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Iron Supplementation and Physical Performance

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1. Introduction

Iron is one of the most abundant elements, essential for the completion of numerous important biological functions, including electron transfer reactions, gene regulation, binding and transport of oxygen, regulation of cell growth and differentiation. In the human body it is mainly found in the oxygen transport and storage proteins haemoglobin (Hb) (60 - 70%) and myoglobin (10%), in various iron-containing enzymes (2%), as well as in the liver, bone marrow and muscle in the form of the storage proteins ferritin (Ferr) and hemosiderin (20 - 30%) [1]. Only a minor quantity (0.1 - 0.2%) of total iron, mostly bound to the iron-transport protein transferrin, circulates in the plasma and other extracellular fluids [1, 2]. Besides its essential character, excessive free iron could adversely affect the human body, by augmenting oxidative stress, mainly via the Fenton and Haber-Weiss reactions. Ferritin, hemosiderin and transferrin, assist the system to maintain iron balance under tight control by keeping free iron levels low and hence restrain the conversion of hydrogen peroxide to the highly reactive hydroxyl radical [3] that disturbs cellular homeostasis when it is increased at toxic levels.

Iron absorption is the main mechanism through which iron balance is maintained. Nevertheless, iron losses may occur at multiple organs, such as the gastrointestinal tract [4-6], the skin [7, 8], the urinary tract [4], and additionally due to several physiological conditions such as the menstrual cycle in women [9, 10]. To compensate for these losses, as well as for satisfying the body's demands during growth and pregnancy, iron is absorbed from the diet. The percentage of food-iron that is absorbed from the intestine is approximately 10%, with heme-iron being absorbed in greater amounts compared with non-heme-iron [11-13]. Thus, from a typical daily diet of 2000 kcal that contains adequate quantities of meat, 1.8 mg of iron per

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day are absorbed [13]. In general, daily iron turnover (absorption and excretion) is approximately 1-2 mg per day [1, 2, 7].

There is a strong body of evidence suggesting that exercise affects iron status [14-17], although other studies do not support this association [18-20]. Iron plays a critical role in oxygen transport as it is necessary for the formation of Hb, the oxygen transport protein that is critical for aerobic capacity. Iron is also needed for the optimal function of many oxidative enzymes affecting the intracellular metabolism (i.e., the electron transport chain and oxidative phosphorylation pathway in mitochondria) [21]. Not only prolonged aerobic exercise but, to some extent, short duration activities (i.e. sprints), may influence the above mechanisms [22]. Consequently, a compromised iron status would negatively affect physical performance. On the other hand, iron deficiency is frequently attributed to exercise [14-16]. Therefore, iron supplementation is commonly used to avoid exercise-induced perturbations of iron homeostasis and maintain the required iron stores that are necessary to address exercise needs or enhance physical performance.

Numerous studies have attempted to clarify the effectiveness of enhanced iron intake, either through diet or through supplement consumption, to restore iron status or to enhance physical performance. Yet, no valid conclusions have been drawn. The results of these studies are contradictory as some of them produced positive effects [23, 24]) whereas others dispute such effects [25]. An important factor in iron absorption seems to be the previous iron status of the individual. This means that, several iron parameters are seen to be ameliorated following iron supplementation in situations of iron deficiency, whereas this is not always the case for individuals with normal iron status.

In this chapter, an attempt will be made, to clarify the effect of exercise on iron status in athletes. Furthermore, an effort will be made to address the role of dietary or supplemented iron on several indices of physical performance. Finally, the mechanisms through which exercise may alter iron homeostasis will also be discussed.

2. The importance of iron in physical activity

Exercise and/or physical activity is characterized by a substantial increase in oxygen needs. Iron is an indispensable factor for the formation of Hb, the protein responsible for oxygen transport from the respiratory organs to the peripheral tissues. Lack of adequate amounts of iron for the formation of Hb due to iron deficiency, can strongly affect physical work capacity, by reducing oxygen conveyance to the exercising muscles [21]. Iron is also a vital component for the formation of myoglobin, the iron-storage protein within the muscle that regulates the diffusion of oxygen from the erythrocytes to the cytoplasm and on to the mitochondria where it is used as the final acceptor of electrons processed by the respiratory chains producing water and forming energy in the process [26, 27]. The concentration of myoglobin in skeletal muscle is drastically reduced (40 - 60%) following iron deficiency, thus limiting the rate of oxygen

diffusion from erythrocytes to mitochondria [28] which ultimately compromises the muscle's oxidative capacity.

Apart from oxygen transport and storage, iron is also needed for the optimal function of many oxidative enzymes and proteins regulating the intracellular metabolism [21, 27, 29]. The mitochondrial content of oxidative enzymes and proteins is an important factor regarding the muscle's capacity for work, as there is a strong association between the ability to maintain prolonged submaximal exercise and the activity of iron-dependent oxidative enzymes [29]. Iron deficiency negatively affects mitochondrial respiration mainly through the decline in heme iron-containing respiratory chain proteins cytochrome c and cytochrome c oxidase, as well as non-heme iron-containing enzymes succinate dehydrogenase and NADH dehydrogenase, but also the non-heme iron-sulfur protein content [27]. Therefore, iron deficiency may have detrimental effects, especially on endurance performance which is susceptible to, and negatively affected by disturbances in skeletal muscle's iron concentrations [27].

Besides athletes' training at sea level, iron deficiency could also affect athletes training at altitude. Staying at high altitude causes an increase in erythropoiesis in the bone marrow, stimulated by hypoxia. This increase in erythropoiesis is followed by an elevation in red blood cells volume and Hb concentration [30, 31]. Iron deficiency could negatively affect the above mechanism by limiting the rate of erythropoiesis and consequently aerobic performance. It has been demonstrated that athletes with low ferritin levels do not increase total red blood cell volume after 4 weeks at altitude, despite an acute increase in erythropoietin [32]. In contrast, a significant increase in erythropoietin but also in reticulocytes occurred in non-iron-deficient athletes during training at moderate altitude [30]. Such data suggests that iron sufficiency is critical for the favorable response of the athletes training to altitude, in an attempt to enhance their performance.

3. Iron needs in athletes

The need for iron supplementation in cases of iron deficiency anemia in athletes is indisputable. Nevertheless, the need for iron supplementation in situations of iron deficiency without anemia for enhanced performance is still under debate, despite the systematic use of iron supplements. The majority of studies do not report significant changes in physical capacity following iron supplementation [25, 33, 34]. Nevertheless, there are studies indicating an improvement of physical performance in iron depleted non anemic athletes following iron supplementation [23, 24].

Athletes at risk of iron deficiency include female and male middle and long distance runners, as well as all female athletes in other disciplines in which running is an important part of training or competition [17]. Iron demands during consecutive periods of intense training or competition are high, and may compromise iron status. In [15] is reported that a brief recovery following the in-season period may be insufficient to restore the reduced iron stores prior to

the start of the subsequent high-intensity pre-season training. Additionally, even when the recommended dietary intake of iron is established through a controlled diet, iron status perturbations may be inevitable. In reference [35] the mean dietary intake of 16.3 mg per day was inadequate to prevent iron deficiency in female collegiate swimmers. Such disturbances however, if not treated, could be a threat, not only for athletic performance deterioration, but also for the athletes' health. In a recent study [36], female collegiate rowers, categorized as iron-depleted non-anemic (Hb ≥ 12 gIdL, Ferr < 20 μg/L), rowed about 4% slower than normal controls with a serum Ferr ≥ 20 μg/L in a self-reported best 2-km simulated race on an row ergometer. These findings point out that non-anemic iron depletion may impair performance.

