or religion, should pay more attention to their dietary iron intake and may require additional supplementation of iron (oral, intramuscular or intravenous). Also, special attention should be paid to female athletes, who are in high-risk of iron deficiency due to heavy menstrual bleeding. Moreover, to avoid the inhibition of iron absorption from the gastrointestinal tract it is recommended to reduce the consumption of such products as tea, coffee, and milk, at least one hour before and after iron supplementation.

Keywords: hemoglobin, iron, iron intake, iron deficiency, hepcidin, ferritin, transferrin, anemia, athletes.

Introduction

Iron is an essential mineral in the human body. It plays a crucial role in carrying reversibly oxygen in hemoglobin molecules in red blood cells and in myoglobin in muscle cells. Another iron's important role consists in contributing to the electron transport chain, enzymes, DNA synthesis, and energy metabolism [1]. Iron is taken up by cells and then transported to mitochondria where it is used to form heme - the form of iron included in hemoglobin and myoglobin molecules [4]. Iron's ability to give and accept electrons is used in many biological processes. For example, working as a cofactor for different kinds of enzymes and proteins iron facilitates redox reactions [10]. However, high levels of iron can be toxic to the human body because of the iron's redox ability to form reactive oxygen species (ROS), which cause cell damage and apoptosis (cell death) [11]. Iron is transferred in the bloodstream with a special transport protein called transferrin, and the excess of iron is stored as ferritin in the liver and the reticuloendothelial system [12]. Ferritin is the most used biomarker which reflects iron status [13]. Most of the iron in the body is used in hemoglobin, myoglobin, and enzymes. Iron storage is approximately 4 g in men and 2.5 g in women body, but only 1–2 mg of iron per day is lost due to intestinal iron absorption and the efficient recycling system of iron. Normal intake of iron is around 10–15 mg per day, but only 10% is absorbed under normal conditions, when iron losses only occur in small doses due to epithelial desquamation and minor bleeding [4].

Iron balance in the blood is carefully regulated by the peptide hormone called hepcidin, which is produced by the hepatocytes in the liver. Hepcidin is upregulated when serum ferritin is high and is regulated by the need for iron for erythropoiesis. Hepcidin inhibits the absorption of iron by binding to its receptor on ferroportin that transports Fe^{2+} from enterocytes to plasma [4].

The term „iron deficiency" includes physiological deficits caused by negative iron balance [5]. Iron deficiency can occur with or without anemia. According to the definition of WHO, iron deficiency without anemia (IDNA) is diagnosed when ferritin levels are low (<30 mg/L), but hemoglobin levels are normal (>130/120 g/L in men/women). Iron deficiency with anemia (IDA) occurs when low ferritin levels lead to low levels of hemoglobin (<130/120 g/L in men/women) [15]. Because of the wide iron's role in biological processes, outside of carrying oxygen in hemoglobin molecules, IDNA may have a negative impact on multiple functions. Metabolic systems with iron-containing proteins can be affected by IDNA itself, such as reactions in the respiratory chain where iron works as a cofactor, thereby reducing oxidative capacity, which again reduces the muscles' ability to use oxygen [4]. As an effect, in IDNA can appear such symptoms as fatigue, reduced concentration, and impaired physical performance [15]. When IDA occurs, the oxygen-carrying capability in the blood is reduced because of lower hemoglobin levels. This reduces physical capabilities because of lack of oxygen to all cells in the body, including those of working muscles during exercise [16].

Iron status in endurance training

Endurance athletes are a constantly studied group because of a higher prevalence of iron deficiency in them, than in the general population [20]. Physical exercise, especially high-intensity and endurance training, result in a relevant reduction of the body's iron stores of up to 70% observed when compared to the general population. Therefore, athletes who undergo intense training are frequently faced with an elevated risk of iron deficiency with or without anemia [6]. Notably, IDNA is more prevalent in female athletes, predominantly due to menstrual blood loss. It affects even 15–35% of female athletes, compared to 5–11% of male athletes [19]. Endure athletes, especially runners, use up their red blood cells very quickly, and thus their iron is also used up very quickly. The average blood cell survives around 120 days in the average adult, but in the average runner it will survive only about 74 days (Weight, 1991). According to the study of R. Terink, 2018 regarding changes in iron metabolism during prolonged and repeated exercise, just a few days after the resumption of an exercise program, iron stores in athletes significantly decrease. Moreover, iron deficiency can affect several of the abilities that athletes need to perform outside of aerobic abilities, including those related to strength, the immune system, fatigue, and mood status [4]. All of these factors can affect power, speed, coordination, concentration, recovery, and consequently, performance in various sports variables.

