REVISIÓN
ARCHIVOS DE MEDICINA DEL DEPORTE

Volumen XXVIII
Número 144
2011
Págs. 266-274

IRON SUPPLEMENTATION IN SPORT ACTIVITY

SUPLEMENTACIÓN CON HIERRO EN LA ACTIVIDAD FÍSICA

Paolo Borrione

Loredana Grasso

Alessia Di Gianfrancesco,

Attilio Parisi

Fabio Pigozzi

Department of Health Sciences University of Rome "Foro Italico" Italy

IRON DEFICIENCY

Iron deficiency is the most common single nutrient disorder and represents a major public health problem worldwide[1]. Among the healthy population, with the exception of pregnant women, adolescents engaged in competitive endurance sports represent the group of subjects with the highest iron demand[2]. Indeed, the sport medical literature is rich of epidemiological studies evaluating the effects of iron deficiency on sport performances as well as the effects, positive or negative, induced by the martial supplementation. However, while the recommendation to pay particular attention in maintaining an adequate consumption of dietary iron would be always advisable, the use of iron supplements should be a careful choice based on a precise hematological evaluation, mainly because of the possible health risks deriving from an unjustified treatment. With particular regard to the sport related supplementation, currently no standardized guidelines for iron administration are available and the decision if administrating or not oral iron in athletes is mainly based on empiric recommendations or on performance enhancing hopes. A more detailed analysis of the iron related issues may guide clinicians in a more scientifically based choice.

IRON METABOLISM

When the body has enough iron to meet its energy demand (functional iron), the remaining is stored in the bone marrow, liver and spleen as part of a precisely controlled system of iron metabolism[3].

Humans maintain iron homeostasis mainly through the regulation of the intestinal iron absorption since the capacity to excrete iron is very limited. Systemic iron homeostasis including the absorption, the functional use and the storage is maintained by several well known molecules such as transferrin and ferritin. Recently, other key molecules such ceruloplasmin, the divalent metal ion transporter 1 (DMT1), hephaestin and hepcidin have been shown to play a significant role in the maintenance of the iron balance[4-6].

Most adults have at least 3000 mg (45mg/Kg) of elemental iron in their bodies. Females generally have lower levels than males because of the iron loss during menses, pregnancy and lactation. Within that pool of total body iron, approximately two-thirds are contained in the heme (mostly incorporated in erythrocyte hemoglobin) and one-third in the storage forms

CORRESPONDENCIA:

Prof. Fabio Pigozzi
Department of Health Sciences, University of Rome "Foro Italico"
Piazza Lauro de Bosis 15, 00194 Rome, Italy
E-mail address: fabio.pigozzi@uniroma4.it

Aceptado: 06.04.2011 / Revisión nº 232

of ferritin. To maintain adequate supplies of iron for heme synthesis, 20 mg of iron is recycled daily, from senescent red cells that are removed from the circulation, to new cells in the bone marrow[7]. Under physiological conditions, about 25 mg of iron per day is consumed by immature erythrocytes in the bone marrow for the heme biosynthesis. The recycling of heme-iron from senescent erythrocytes constitutes the main iron source for supporting erythropoiesis. Macrophages in the liver and spleen are responsible for this recycling. Around 1-2mg/day of additional dietary iron is needed to balance losses in urine, sweat, and stool. Over the last decade, it has been progressively clarified that systemic iron homeostasis depends on the modulated expression of hepcidin, a circulating peptide hormone that regulates the entry of iron into plasma. Hepcidin, primarily released by the liver, negatively regulates iron output from intestinal cells and macrophages by altering the expression of the cellular iron exporter ferroportin[8-10]. Therefore, hepcidin acts as the key regulator of the total body iron, by modulating intestinal iron absorption, as well as iron availability for erythropoiesis by affecting the efficiency of macrophages mediated iron recycle[11]. If dietary intake is inadequate to replace the 1-2 mg/d of obligate iron loss or to replace additional losses, iron deficiency will develop[12,13].

Iron deficiency anemia results from a variety of causes that fall into the following four general categories: a) increased iron loss, b) decreased iron intake, c) decreased iron absorption and d) increased iron requirements. In the vast majority of cases, the cause of iron deficiency results in an anemia that is both avoidable and reversible by increasing iron supplementation or reducing iron loss. However, the fact that many people continue to show iron deficiency anemia[14] suggests that generic therapeutic approaches remain suboptimal. It may be necessary to re-consider general treatment approaches in order to reduce the incidence of iron deficiency anemia.