On the other hand, unjustified and uncontrolled iron supplementation could lead to iron overload that could be toxic and hazardous for the athletes' health. Athletes with the homozygous form of hemochromatosis gene may be at risk of excessive iron storage due to excessive iron absorption [17]. According to the Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) [37], hemochromatosis symptoms are non-specific, but the most commonly associated early hemochromatosis symptoms may include fatigue, weakness, weight loss, abdominal pain, and arthralgia. The simplest tests that indirectly indicate iron overloading are transferrin saturation (TS) and serum Ferr [37, 38]. TS levels >45% and Ferr >200 μg/L for premenopausal female or >300 μg/L for postmenopausal female and >300 μg/L for male, are indicative of iron overload. Nevertheless, the confirmation of hemochromatosis can be achieved indirectly by quantitative phlebotomy and hereditary hemochromatosis genotyping, or indirectly by liver biopsy [37, 38].

Taking the above under consideration, iron supplementation should be decided only after a thorough examination of athletes' hematological and iron status at the beginning, in the middle, as well as at the end of training or the competitive season. Controlled iron supplementation for all athletes with serum Ferr below 35μg/L is recommended for the replenishment of iron stores.

4. Evaluation of iron status in athletes

Due to the significant role of iron in optimal physical performance and health, the evaluation of iron status in athletes is of great importance in order to prevent iron deficiency. According to the World Health Organisation [39], iron deficiency progresses in three stages: in the first stage iron stores in bone marrow, liver, and spleen are depleted (serum Ferr concentrations <12μg/L); in the second stage, erythropoiesis decreases as iron supply to erythroid marrow is reduced (TS <16%); in the final stage Hb production falls drastically (Hb concentration <12g/L) resulting in anemia.

Iron status evaluation is not a single-parameter estimation. Day-to-day or acute phase response variations occur in several indices of iron status. Therefore, in order to make a valuable and more accurate assessment, the estimation of iron status indices and several hematological parameters is needed. These will be described in the following sections. Additionally, the

reference range for the main indicators of iron status, as well as reported values in elite athletes is presented in Table 1.

4.1. Estimation of red blood cell parameters

The most commonly used hematological index is haemoglobin which reflects the effects of mechanisms that control the red cell mass (RCM) and plasma volume (PV). It is used as an indicator of anemia, that is when an individual's Hb concentration falls below the normal threshold of the person's corresponding age and sex category, (then the third stage of iron deficiency anemia has been developed [40]). Normal values lie between 11.7 - 155 g/dL and 12.8 - 17.3 g/dL for women and men, respectively [41, 42]. According to WHO the recommended Hb values (in g/100 ml of venous blood) below which anemia develops, are <13 g/dL for adult men, <12 g/dL and <11 g/dL for non-pregnant and pregnant adult females, respectively, while in children aged 6 months - 14 years the corresponding values are between 11 g/dL and 12 g/dL [40]. Haemoglobin concentrations are normally stable demonstrating a relatively low day-to-day variation of 2 - 4% [39]. Alongside Hb, hematocrit (Hct), the mean corpuscular haemoglobin concentration (MCHC), as well as the size and volume of red blood cells (RBC) are also useful markers for anemia [16,29].The classic Hb and Hct changes as a result of acute or chronic exercise should be kept in mind before a diagnosis is to be made. Namely, acute strenuous and prolonged exercise typically leads to an increase of Hb and Hematocrit due to hemoconcentration [43]. On the other hand, a decrease in the concentration of these indices may be seen within the first days of a regular cardiovascular training program due to hemodilution. This decrease is temporary and most athletes demonstrate normal Hb levels at the completion of training or the end of a competitive phase [43, 44]. Hence, when determining hematological changes in athletes the above changes should be also taken into account in order to avoid a misleading interpretation of "sports anemia" or "pseudoanemia".

4.2. Estimation of body iron stores

Serum Ferr concentration is one of the most frequently used indices in iron status examination. Serum concentration of Ferr and, in conditions of iron overload hemosiderin [2], serve as an indicator for body iron stores, available for protein and heme synthesis. Serum Ferr concentrations normally range within 10 - 300 μg/L [40, 42], whereas values lower than 12 μg/L reflect the absence of measurable iron stores in bone marrow, liver and spleen. Such values indicate the onset of a first stage iron deficiency [40]. Ferritin seems to be age- and sex-dependent, since lower values are reported for children and pre-menopause women as compared to adults and men, respectively.

Nevertheless, the expression and appearance of Ferr in serum are influenced by other factors as well. Ferritin is an acute-phase reactant and its serum concentration may be increased by liver disease, infections and other inflammatory conditions, malignant diseases, renal failure, cardiovascular diseases, high alcohol consumption, and aging [44-46]. Some types of physical activity are accompanied by inflammation-like reactions that can induce an acute phase response and increased Ferr levels for several days. In case of exercise-induced inflammation, normal Ferr levels could be deceptive, reflecting rather an acute phase response than the true

efficiency of the athletes' iron stores. Day-to-day variability in Ferr has been estimated in the range of 13% - 75% in endurance athletes [19] and therefore, its serum concentrations cannot independently be equated to iron stores [47]. In summary, although serum Ferr concentration is commonly reported to be affected by training [4, 16, 35], there should be some caution before iron adequacy or inadequacy is diagnosed in athletes when ferritin is the only available evaluating index.

4.3. Estimation of plasma or serum iron status

Iron concentration, together with Total Iron Binding Capacity (TIBC) and TS provide information about iron status in plasma or serum.

Iron concentration expresses the total iron content per unit of serum volume, and its normal values typically range within 50 - 175 µg/dL [42, 48]. Iron concentration demonstrates a day-to-day variation of 15% - 26%, and a 10 - 20% variation during the day [49], and as a consequence, the measurement of serum iron concentration alone, cannot be rendered a valuable index of iron status.

Total Iron Binding Capacity (TIBC) reflects the total number of binding sites for iron atoms on transferrin per unit volume of plasma or serum [48]. The reference range for TIBC lies between 250-425 µg/dL (Tietz, 1995) and is a more stable indicator of iron status than iron concentration, with its day-to-day variation ranging within 8% - 12% while its diurnal variation is less than 5%. TIBC does not change before iron stores are depleted [48]. In depleted iron stores a rise in TIBC levels occurs as more free binding sites on transferrin are available for iron.

Transferrin is the iron binding protein that delivers iron to cells [48]. Transferrin levels are not affected by inflammatory reactions or other diseases and can therefore be used for diagnosing iron deficiency even under such conditions [44]. Transferrin saturation is the percentage of serum iron to TIBC, and values < 15% are indicative of a second stage iron deficiency. This stage is characterized by iron deficient erythropoiesis, with a restricted iron supply in the absence of anemia [40]. Its normal values range within 20% - 50% and 15% - 50% for men and women respectively [42]. Since TIBC is rather stable, any alteration in plasma TS will be the result of changes in iron concentration. Consequently, anything that alters iron concentration will alter TS as well [48]. Transferrin saturation in conjunction with serum Ferr concentration and Hb are the three critical parameters for the determination of the severity of iron deficiency.