Main causes of iron loss in endure athletes

Endurance athletes are put under large training loads and experience immense physical stress, with the aim of enhancing their athletic performance. Therefore, the most common metabolic dysfunctions seen in endurance athletes are iron deficiency with or without anemia, both of them have detrimental effects on aerobic exercise performance and health [17]. The high incidence of iron deficiency in athlete populations is a result of a complex combination of mechanisms that co-exist to create acute situations of iron loss, in addition to difficulties with consuming or absorbing sufficient amounts of iron from the diet to support increased demands (i.e., for replacement and adaptation). Such acute mechanisms of iron loss may include: sweat-related iron loss, gastrointestinal bleeding, urinary-tract blood loss, hemolysis gastrointestinal bleeding, sweating, hemoglobinuria, and red blood cell hemolysis, which can occur from a combination of fluid loss, dehydration, and the mechanical stress of exercise itself [7]. Let's look at them in more detail.

Sweat-relating iron loss

Sweating is involved in thermoregulation and is important in physical exercise [3]. Via sweat iron loss is estimated to occur at 1% to 3% recommended daily intake of iron per two hours of exercise for women and men, respectively (DeRuisseau KC, 2002) [18].

Gastrointestinal bleeding

Bleeding into the stool that is not visible is very common among distance runners. Even 85% of runners, participating in one 100-mile race were found to have "occult" (or invisible) blood in their stool after the finish. Bleeding from the gastrointestinal tract is believed to be caused by decreased blood flow to the gastrointestinal tract during the exercise or increased acidity directly breaking down the gastrointestinal tract and causing bleeding [18].

Urinary-Tract Blood Loss

Iron loss through urine mostly results from such mechanisms as mechanical trauma in the kidney or bladder wall, the breakdown of red blood cells in the bloodstream (hemolysis), which leads to loss of hemoglobin via the kidney [18].

Hemolysis

The breakdown of red blood cells occurs in many forms of exercise, but predominantly occurs in running (Telford, 2003). According to the study mentioned above, the breakdown of red blood cells, and therefore iron loss occurs due to foot-strike hemolysis (Telford, 2003). The foot-strike hemolysis relies on the repeated and forceful impact of the feet with the ground which causes direct injury to the erythrocytes within the capillaries. Indeed, runners who wear more cushioned shoes have less hemolysis (Dressendorfer, 1992) [18].

Hepcidin and Inflammation

Systemic inflammation related to intense training or overtraining and/or muscle breakdown can actually decrease iron levels via a hormone called hepcidin. There is a direct relationship between the initiation of an exercise program, decrease in iron level, and increase in hepcidin levels (Terink, 2018). Hepcidin sends signals for immune cells called macrophages and liver cells - hepatocytes to „hide" iron away inside of them to and also causes decreased absorption of iron from the gastrointestinal tract to prevent the iron loss [18].

Travel to Altitude

Traveling to higher altitude also has an effect on iron status, While increasing altitude the red blood cells production increases as well, requiring more iron [18]. Increased production of red blood cells, called polycythemia, occurs as an acclimatization to altitude. With increasing altitude grows the oxygen tension in inspired air. As an effect the red blood cell formation disturbs, which leads to iron deficiency.

Hormones

Hormones also play a significant role in the etiology of iron deficiency in female athletes. Large training loads suppress gonadotropin-releasing hormone, which leads to decreased production of luteinizing and follicle-stimulating hormones. This process conducts to decreased estrogen levels. As an effect the hepcidin concentration in the body increases disturbing iron absorption in the gastrointestinal tract. Furthermore, extreme acute endurance exercises, such as Ironman competitions affects male hormones as well, reducing testosterone levels, which, in turn, suppress hepcidin, further influencing iron levels [19].