The maintenance of body iron homeostasis is the result of a precise balance between intestinal absorption and losses. When considering the lack of a specific excretory system, iron losses are mostly associated with bleeding and tissue sloughing that, in healthy individuals, are usually compensated by similar amounts of iron absorbed in the duodenum. Characteristically, intestinal iron absorption is divided into three steps, namely the uptake phase, the intracellular phase and the transfer phase[15]. The former phase involves the transport of iron from the intestinal lumen into the enterocyte cytoplasm. This phase is controlled by membrane transporters such as the heme carrier protein 1 (HCP1, SLC46A1)[16] and the divalent metal transporter 1 (DMT1, SLC11A2)[17,18]. The following transfer phase involves the transport of intracellular iron from the cell cytoplasm into the blood circulation. This process is mediated by the iron-export transporter ferroportin1 (SLC40A1)[19-21]. Little is known about the intracellular phase, although 80-90% of the incoming iron is retained intracellularly[22,23]. When considering the iron storage, ferritin is the only well characterized iron-storage protein in living organisms[24]. It is composed by 24 subunits in maxi-ferritin form accepting up to 4,500 $Fe^{3}+$ atoms in the form of crystallized diferric oxo-hydroxyl complexes[25]. In intestinal cells, ferritin concentrations are regulated by an iron dependent control of protein synthesis and degradation[26-28].

DIETARY

Assuming an average absorption of 10% of the iron in a medicinal form, the daily elemental iron requirement is 10 mg in children, adult males and post menopausal women (to provide 1 mg to the body), 20 mg in young non-pregnant women and 30 mg in pregnant women[29]. The nutritional value of food depends on both the amount of nutrients and its bioavailability[30,31].

With regard to the iron content, the mineral in food is found in two different chemical forms: the heme iron and nonheme iron. Heme iron content is found mainly in meat foods, in the hemoglobin and myoglobin form. Its absorption, usually ranging from 15 to25% of the intake, is not modified by other elements since it is directly absorbed as porphyrin complex[32].

Nonheme iron absorption is low, usually ranging from 2 to5% of the intake, and it is highly susceptible to wide variations depending on the different composition of the diet. About 90% of the dietary iron is in the oxidized form (iron ferric, Fe^3+, non-heme iron) poorly absorbed (legumes, cereals, vegetables, fruit, eggs, milk and dairy products) while only the remaining 10% is present as reduced iron (ferrous iron, Fe^2+, heme iron), easily absorbed (meat and fish)[33]. Bioavailability means the proportion of the nutrient that is absorbed, transported to the site of action and converted into the biologically active form. Factors affecting the bioavailability can be divided into factors depending on the body itself, and factors related to the food containing the nutrients[34,35].

Iron absorption changes with age, health status and condition of the body reserves. Iron deficient subjects absorb more iron than subjects with intact iron stores. This increased absorption relies mainly in the heme iron, which increases by 25-35% in those conditions. On the contrary, non-heme iron absorption albeit more modestly (10-20%). Moreover, several factors in the diet may promote or inhibit the absorption of non-heme iron. The ascorbic acid reduces ferric iron to ferrous and binds to it thus increasing bioavailability of non-heme iron up to 2-3 times. On the contrary, other chelators (phytates, soluble and insoluble fiber, oxalic acid, polyphenols, calcium and phosphorus, gallic acid and tannic) significantly inhibit iron absorption[36,37]. Additional conditions may play a significant role in modifying iron absorption. With this regard, it has been demonstrated that, in conditions of reduced iron stores, athletes may show decreased iron absorption (16,4% when compared to sedentary subjects) probably as a consequence of an increased intestinal transit[38,39].

IRON DEFICIENCY AND PERFORMANCES

Alterations of iron metabolism in athletes are very well described in literature, especially in subjects who engage in endurance sports, from the simple reduction of the iron stores, up to a true iron deficiency anemia. For this reason, sports medicine has always paid particular attention to iron metabolism since its deficiency may adversely influence athlete's performance[14].

With this regard, it is important to underline two different hematological conditions that may occur in athletes and that may contribute as "confounding" factors in the interpretation of the iron status of those subjects: sport related acute anemia and pseudo-anemia[40,41]. The first one typically occurs among untrained subjects undertaking a strenuous exercise, but is also described in trained subjects engaged in exercises of long duration or in repeated high intensity performances. The pathogenesis of this acute anemia is multifactorial. Typically, mechanical factors, such as the repeated impact of the superficial vessels of the foot against hard surfaces, and chemical factors, such as changes of the erythrocyte osmotic resistance, the rise of free radicals and lactic acid and the increased body temperature are described as contributing factors[42-44].

The second condition, which typically occurs among the athletes engaged in endurance activities, is the so called pseudo anemia by hemodilution. The initial hemoconcentration, stimulates the release of rennin , aldosteron and vasopressin (ADH), causing an increased osmotic pressure of plasma. This condition determines, mainly in the early stages of training, haemodilution with a consequent reduction in the concentration of hemoglobin. This dilution may also cause an apparent reduction of plasma ferritin thus simulating a condition of iron deficiency[45,46].