4.4. Estimation of erythropoiesis into the bone marrow

Erythrocyte Protoporphyrin (EP) or Zinc Protoporphyrin (ZPP), and the soluble Transferrin Receptor (sTfR) reflect the adequacy or inadequacy of iron for erythropoiesis into the bone marrow and tissues.

Protoporphyrin is a carrier molecule and together with ferrous iron forms the heme group of Hb, myoglobin and other heme-containing enzymes. In cases of iron absence, instead of iron, zinc is incorporated to protoporphyrin and ZPP is formed. A rise in ZPP concentration is one of the first indicators of insufficient iron levels in bone marrow [50, 51]. Additionally, the ratio

of EP to Hb is an excellent indicator of iron failure to meet the normal demands of bone marrow [50]. In healthy individuals, EP concentration is < 40 - 50 μg EP/dl of red blood cells. When TS falls below 15%, EP concentration increases rapidly to more than 70 - 100 μg/dl, whereas concentrations as high as 200 μg/dl may be reached in cases of prolonged or severe iron deficiency. Day-to-day variation of EP concentration is reported to fall around 6.5% [52].

The concentration of sTfR has also been used as an indicator of iron deficiency erythropoiesis [19, 41]. Plasma sTfR is a truncated form of the cellular receptor (TfR), which is responsible for binding and transferring iron into the cell. Transferrin receptor is upregulated when the cell needs more iron, and sTfR is proportional to the cellular TfR content. Normal concentration of sTfR ranges within 1.15 - 2.75 mg/L [41]. When iron stores become depleted and the functional pool of iron diminishes, the levels of sTfR increase [41, 53]. In contrast to Ferr, sTfR is not an acute phase protein, and its concentration is not affected by infections or other inflammatory conditions [16, 54]. Additionally, the much lower day-to-day recorded variability of 4% - 16% for the sTfR compared with the corresponding value of Ferr (13% - 75%) [19] may render sTfR a more accurate index for the estimation of athletes' iron status and the exercise-induced changes in iron metabolism [55]. The sTfR/log Ferr index with normal values ranging within 0.63 - 1.8 [41], is believed to be a more reliable index, as it is less variable and takes into account both the iron stores and the iron pool. Hence, it may reflect more accurately athletes' iron status.

4.5. Estimation of hemolysis

Haptoglobin (Hp) is used as an index of hemolysis. The destruction of the red blood cells membrane due to hemolysis allows Hb and its associated iron held within the cell to be released into the surrounding plasma. Haptoglobin binds free Hb released from erythrocytes, inhibiting its pro-oxidative activity [44]. The binding of Hb to Hp causes a decline in Hp levels, and the formed haemoglobin-haptoglobin complex is taken up exclusively by hepatocytes, thus preventing the excretion of free Hb in the urine [20]. Hence, the decline in Hp levels below normal values, which range between 15 - 200 mg/dL[42], reveals the occurrence of hemolysis. As a result, the regular return of catabolized red blood cells to the reticuloendothelial system (RES) is diminished. Therefore, the observed lower Hb concentration often seen in long distance runners may not always reflect iron deficiency. The shift of iron turnover from hepatocytes rather than the RES may represent an alternative explanation of the observed compromised iron status [20]. The estimation of Hp levels could be of great importance in the verification of true iron deficiency even when other parameters such as Hb, serum Ferr, or bone marrow hemosiderin appear to be lower than normal values.

Taking the above into consideration, an integral evaluation of an athlete's iron status should not be based on the estimation of one parameter alone. Additionally, day-to-day variations of the estimated indices, as well as exercise-induced changes in blood volume, acute phase reactions, infections, or other inflammatory conditions, should also be considered. This way, the assessment would be more integrated, and false conclusions about the effect of exercise on the athlete's iron status would be avoided.

		Hb g/dL	Hct %	RBC x 10^6 c/µL	MCV fL	MCH Pg/cell	MCHC g Hb/dL	RTC count % RBC
Reference values for non-athletes adults*	Males	13.2-17.3	39-49	4.3-5.7	80-99	27-34	32-37	0.5-1.5
	Females	11.7-15.5	35-45	3.8-5.1	81-100	27-34	32-36	0.1-1.5
Reported iron status indicators in elite Athletes (M±SD)								
Koehler et al. (2012)√ (several sports)	Males	14.7±1.1	42.3±2.6					
	Females	13.2±0.9	38.6±2.4					
Della Valle & Haas, (2012)√	Females (N)	13.1±0.7	40.1±2.1		88.8±3.6			
	(D)	13.0±0.7	40.2±2.1		87.9±4.6			
Reinke et al. (2012) ↑	Males (CS)	12.2-17.1						
	(R)	11.6-17.2						
	(P)	12.4-16.5						
Schumacher et al. (2002)√	Males (EA)	15.7±1.0	46.6±3.3	5.24±0.52				
	(PA)	16.4±1.0	47.4±3.1	5.47±0.36				
Malczewska et al. (2001)√	Males (N)	16.38±1.1	0.49±0.0¥	5.26±0.36	90.9±3.9	31.2±2.4	34.3±4.5	
	(D)	15.92±1.1	0.47±0.0¥	5.12±0.32	91.7±3.3	31.2±1.7	33.7±1.5	
	Females (N)	14.5±0.9	0.42±0.0¥	4.5±0.37	91.8±4.9	32.3±3.0	35.0±2.9	
	(D)	13.8±0.8	0.42±0.0¥	4.6±0.33	88.9±3.3	29.9±1.8	33.2±1.6	
Rowland et al. (1987)	Males	14.7±1.0						
	Females	13.3±0.4						
Magnuson et al. (1984)	Males	14.6±0.9			87.9±7.2	31.3±2.1	35.8±1.8	

		Ferr µg/L	Iron µg/dL	TIBC µg/dL	TS %	sTFR mg/L	Hp mg/dL	EP µg EP/dL
Reference values for non-athletes adults*	Males	20-300	65-175	250-425	20-50	1.15-2.75	15-200	< 40-50
	Females	10-120	50-170	250-425	15-50	1.15-2.75	15-200	< 40-50
Reported iron status indicators in elite Athletes (M±SD)								
Koehler et al. (2012)√ (several sports)	Males	55.4±36.7						
	Females	35.4±22.0						
Della Valle & Haas, (2012)√	Females (N)	43.0±20.3					6.4±2.5	
	(D)	13.9±5.1					6.4±2.1	

Reinke et al. (2012) ↑	Males (CS)	6-127			10.7-85.4			
	(R)	20-133			9.0-54.2			
	(P)	15-148			13.9-43.2			
Schumacher et al. (2002)√	Males (EA)	125.6±91.5	125.0±50.2				73.0±38.9	
	(PA)	82.3±61	105.5±38.6				55.2±30.7	
Malczewska et al. (2001)√	Males (N)	65.9±1.83	104.3±28.2	310±36.7		1.78±1.3	1.29±0.58	
	(D)	19.5±2.14	72.8±20.5	348±41.2		3.15±1.2	1.16±0.54	
	Females (N)	40.6±1.76	105.3±32.9	315±42.6		1.72±1.2	1.29±0.89	
	(D)	20.1±1.54	81.7±20.4	344±49.2		4.36±2.5	1.43±0.60	
Rowland et al. (1987)	Males	29.4±17.8						
	Females	26.6±11.4						
Magnuson et al. (1984)	Males	64.3±47.8	19.1±7.3 ˚		31.8±11.6		52.0±32	27±l8