Iron supplementation in endure athletes

Due to intensified iron loss during exercises, there is no adequate mechanism to replace it, so iron must either come through the diet or supplementation (Ottomano, 2012) [18]. Studies demonstrated that iron supplementation is necessary for normal ferritin levels for training in a hypoxic environment, even in those athletes with sufficient levels of iron because of the increased iron utilization while training. Okazaki et al. calculated that runners in altitude need an extra 4.9 mg iron a day in addition to the daily requirements. And an extra 1.9 mg/day for women and 2.3 mg/day for men training at sea level [4].

Iron supplementation strategies are multi-faceted [2]. The primary ways to replenish iron deficiency are dietary counseling and oral iron supplementation. If initial steps of oral iron supplementation are not enough, then the intramuscular and intravenous iron repletion is recommended to improve athlete's medical condition and sports performance [1].

Dietary counseling

Dietary iron is available in two forms: heme or non-heme. Heme iron is contained in animal sources, such as meat, poultry and seafood. Whereas non-heme iron is derived from plant sources - for example, lettuce, spinach, nuts. Heme iron is absorbed more efficiently from the gastrointestinal tract with a 25% absorption rate, in contrast to 17% observed for non-heme iron. Thus, to achieve a superior bioavailability of iron, it is recommended to eat more high-iron foods derived from animal sources. Diete poor in heme form iron can complicate the treatment of IDNA and may be not sufficient to correct the iron deficiency, for example, in vegans and vegetarians athletes. Moreover, several iron-binding ligands from our diet act as inhibitors of iron absorption.

Chemical compounds such as phytates and polyphenols (contained among others in tea, coffee, cocoa and red wine) form a metal complex with iron hindering its absorption from the gastrointestinal tract. Calcium and zinc also showed an inhibitory effect on iron absorption, affecting both heme and non-heme iron absorption. Therefore, it is recommended to take into account the facts mentioned above to provide an adequate dietary iron intake. [6].

Oral Iron Treatment

Oral iron supplementation therapy remains the preferred, optimal, economical, and safest treatment. A study was conducted on 42 women with IDNA, given either oral 100 mg of ferrous sulfate daily or placebo for 6 weeks, and were subjected to training for 30 min per day and 5 days of the week. Also, it was reported that supplementation increased serum ferritin in the experimental group compared to the placebo. The study concluded that IDNA impairs favorable adaptation to aerobic exercise [21]. Iron can be supplemented in the form of inorganic salts, such as sulfates, or in the form of organic iron as complexes with amino acids or hydrolyzed protein. Organic iron formulations such as ferrous gluconate exhibit higher bioavailability than inorganic ones like ferrous sulfate. In addition, supplements that are formulated as ferrous (Fe^{2+}) salts such as ferrous gluconate, ferrous sulfate, and ferrous fumarate are absorbed superiorly as compared to ferric (Fe^{3+}) formulations. From all the ferrous formulations, ferrous gluconate is more tolerated compared to the other two formulations. Moreover, such supplements also contain large amounts of elemental iron in them, which in turn determines their efficacy. Approximately 10% of the oral elemental iron is absorbed by the body [6].

Intramuscular Iron Treatment

Intramuscular injection of iron is not widely used due to the pain, soreness, and the discoloration at the site of injection, which can be bothersome to athletes during training and performance, decreasing their performance. However, some studies revealed that intramuscular iron injections in women with IDNA are much more effective in raising serum ferritin levels than oral supplementation. In a study of 15 elite female athletes with IDNA, the group that received 5 × 2 mL of iron intramuscular showed significantly increased serum ferritin levels compared to the placebo group [6].

Intravenous Iron Treatment

Intravenous iron treatment in athletes can be used in case of intolerance of oral iron supplementation or when other methods of restoring iron levels fail. The study of Burden et al.

2015, revealed that a single intravenuose dose of 500 mg of iron in 15 runners with IDNA normalized the iron deficiency in only 4 weeks. However, parenteral treatment can also cause side effects such as skin discoloration, headaches or even anaphylaxis in severe cases [6]. So, intravenous iron treatment should not be used routinely, only if there are strict medical indications for it.

Conflicts of interest: the authors declare no conflict of interest.

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