The negative influence of anemia by iron deficiency on physical performances has been well described in several studies. On the contrary, in trained athletes, levels of serum ferritin (SF) between 15 and 30 μg/L, reflecting an iron deficiency without anemia, are frequently observed. For this ferritin range, which does not appear to affect athletic performance, the real usefulness of iron supplementation is still matter of debate. In addition, to date there is no standardized ferritin

level to which supplementation is recommended, and no consensus exists as to the appropriate maintenance of ferritin levels, neither in adult nor in young athletes[47-50]. Moreover, some studies have also shown that the practice of physical activity may determine a reduced use of the iron itself even if the body tissue reserves are appropriate[51].

The literature presents different opinion when considering the influence of iron supplementation on performances. This divergence is mainly due to the diversity of the methodological approaches used, to the different methods adopted for the determination of the iron status and to the different sport disciplines examined. However, it is well known that among athletes, especially those engaged in endurance disciplines, it has to be taken into consideration a significant loss of iron mainly due to gastro-intestinal bleedings, sweat and increased desquamation of cells suggesting the need for iron supplementation[52-54]. On the contrary, the damage caused by improper supplementation of iron (e.g. hemochromatosis in individuals homozygous for the widespread C282Y polymorphism of the HFE gene[55] or the potential oxidative damage resulting from "free iron" released during exercise[56], confirms that the choice of iron supplementation should be based on a careful hematological evaluation, considering the possible health risks deriving from an unjustified treatment.

IRON SUPPLEMENTATION

When considering non anemic subjects, the evaluation of the iron status, is usually based on serum ferritin (SF) levels[57-59]. It is known that values lower than 12 μg/L undoubtedly represent a condition of iron deficiency requiring iron supplementation[57]. However, in trained athletes, levels of ferritin between 12 and 30 μg/L, reflecting an iron deficiency without anemia, are frequently observed. For this ferritin range, which does not appear to affect athletic performance, the real usefulness of iron supplementation is still matter of debate. In addition, to date there is no standardized ferritin level to which supplementation is recommended, and no consensus exist as to the appropriate maintenance of ferritin levels, neither in adult nor in young athletes.

To better evaluate the iron status several biochemical parameters have been used including serum iron, total iron binding capacity[60], transferrin saturation[61], transferrin receptor concentrations and transferrin receptor-ferritin ratio[2,61]. However, none of these variables have been identified as an effective marker for deciding when to start a justifiable iron supplementation.

Recently, our research group evaluated the possibility of investigating the iron status of athletes through the evaluation of hepcidin levels. Indeed, hepcidin is a circulating peptide hormone that regulates the entry of iron into plasma. Hepcidin, primarily released by the liver, negatively regulates iron output from intestinal cells and macrophages by altering the expression of the cellular iron exporter ferroportin[9,10]. Therefore, hepcidin acts as the key regulator of the total body iron, by modulating intestinal iron absorption, as well as iron availability for erythropoiesis by affecting the efficiency of macrophages mediated iron recycle[11].

Different studies have demonstrated that hepcidin is an useful tool for the diagnosis and clinical management of several iron related disorders[62-64] but only few studies have investigated hepcidin in healthy subjects. In particular, studies in athletes, are limited in number and mainly carried out in analyzing the variations of urinary hepcidin concentrations only in relation to physical efforts[64-69]. In this setting, we have suggested that hepcidin assessment may represent an alternative method to define the real necessity of iron supplementation in specific conditions. We have also confirmed that SF below 30 μg/L indicates an asymptomatic iron deficiency condition inhibiting hepcidin expression. Conversely, SF above 30 μg/L indicates adequate iron stores inducing the up-regulation of hepcidin to prevent unnecessary iron absorption.

The immediate clinical consequence of these findings relies in the observation that an iron

supplementation would be useful when administered to athletes with SF below 30 μg/L in whom hepcidin levels are low to promote iron absorption. On the contrary, it would be not indicated in athletes with SF exceeding 30 μg/L in which hepcidin levels are consistent with sufficient body iron.

CONCLUSIONS

At present, iron supplementation is frequently referred from trained athletes (up to 30% in epidemiological studies); the majority of whom justifies this practice with a possible ergogenic effect, without taking into consideration neither the recommended dosages nor the possible side effects deriving from an inappropriate supplementation[70].