Hb: Haemoglobin, Hct: Hematocrit, RBC: Red blood cells, MCV: Mean corpuscular volume, MCH: Mean corpuscular Hemoglobin concentration; RTC: Reticulocytes count, Ferr: Ferritin, TIBC: Total iron binding capacity, TS: Transferrin saturation, sTfR: soluble transferrin receptor, Hp: Haptoglobin, EP: Erythrocyte protoporphyrin

√Values reported in Mean±SD, ↑ the observed ranges, ¥Values reported in L/L, ˚ Values reported in μmol/L

N: normal iron status, D: iron deficiency, CS: Competitive season, R: Recovery, P: Preparation, EA: Endurance trained athletes, PA: Power trained athletes

* WHO, Assessing the Iron Status of populations (2004); Suominen et al., 1998; Tietz, 1995; Lynch, 2004; Beard, 2004; Labbe et al., 1999;

Table 1. The main iron status indicators: reference values for non-athletes and reported values in elite athletes

5. Exercise-induced alterations of iron status in athletes

5.1. Chronic exercise

There is a great body of evidence indicating that several hematological and iron status parameters often appear altered as a result of chronic exercise (Table 2) giving the impression that athletes may be iron-deficient [14-17, 22, 43].

Several hematological variables in strength-trained athletes have been reported to be similarly low or even lower than that of endurance athletes [14, 56]. Nevertheless, it is mostly the endurance type of training that has been linked to lower values of several hematological indices [35, 43]. Actually, although within normal values, lower levels of RBC have been reported in endurance and/or power athletes as compared to sedentary individuals, while Hb and Hct were significantly lower in endurance athletes only when compared with power athletes [43]. These lower levels in endurance athletes have been attributed to reticulocytosis and expansion of plasma volume associated with chronic aerobic training [35, 43, 56]. However, abnormal Hb concentration (< 13 g/dL) was not only reported in endurance athletes, but in male athletes of

combat sports as well [14]. What is more, even Hb levels below 12 g/dL, defining iron deficiency anemia, has been reported for female rowers, indicating that abnormal decrements in Hb concentration can be found in athletes other than runners [36].

While in the general population a serum Ferr concentration below 12μg/L is used for the identification of first stage iron deficiency, wider serum Ferr cut-offs values (ranging from 12 to 40 μg/L) have been adopted for the identification of diminished iron stores and iron deficiency in athletes [14, 15, 24, 33, 34 36]. Additionally, iron deficiency has also been distinguished to absolute, when serum Ferr is below 30μg/L, or functional, when serum Ferr is within 30 - 90μg/L or serum Ferr is within 100 - 299μg/L and TS is below 20% [15].

Although within normal range, athletes demonstrated lower values of serum Ferr but similar transferrin and Hp values compared with sedentary controls [43]. Similarly, in [56] significantly lower Ferr concentration in endurance athletes is reported compared with strength-trained athletes and controls, and Ferr levels below 50μg/L in 18% of endurance athletes as compared to 12% in controls.

Decreased serum Ferr values (< 35 μg/L) were recorded to one third of elite athletes [14]. These results are in agreement with those in reference [4] where decreased serum Ferr values (< 35 μg/L) and low, instead of normal, hepatic iron stores were also reported in male distance runners, indicating a true prelatent iron deficiency. The lower cut-off point of < 20 μg/L for Ferr adopted by the authors in reference [36], identified 30% of the rowers as being non-anemic iron-depleted at the beginning of a pre-training period, while another 10% were identified as anemic according to Hb values of less than 12.0 g/dl.

A very intense training or competitive period may lead to absolute (Ferr < 30μg/L) and functional (Ferr within 30 - 90μg/L or Ferr within 100 - 299 μg/L + TS <20%) iron deficiency in professional male soccer players [15, 57], elite rowers [15] and female swimmers [35]. In some cases, the allowed recovery period before the next training phase may not be sufficient for the replenishment of the depleted iron stores [15], and this point definitely needs closer attention.

Based on data of several investigations, iron status disturbances are more frequent in female than in male athletes. In reference [14], female athletes were about twice as likely to exhibit reduced Ferr levels. In that study, 58.8% of females had Ferr below 35 μg/L, whereas the corresponding percentage of their male counterparts was 31.2%. In another study [58], 45% of the female cross country runners became iron-deficient at the end of the competitive season, while in males only 17% of them were characterized as iron-deficient. Similarly, the prevalence of iron deficiency was greater in female athletes of several events, as compared to male athletes. Determination of the transferrin receptor-ferritin index (sTfR/logFerr) revealed values of 2.62±0.94 and 3.33±1.71 for iron-deficient male and female athletes, respectively [16]. Additionally, critically low Ferr levels below 15μg/L or even below 12μg/L have also been reported for female runners [58- 60].

The cause of reduced levels in Ferr or serum iron in athletes is not fully understood. Exercise-induced hemolysis, as documented by the reduced Hp values, may offer a plausible explanation. In reference [20], although no differences were observed in Hb concentration, the levels of iron concentration, Hct, Ferr, TS, and bone marrow hemosiderin were lower in athletes compared

to controls. However, no true iron deficiency was established based on the normal mean cell volume (MCV) and EP values, as well as on the normal sideroblast count in bone marrow smears of all athletes, confirming an adequate supply of iron to normoblasts. The lower Hct and Ferr values in athletes could be explained by the simultaneous marked decline of Hp levels, indicating a shift of iron to the hepatocytes as a result of increased intravascular hemolysis. Thus, diagnosing iron deficiency solely based on reduced Ferr or hemosiderin levels, could lead to an underestimation of iron reserves and a possible false-positive diagnosis of ''sports anemia''.

5.2. Acute exercise

Not only chronic exercise, but also acute strenuous physical activity may alter several indices of iron status. A significant reduction in serum iron levels of 12.2 μmol/L was reported after a triathlon completion [61]. The authors proposed that heavy sweating or a prelatent iron deficiency may explain the observed severe reduction of serum iron. However, sweat iron concentration does not correlate with the increased whole body sweat rates [8].

A slight increase in sTfr, although within the normal range, has also been recorded after incremental running to exhaustion, but not after 45 min of submaximal exercise or after 3 consecutive days of aerobic training in highly trained endurance cyclists [55]. After the incremental running, an increase in Ferr, as well as in Hb and Packed Cell Volume (PCV) was also observed. This increase was mainly attributed to the concurrent hemoconcentration, as evidenced by the pronounced fall in plasma volume.

Regardless the acute or chronic character of exercise where most studies report variable responses in iron status, there are also studies that do not support significant differences in iron status between trained and untrained individuals. Indeed, similar incidence of iron deficiency between male endurance young athletes and non-athletes involved in several sport disciplines has been reported [18]. High physical activity of athletes did not affect iron stores, as it was found to be higher than in control subjects. It has to be mentioned though, that athletes had higher iron intake from the diet than controls, and that 18% of those that were iron-sufficient reported consumption of iron supplements. In a more recent study of the same institute [19] that involved female endurance athletes, lower incidence of iron deficiency was reported in athletes as compared to controls. These studies may lead to the assumption that the increased iron dietary intake and dietary factors involved in iron metabolism compensated for the augmented, exercise-induced losses of iron in young athletes. Regarding iron deficiency in athletes whose iron intake was sufficient, the authors attributed its prevalence in its diminished absorption for the male, and its leak to the blood due to menstrual cycle for the female athletes.

Taken together, these studies that attempted to evaluate the effects of exercise on iron status of athletes suggest that high volume training during a competitive season may compromise iron homeostasis. One determining factor that could help explain the reported discrepancies in iron status due to acute or chronic exercise is diet. Unfortunately, not many studies report athletes' daily dietary intake of iron, and since iron intake or absorption are determining factors for iron balance future studies need to address this issue.

Study	Study protocol	Subjects	Estimated indices	Results
Compromised iron status				
Chronic exercise				
Kohler et al (2012)	Retrospective estimation of iron status in athletes from 25 different events	96 males 16.1±2.3yo and 97 females 16.3±3yo elite athletes	Nutrition, Ferr, Fe, hematological parameters, CK, VO_{2peak}	**Dietary iron:** 81% of male and 39% of female athletes reached the RDA; iron density was lower in males; 57% of the females and 31% of the males had Ferr<35µg/L; similar VO_{2peak} in athletes with low and normal iron status
Della Valle & Haas (2012)	Determination of the impact of iron depletion on performance at the beginning of a training season	165 female rowers (19.7±1.2yo)	Hb, Ferr, sTfR, 2-km TT	30%of the athletes were iron deficient (**Ferr** < 20µg/L) 10% of the athletes had iron deficiency anemia (**Hb** < 12 g/dL)
Reinke et al (2012)	Assessment of iron status after 3 seasons: championship, recovery, preseason training	10 professional male soccer players 20-36yo, 20 elite rowers 21-35yo	Hematological indices, Ferr, TS	27% of the athletes had iron deficiency after championship season which persisted in all time points in 14% of the athletes; **Ferr:** no significant increase during recovery; **sTransf:** ↑ in the recovery period, and ↓in the pre-season training; **Hb:** 10% of the athletes had apparent or border line anemia in all time points
Schumacher et al (2002)	Epidimiological study, estimation of hematological and iron status in endurance, mixed or power athletes	747 male athletes (24.2±8yo), 104 controls (29.9±6.9yo)	RBC,Hb, Hct, Fe, Ferr, Tf, Hp, VO_{2peak}	**Hb, Hct, RBC**: ↓in athletes than controls; ↓in endurance athletes **Ferr:** ↓in athletes than controls; **Fe, Tf, Hp:** no differences; **VO_{2peak}:** ↑in endurance athletes
Malczewska et al (2001)	Assessment of frequency of iron deficiency in athletes	131 males, 121 females of several events 16-36 years old	sTfR, Fe, TIBC, Ferr, Hp , TfR/log Ferr index	Latent iron deficiency in 29% of female and 11% of male athletes; higher sTfR and TIBC, lower Ferr levels in iron

Study	Study protocol	Subjects	Estimated indices	Results
				deficient compared with normal only in females
Nachtigall et al (1996)	Estimation of iron status and iron metabolism throughout a training period	45 male distance runners	Ferr, ^{59}Fe absorption	Ferr values <35µg in 51% of the athletes; up-regulated ^{59}Fe absorption, decreased liver iron concentration
Spodaryk et al (1993)	Estimation of hematological and iron status in endurance (E), strength-trained (S) athletes and controls (C)	39 male athletes from the 1988 Polish Olympic team (20.4 ± 2.2yo)	Hb, PCV, RBC, Ret, Fe, Ferr, Tf, Hp, TS	**Hb, PCV, RBC, TS:** ↓in E compared with C; **Ferr:** ↓in E compared with S and C; **Ret, GOT:** ↓in E compared with S
Brigham et al (1993)	Estimation of iron status during a competitive season	25 female varsity collegiate swimmers	Hb, Ferr	At baseline 17 athletes were iron depleted and 5 athletes were anemic. After 5 wk Hb decreased (≥6 g/L) in 44%, and Ferr (≥5 µg/L) in 24% of the athletes
Nickerson et al (1989)	Estimation of stage II iron deficiency (Ferr<12ng/ml and TS<16%) during the running session; iron supplementation or iron-rich diet or controls	41 female and 25 male cross-country runners and controls (15-18yo)	Ferr, TS, blood losses	**Iron deficiency:** 34% of females and 8% of males became iron deficient by the 45th or 75th day of running **Blood losses:** 14 stools in females and 1 stool in males with "/>4mg Hb/g of stool
Rowland et al (1987)	Estimation of iron status during a competitive season; supplementation of iron in the iron	30 male and 20 female cross country runners (14.3-18.6yo)	Ferr, Hb, RBC parameters	45%of females and 17% of males identified as iron deficient during the season;
Magnusson et al (1984)	Hematological and iron status comparison between distance runners	43 runners (19-46yo) and 119 controls (19-37yo)	Hb,Hct, MCV, MCHC, EP, Fe, TS, Ferr, BMHem, Sideroblasts, Hp	**Hb:** no differences between groups; **Hct, Fe, Ferr, TS, BMHem:** ↓in athletes; **Hp:** 0.52±0.32 g/L in athletes (11athletes had Hp<0.2g/L); **MCV, EP, MCHC:** no iron deficiency

Study	Study protocol	Subjects	Estimated indices	Results
Acute exercise				
Rogers et al (1986)	Evaluation pre, post, and 30 min, 24h, and 48h after a 160-km triathlon (canoeing, cycling, and running)	18 triathlon athletes	Fe, TIBC, lactoferrin, Ferr, Hp, cortisol, WCC, CRP, various enzymes	Post: ↑ in cortisol, WCC, lactoferrin and ↓ in Fe and TS; 24h: ↑by 300% in CRP, ↓ in Hp
Schumacher et al (2002)	Estimation of exercise on sTfR and other variables after an incremental running test till exhaustion (IRTTE), 45min submaximal running, 3d aerobic cycling	39 athletes (33 men, 6 women) (19.6 – 32.5yo)	Hb, Hct, BV, PV, RCV, sTfR, Ferr, Fe	**Hb, Hct:** ↑ after exercise; **PV, BV:** ↑after incremental and submaximal running; ↓after 3d aerobic cycling; **sTfR:** ↑after the incremental running; **Ferr:** ↑after incremental and submaximal running;
No alterations in iron status				
Malczewska et al (1997)	Estimation of iron status in endurance athletes	178 male athletes, 52 male controls 18-20 years old	Hb, PCV, RBC, WBC, MCHC, MCV, MCH, Fe, TS, TIBC, Ferr, Hp	Similar iron depletion in athletes (19%) and controls (20%); ↓ Ferr, Fe and ↑TIBC in the iron depleted subgroups
Malczewska et al (2000)	Estimation of iron status in endurance athletes	126 female athletes, 52 female controls 16-20 years old	Hb, Hct, RBC, WBC, MCHC, MCV, MCH, Fe, TIBC, TS, Ferr, Hp	Lower iron deficiency (26%) in athletes than controls (50%); ↓ Ferr, Fe and ↑TIBC in the iron deficient subgroups