Recent studies have permitted to define a specific and sex-independent ferritin cut-off below which an oral iron supplementation is useful and advantageous and above which this practice would not be advisable because useless and potentially hazardous to the athlete's health. In fact it is becoming scientifically clear that conditions characterized by a reduced transfer of dietary iron from duodenal enterocytes to plasma rises intracellular iron concentration. An oral iron supplementation in these subjects would be not only unnecessary but also potentially disadvantageous because of the likely side effects deriving from the increased intracellular iron concentration in the gastro-intestinal tract including discomfort, nausea, vomiting, diarrhea, or constipation[71]. Such side effects gain even more importance in athletes because of the negative consequences on training capacity and performances that they imply. With this regard, the use of iron supplements must be a cautious choice based not on the likelihood of anemia but, ideally, on hematologic evaluation. Additionally, it has to be underlined that the use of complex preparations may provide less iron than anticipated and warrant a careful re-examination with regard to the efficacy[72]. Supplementation is not without consequence, however; the use of high doses of supplemental iron is often associated with gastrointestinal distress and constipation and a subsequent decline in patient compliance and performances. Moreover, in subjects who are genetically predisposed to iron imbalance, hemochromatosis may develop after iron supplementation. Iron toxicity may develop even in subjects who are not genetically predisposed to iron deficiency who ingest doses of $\geq$75 mg supplemental Fe. Other data illustrate the potential oxidative damage that may result from "free iron" released during exercise[56]. Thus, personalized doses of supplemental iron are recommended to avoid possible accumulation of an iron burden[73]. A scientifically based approach and the eventual study of new parameters should always guide clinicians to define the real necessity of iron supplementation. This approach may reduce possible contraindications and side effects linked to improper iron supplementation. In fact, an incorrect supplementation may negatively affect the performance, rather than improve it.

SUMMARY

While the recommendation to pay particular attention in maintaining an adequate consumption iron would be always advisable in a dietary strategy, the use of iron supplements should be a cautious choice based on a careful hematological evaluation, mainly because of the possible health risks deriving from an unjustified treatment. With particular regard to the sport related supplementation, currently no standardized guidelines for iron administration are available and the decision if administrating or not oral iron in athletes is mainly based on empiric recommendations or on performance enhancing hopes. Recent studies have permitted to define a specific and sex-independent ferritin cut-off below which an oral iron supplementation is useful and advantageous and above which this practice would not be advisable because useless and potentially hazardous for the athlete's health. In fact, it is becoming scientifically clear that conditions characterized by a reduced transfer of dietary iron from duodenal enterocytes to plasma rises intracellular iron concentration. An oral iron supplementation in these conditions would be not only unnecessary

but also potentially disadvantageous because of the likely side effects deriving from the increased intracellular iron concentration in the gastro-intestinal tract including discomfort, nausea, vomiting, diarrhea, or constipation. Such side effects gain even more importance in athletes because of the negative consequences on training capacity and performances that they imply. A scientifically based approach and a possible study of new parameters should always guide clinicians to define the real necessity of iron supplementation. This approach may reduce possible contraindications and side effects linked to improper iron supplementation. In fact, an incorrect supplementation may negatively affect the performance, rather than improve it.

Key words: Iron. Supplementation. Physical activity. Side effects. Sport.

RESUMEN

Mientras que la recomendación de prestar una especial atención para mantener un consumo adecuado de hierro siempre es una estrategia dietética aconsejable, el empleo de suplementos de hierro debería ser una opción cautelosa basada en una cuidadosa evaluación hematológica, principalmente por los posibles peligros para la salud que provienen de un tratamiento injustificado.

Respecto a la suplementación en el deporte, actualmente no existe ninguna directriz estandarizada para la administración de hierro y la decisión sobre administrar o no hierro oral en deportistas se basa principalmente en recomendaciones empíricas o en la esperanza de mejorar el rendimiento.

Estudios recientes han permitido definir un nivel de ferritina, independiente del sexo, en el que una suplementación oral de hierro es útil y ventajosa y por encima de la cual esta práctica no sería aconsejable por no ser útil y ser potencialmente peligrosa para la salud del deportista. De hecho, se ha clarificado científicamente que algunas situaciones que se caracterizan por una transferencia reducida de hierro de los enterocitos duodenales al plasma aumenta la concentración intracelular de hierro.

En estas condiciones, la suplementación oral de hierro no sólo sería innecesaria, sino también potencialmente contraproducente debido a los posibles efectos secundarios en el tracto gastro-intestinal derivados del aumento de la concentración intracelular de hierro como malestar, náuseas, vómitos, diarrea, o estreñimiento. Tales efectos secundarios adquieren aún más importancia en los deportistas debido a las consecuencias negativas sobre la capacidad de entrenamiento y de rendimiento que pueden producir.

Un abordaje científico y un posible estudio de nuevos parámetros podrían guiar a los clínicos hacia la definición de la verdadera necesidad de suplementación con hierro. Este abordaje reduciría las posibles contraindicaciones y efectos secundarios relacionados con una inapropiada suplementación de hierro. De hecho, una suplementación incorrecta podría afectar negativamente el rendimiento, antes que mejorarlo.

Palabras clave: Hierro. Suplementación. Actividad física. Efectos secundarios. Deporte.

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