VO_{2max}: Maximum Oxygen Consumption, TT: Time Trial, CK: Creatine Kinase, Ferr: Ferritin, Fe: Iron, Tf: Transferrin, TS: Transferrin Saturation, sTfR: Soluble Transferrin Receptor, TIBC: Total Iron Binding Capacity, Hb: Haemoglobin, Hct: Hematocrit, PCV: Packed Cell Volume, Ret: Reticulocytes, WCC: White Cells Count, RBC: Red Blood Cells, RCV: Red Cells Volume, WBC: White Blood Cells, MCH: Mean corpuscular Haemoglobin, MCHC: Mean Corpuscular Haemoglobin Concentration, MCV: Mean Corpuscular Volume, BMHem: Bone Marrow Hemosiderin, EP: Erythrocyte Protoporphyrin, Hp: Haptoglobin, PV: Plasma Volume, BV: Blood Volume, GOT: Glutamic Oxaloacetic Transaminase, CRP: C Reactive Protein

Table 2. Iron status in competitive athletes

6. Potential mechanisms for iron balance disturbances due to exercise

Iron absorption mainly, and to a lesser extent iron nutrition, are the two critical mechanisms by which iron balance is maintained since there is no other physiological process for iron excretion. The repletion of iron due to increased losses as well as the body's need during growth and pregnancy are covered by dietary iron intake. Consequently, a low dietary iron intake, could lead to compromised iron status [9]. According to values reported by the Institute

of Medicine, Food & Nutrition Board [62], the recommended dietary intake (RDI) for total iron is 8 mg/day for adult men and 18 mg/day for menstruating women. Usually, male, but not female athletes achieve the RDI for iron [14, 17, 63]. The mechanism of iron absorption by the intestine is regulated by iron bioavailability in diet and by individual's iron status. Iron bioavailability has been found to be affected by the type of the diet and by the type of dietary iron [11]. Hence, mixed diet and heme iron provide greater bioavailability and absorption as compared to a vegetarian diet and nonheme iron, [11-13]. Furthermore, iron deficiency augments iron absorption.

Besides iron absorption and intake, several other mechanisms have been proposed to account for iron loss and iron balance disturbances, and ultimately the prevalence of iron deficiency in athletes. These mechanisms include increased gastrointestinal blood loss, hematuria, hemolysis [5, 6, 17, 64-67], increased iron loss in sweat [7, 8], as well as menstruation in women [9, 10, 68].

In athletes, gastrointestinal bleeding usually accompanied by occult blood, is a well-established phenomenon, mostly seen in distance runners [6, 60]. Gastrointestinal blood loss has shown to be the main contributor to the negative iron balance, as the excretion of ^{59}Fe in sweat and urine appears to be negligible compared to fecal excretion of 3 - 5 mg/day [4]. Running a marathon was associated with a gastrointestinal blood loss [67], and positive occult heme stools were found in runners after intensive training or competitive running [4, 5, 60, 67]. The origin of running-related intestinal bleeding has still to be clarified, but endoscopic examination has revealed bleeding lesions in the stomach and colon [65, 66]. Gastrointestinal bleeding is partly attributed to ischemic injury, and running has been shown to reduce visceral blood flow by up to 43% of pre-exercise levels [69] due to the diversion of blood flow from the splanchnic viscera to the working muscles. Exercise intensity, seems to play a significant role in the development of gastric ischemia [70], which increases mucosa permeability and enhances occult blood loss [6].

Increased iron loss through sweat has also been proposed as a mechanism related to the compromise of iron status as a result of increased sweat rates during exercise in athletes, or increased temperature in individuals living and exercising in hot climates. The daily loss of iron from the skin has been reported to be 0.24 mg/d [71] or 0.33 mg/d [72]. The reported 0.183 mg of iron loss during prolonged exercise at 50% of VO_{2max}, represented the 55% - 76% of the estimated daily iron loss from the skin, and the 23% for men and 10% for women of the estimated total daily iron loss [8]. It has to be mentioned that although the sweat rate increases during the 1st hour of exercise and remains constant thereafter, and males have higher sweat rates than females, the iron loss in males and females remains comparable. Additionally, the sweat iron loss declines in both genders during the 2nd hour of exercise [8], or after the first 30 min in a hot environment [7]. This reduction could be attributed to the initial sweat containing iron present in cellular debris [7], to the increased sweat rates while the total iron loss remains constant, or to a conservation mechanism that may prevent excessive iron loss during exercise [8]. Still, iron loss in sweat remains insignificant compared to that of the gastrointestinal tract.

Another explanation for compromised iron status in athletes is the shift of iron return to hepatocytes, rather than the RES, as a consequence of the increased intravascular hemolysis

occurring mostly in weight-bearing activities, such as running. In these activities, hemolysis is due to the impact forces generated by the foot strike [73, 74]. Increased intravascular hemolysis has been reported in runners [20] and female artistic gymnasts [73]. However, foot strike cannot totally explain the exercise-induced hemolysis since hypohaptoglobinemia, a situation that reveals the presence of hemolysis, has also been observed in swimmers [75]. In non-weight-bearing activities hemolysis may result from the compression of the blood vessels caused by the vigorous contraction of the involved muscles [75].

Female athletes seem to be more prone to the development of iron deficiency [14, 16] and blood loss during menstruation may further explain this greater prevalence. Although menstrual blood loss in a single woman is very constant during menarche and throughout the fertile life, there is a large variation in blood loss among women [68]. Thus, in a mean cycle length of 28 days, menstrual blood loss may vary by as much as 26 - 44 ml, with a corresponding daily iron loss of about 0.5 - 0.7 mg [9, 76]. This great variation in blood and iron loss reported by these two studies could be associated with an extensive use of oral contraceptives which are known to reduce the amount of blood loss during menstruation [77]. Finally, menstrual iron loss in women has been shown to negatively correlate with serum Ferr, and iron status to significantly correlate with the duration and intensity of the menses in endurance athletes [19]. Taking into consideration the iron loss during menstruation along with the relative failure to achieve the daily RDI for iron the greater frequency of iron deficiency in female athletes can be justified.

7. Iron supplementation and exercise-induced alterations of iron status

7.1. Iron supplementation in iron-deficient individuals

Whether the increased uptake of iron through diet or supplements improves iron status in athletes is still under debate. This is mainly due to the great divergence of iron doses, intervention period, population, and exercise regimens used between studies. In situations of iron deficiency a proposed minimum therapeutic requirement corresponds to 100 mg/day of elemental iron, for a period of 12 weeks [17]. However, in several studies, much lower quantities of 20 - 50 mg/day of elemental iron for 12 weeks [10, 35] or smaller duration (of even two weeks) of iron supplementation have also been used and reported to be adequate to restore iron status to normal [78]. Table 3 summarizes the effects of iron supplementation on several indices of iron status.

A treatment with 100 mg/day of ferrous iron for 3 months, significantly increased the values of serum Ferr (from 34±11 to 54±18 µg/L) and liver iron (from 105±42 to 227±67 µg/g liver) [4]. In this study, 23 out of 45 athletes showed decreased baseline serum values (<35µg/L), and the typical iron deficiency in runners was confirmed in a subgroup of eight athletes in which iron metabolism was studied in detail using radio-iron labelling and liver iron quantification. These eight athletes showed up-regulated ^{59}Fe absorption and a decreased liver iron concentration as compared to a control group. The results of the eight athletes confirm that in cases of true iron deficiency, iron absorption is greater.

A moderate dose of 39 mg/day of elemental iron for 5 weeks effectively prevented the negative changes of iron status over the course of a competitive season in female collegiate swimmers

[35]. Absence of iron supplementation resulted in decreased Hb levels despite mean dietary iron intakes of 16.3 mg/day.

The ingestion of 105 mg/day of elemental iron combined with 500 mg of Vitamin C for 60 days resulted in the amelioration of iron status of previously iron-depleted, non-anemic elite female athletes [79]. The improved iron stores were reflected by the increase of Ferr in conjunction with the decrease of transferrin, sTfR and sTfR/log ferritin index.

Taken together the aforementioned results suggest that the initial stage of either iron suffi-ciency or iron deficiency, combined with the amount of iron ingested, plays a critical role in the absorption of iron from diet or supplementation.

7.2. Iron supplementation in individuals with normal iron status

Supplementation of iron is commonly used, not only in iron-deficient athletes, but also in athletes with normal iron status. The rationale behind this practice dictates that supplemen-tation will preserve or enhance their performance. This concept is probably based on the catalytic role of iron on the oxygen transport and optimal function of oxidative enzymes and proteins during exercise. The hypothesis could be that with increased consumption of iron, the above mechanisms would be reinforced and exercise performance would be improved. Nevertheless, unlike the numerous studies addressing iron-deficient individuals, only few [25, 57, 63] have focused in iron-sufficient athletes.

The response of iron stores during a sports season was assessed in professional football players with normal iron stores at the beginning of the season [57]. The players consumed 50 mg/day of elemental iron over two periods during the training season. Supplementation took part for 15 days prior to the beginning of the season and 15 days during the middle season. Blood was collected three times during the season, one following the first supplementation period, another following the second supplementation period and a third time at the end of the season, where no iron supplementation had occurred. Ferritin, as well as calculated iron stores, showed a significant reduction at the end of the season which coincided with the absence of iron supplementation. In contrast, Ferr and iron store levels remained stable following supplementation regardless of the intensive training.

In another study, non-anemic, non-iron-deficient adolescent male and female swimmers aged 12-17 years old were either supplemented with 47 mg of elemental iron daily or consumed a diet rich in iron [25]. Both approaches failed to affect the athletes' iron status. In that study, despite the significant fluctuations during the six months of training, iron levels, TS and Ferr levels were similar at the end of the study as compared to baseline values. The authors attributed the failure of high iron intake to affect iron status to homeostatic mechanisms such as iron absorption. It could also be suggested that the quantity of elemental iron was not enough to improve iron status and that higher doses of iron are needed to achieve a favorable change in iron status. The younger age and the possible higher demands in reference [25] compared with that of reference [57], may have influenced the absorption of iron that resulted in different responses in these two studies.

Studies	Study protocol	Subjects	Estimated Indices	Results
Improvement in iron status				
Nachtigal et al. (1996)	100mg/d of elemental iron for 3 months, radio-iron labeling (^{59}Fe) in 8 iron deficient athletes	45 runners (23 out of 45 were iron deficient, Ferr<35 µg /L), and controls	Ferr, liver iron, iron absorption	Ferr: ↑ from 34±11 to 54±18 µg/L; liver Fe: ↑from 105 ±42 to 227±67 µg/g liver
Brigham et al. (1993)	39mg/d of elemental iron (IG) or placebo (PG) for 5 wks	25 female, iron depleted, varsity collegiate swimmers	Hb, Ferr	Hb:↑ in 24% of the subjects in the IG and in 12% in PG Ferr: ↑ in 68% of the subjects in the IG and in 4% in PG
Pitsis et al. (2004)	105mg/d elemental iron + 500mg/d Vit C for 60 days	36 elite iron-depleted, non-anemic female athletes of several disciplines (13-26yo)	Red cell and reticulocyte parameters, Fe, Ferr, Tf, TS, sTfR	Ferr: ↑; Tf: ↓; sTfR: ↓; sTfR/ log Ferr: ↓ Red cell and reticulocyte parameters: no changes
Rowland et al. (1987)	Estimation of iron status during a competitive season; supplementation of iron in the iron deficient athletes (IG) in the midpoint of the season (the dose is not reported)	30 male and 20 female cross country runners (14.3-18.6yo)	Ferr, Hb, RBC, MCV, RBCDW,	Ferr: ↑in IG and ↓in untreated athletes at the end of the season; Hb, RBC, MCV, RBCDW: no changes
Escanero et al. (1997)	Variation of iron metabolism through a season; 50mg of iron/day for the last 15 days at the beginning (A) and the middle of (B), but not at the end (C) the season	9 soccer players at the 1st division (24±2.1yo)	RBC, MCV, MCH, MCHC, Fe, Tf, Ferr, TIBC, TS	Ferr, Iron stores: ↓at the end of the season (no iron supplement); remained stable at the beginning and the middle of the season (iron supplementation)
Improvement of performance				
Friedmann et al. (2001)	2 x 100mg/d elemental iron (IG) or placebo (PG) for 12 wks; the usual training	40 iron depleted endurance athletes (13.6-21.1yo, Ferr < 20 ng/mL) IG: 20 males and females (PG: 20	Hematological indices, Fe, Ferr, Trf, TS, BV, PV, VO$_2$, VCO$_2$, VE, MAOD, LA	IG: VO$_{2max}$, VO$_2$, TTE: ↑; Ferr: ↑ 20.1µg/ L, Tf: ↓ PG: no changes

Studies	Study protocol	Subjects	Estimated Indices	Results
		females and 8 males 14.5 -17.5yo)		
Rowland et al. (1988)	975mg/day ferrous sulfate (IG) or placebo (PG) for 4 wks (time C), after a 4wk control period (time B)	14 iron-deficient (Ferr < 20ng/mL) female cross-country runners (high-school age)	TTE, HR, VO_{2max}, VE, Hb, MCV, RBCDW, Ferr	TTE: ↑in both groups at time B, ↑ in IG and ↓in PG at time C; Ferr: ↓at time B in both groups, ↑at time C in IG; Hb, MCV, RBCDW: No changes in both groups
No changes in iron status or performance				
Peeling et al. (2007)	Intramuscular iron injections (5 x 2mL Ferrum H/day) (IG) or placebo for 20 days	16 iron depleted, female distance runners and controls	VO_{2max}, HR, LA, run-TTE, 10min submaximal economy test, Ferr	Ferr: ↑in IG; HR, LA, TTE: no differences between IG and PG
Tsalis et al. (2004)	47mg/d (IG) or dietary plan rich in iron (DIG) or regular diet for 6 months (endurance training: 3m; power training: 2m; tapering: 1m)	21 males and 21 females, 12-17yo, non-anemic, non-iron-deficient	Hematological indices; Fe, TIBC, TS, Ferr; swimming tests: 2000m, 800m, 200m and 25m sprint	Fe, TIBC, TS, Ferr: fluctuations within the phases; At m6: no differences from baseline; RBC, Hb and PVC: ↑at m6; performance tests: similar ↑in all groups
Klingshirn et al. (1992)	8wks of iron supplementation (IG), or placebo (PG)	18 iron depleted, female distance runners and controls, 22-39yo	VO_{2max}, endurance run-TTE, LA, iron status	Ferr, TIBC: ↑ in IG compared with PG at wk 8 Endurance performance, LA: similar ↑ both groups
Powell & Tucker (1991)	130mg of elemental iron /day (IG) or placebo (PG), for 2wks; single blind design	10 female cross-country runners (20.2±1.3yo) with normal iron status	VO_{2max}, CO2, RER, VE, Fe, TIBC, Ferr, Hp, Hb, Hct, MCHC, MCV, WCC, LA	Hematological & iron status parameters: no significant changes; Metabolic parameters: no changes

VO_{2max}: Maximal Oxygen Consumption, VCO_2: Exhaled Carbon Dioxide, VE: Ventilation, MAOD: Maximal Accumulated Oxygen Deficit, TTE: Time to Exhaustion, HR: Heart Rate, CK: Creatine Kinase, LA: Lactate, Ferr: Ferritin, Fe: Iron, Tf: Transferrin, TS: Transferrin Saturation, sTfR: Soluble Transferrin Receptor, TIBC: Total Iron Binding Capacity, Hb: Haemoglobin, Hct: Hematocrit, PCV: Packed Cell Volume, MCHC: Mean Corpuscular Haemoglobin Concentration, BV: Blood volume, PV: Plasma Volume, MCV: Mean Corpuscular Volumes, RBC: Red Blood Cells Count, RBCDW: Red Blood Cell Distribution Width, WCC: White Cells Count, MAOD: Maximal Accumulated Oxygen Deficit

Table 3. The effect of dietary or supplemented iron on exercise-induced changes of iron status and physical performance

8. Iron supplementation and physical performance

8.1. Iron supplementation in iron-deficient individuals

There is no doubt that iron-deficiency anemia, which amongst other indicators (e.g. Ferr<12µg/L, TS<16%), is characterized by a decline in blood Hb concentration, clearly impairs physical performance by limiting oxygen transport to exercising muscles [22]. However, the need for iron supplementation in cases of depleted iron stores without observed anemia for optimal physical performance is still under debate (Table 3). Some studies have shown that iron supplementation improved physical performance [23, 24], whereas others report no alterations following iron supplementation [25, 34, 63].

The improvement of iron status due to iron supplementation has been accompanied by an improvement in endurance capacity [23, 24]. In young elite athletes with normal Hb concentrations, the return of low Ferr to normal values following supplementation of 200 mg/day of elemental iron for 12 weeks, even in the absence of increased erythropoiesis, has been shown to improve maximal aerobic capacity [23].

Iron supplementation also prevented the decline in performance that was associated with the progressive reduction of serum Ferr levels [24]. Iron deficient cross-country female runners were treated with 975 mg/d of ferrous sulfate or placebo for 4 weeks. Iron supplementation resulted in an increase in ferritin levels which was accompanied by an improvement of physical performance. Subjects not receiving iron therapy exhibited a decline in their performance [24].

Besides the aforementioned positive results in exercise performance there are studies reporting no beneficial effects due to iron supplementation [25, 34, 63]. In reference [63], no significant improvement of iron status or metabolic parameters related to running performance was found after 2 weeks of 130 mg elemental iron supplementation in non-anemic, iron-deficient female cross-country runners. Likewise, in [34], 8 weeks of iron supplementation in iron-depleted, non-anemic female distance runners, resulted in similar improvement of the endurance capacity in the supplemented and the placebo group, despite the improved iron status in the iron-supplemented group. In another study, the injection of 2 mL of Ferrum H (100mg of elemental iron) five times daily for 10 days did not result in any beneficial outcomes on submaximal economy, VO_{2max} and time to fatigue in non-anemic, iron-deficient female runners [33]. This study, failed to demonstrate any beneficial effect of iron supplementation on aerobic capacity, despite a significant rise in serum Ferr levels (from 19 to 65µg/L).

8.2. Iron supplementation in individuals with normal iron status

In one of the very few studies that used healthy, non-iron-depleted and non-anemic adolescent swimmers, the enhanced iron intake either through supplement or diet ranging from one to five times the RDA, did not change iron status or result in favorable changes of physical performance [25]. The authors attributed the observed fluctuations over the training period of six months to the different demands of each training phase irrespective of iron treatment. These

observations strengthen the notion that the initial levels of iron status are of critical importance in the improvement of physical performance as a result of iron supplementation.

In [35], the mean dietary intake of 16.3 mg/day was not adequate to prevent the disturbance of iron status in female collegiate swimmers. Haemoglobin levels decreased at about 6 g/L in 44% of the athletes given placebo treatment, whereas the corresponding decrement in plasma Ferr was 5μg/L in 24% of the swimmers given the iron supplement. Consequently, the reductions in Hb and Ferr levels were lower in the athletes that were under iron supplementation.

9. Future research

Although the favorable effects of iron supplementation on physical capacity in iron-deficient anemic athletes has been well established, relatively little research has been conducted addressing iron-deficient non-anemic athletes. Therefore, further research is needed to clarify the necessity of iron supplementation in athletes with depleted iron stores, yet, normal Hb concentrations for improvement of their performance.

Despite the great importance of iron balance in athletes, no normative data for athletes exist and hence it is essential such norms are established. Such data would be more critical if appropriate discriminations were made, e.g. regarding the type of training (endurance or power-training athletes), sex, age, or seasonal demands and so on.

The commonly used parameters for the estimation of iron status in the general population (Hb, Hct, Ferr, iron concentration, TIBC, TS), may not always be adequately representative for athletes. Therefore, it would be useful if future studies incorporated additional parameters such as erythrocyte protoporphyrin, soluble transferrin receptor or haptoglobin, in order to get more accurate and complete estimation of iron status.

10. Conclusions

Iron is one of the most important elements for health and exercise performance. It is unclear whether iron intake by an athlete through diet is adequate in order to prevent iron balance disturbances and further research is needed to clarify dietary methods to prevent iron deficiency. It seems that exercise, acute or chronic, results in significant disturbances in iron balance due to different reasons. Changes in iron absorption and iron intake due to exercise, iron losses through the gastrointestinal tract, intravascular hemolysis, and to a lesser extent iron losses through sweat, are probable mechanisms for iron balance disturbances during exercise.

Alterations in iron status balance are reported as a result of exercise, especially in endurance trained, and women athletes. Iron-deficiency without anemia is a very commonly reported phenomenon among athletes, and occasionally iron deficiency anemia is also reported.

Iron balance is of great importance for optimal work capacity, and a compromise of iron status would have detrimental effects on physical performance in iron-depleted anemic athletes. In these situations, iron supplementation is required for restoration of iron levels and optimization of the athlete's performance and health. However, similar effects have not been well documented for athletes that are iron-deficient without the presence of anemia. Nevertheless, iron supplementation among athletes is a very common practice, despite the discrepancy regarding its beneficial effects in non-anemic, iron-depleted, or even normal iron status athletes. This discrepancy is attributed to the divergence in iron doses, athletic population, and the great variance in the intervention period, and exercise regimens that are used between studies.

Because of the different demands in iron through the several phases of training or competitive periods, evaluation of iron status of the athletes should be performed at the beginning, at the midpoint, and finally at the end of the season. Controlled iron supplementation for all athletes with serum Ferr below 35μg/L is recommended for the replenishment of iron stores.

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