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Effects of Exercise on Iron Transfer in the Body

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ABSTRACT

Although iron is found in trace amounts in the body, it plays an important role in oxygen transport and energy metabolism. Iron is therefore very important for athletes with high oxygen requirements, especially endurance athletes. Despite its importance, many athletes are diagnosed with iron deficiency. The relationship between iron regulation and exercise has been a focus of research, as it has been suggested that athletic performance is related to iron regulation. In particular, the discovery of hepcidin, an iron-regulating hormone synthesised in the liver, has received much attention. Hepcidin is known to inhibit iron absorption from the intestinal tract and promote iron excretion, and is closely related to iron nutritional status in vivo. In addition, the inflammatory cytokine interleukin-6 (IL-6) has been found to be an inducer of hepcidin expression. Much research has been conducted on the effects of training and diet (nutrients) on iron status in athletes. However, the detailed mechanisms of exercise-induced iron deficiency in athletes remain unclear. This paper summaries the less commonly reported effects of exercise on iron movement and diet on iron status.

In particular, we will focus on the impact of exercise on iron levels in the body, and the impact of meal timing and composition on iron levels.

Keywords: Athlete, Exercise, Iron deficiency, Sports nutrition

Introduction

Iron deficiency is one of the most common nutritional problems worldwide. It is defined as insufficient iron reaching the body's stores or various tissues. Biological iron metabolism is a semi-closed circuit whose basic functions are the absorption, storage, and reuse of iron. However, depending on the imbalance between iron intake, storage and requirements, deficiencies can develop either rapidly or very slowly. This may be due to inadequate iron intake, certain diseases or, in women, menstrual bleeding. The rate at which iron deficiency develops in individual tissues and intracellular organelles also depends on iron recycling within cells and the metabolic turnover rate of iron-containing proteins.

Iron plays a role in many metabolic processes, including electron transfer in mitochondria, neurotransmitter and protein synthesis, and organ formation. Therefore, when iron is depleted in vivo, many biological functions, such as immune function, sympathetic nerve function, endocrine metabolism and thermoregulation, are impaired[1-4]. Additionally, iron deficiency significantly reduces the content of iron-sulphur and cytochromes in mitochondria, as well as total oxidative capacity. Furthermore, iron deficiency restricts hematopoiesis in hematopoietic tissues, resulting in decreased hemoglobin concentration and iron deficiency anemia. Decreased hemoglobin concentration significantly reduces physical work capacity by decreasing the supply of oxygen to exercising muscles. In other words, iron deficiency reduces exercise capacity due to decreased oxygen-carrying and diffusion capacities in athletic tissues, as well as decreased muscle oxidative capacity[5].

In a recent human study, women with low serum ferritin and iron deficiency, but normal hemoglobin concentrations, were asked to take iron supplements or a placebo alongside four weeks of aerobic exercise for six weeks. The placebo group showed a decrease in serum ferritin and transferrin saturation, while the iron supplement group showed an increase. Both groups showed improvement in VO_2 max, but the iron supplement group showed greater improvement. These results suggest that tissue iron sufficiency, as well as hemoglobin, is important for increasing maximum oxygen uptake. Many studies have investigated the effects of exercise and nutrition on iron status, and it is well established that exercise itself can alter this. Recently, it has been reported to be associated with the development of symptoms of apathy and negative mood disorders[6,7]. However, the detailed mechanisms of exercise-induced iron deficiency in athletes remain unclear. In this paper, we discuss the impact of exercise on iron levels in the body, as well as the influence of meal timing and composition on iron levels.

Regulators of iron in the body

Many studies have been conducted on the effects of training and nutrition (nutrients) on athletes. In particular, hepcidin, an iron-regulating hormone synthesized in the liver, has attracted considerable attention. Hepcidin plays an important role in iron homeostasis[8,9]. Hepcidin, a peptide hormone, is secreted by hepatocytes[10]. The main iron flux of hepcidin is shown in Figure 1[11].

(1) HEPCIDIN EXPRESSION

Pigeon et al. found that iron overload causes hepcidin overexpression, suggesting that hepcidin has roles other than antibacterial properties. Hepcidin plays an important role in iron metabolism in the body. The basolateral membrane contains an iron transporter called ferroportin, which removes iron from the cells. Hepcidin regulates iron levels by binding to ferroportin. In other words, hepcidin produced in the liver binds to ferroportin, and moves from the cell membrane to inside the cell, where it is degraded in lysosomes. When iron is not needed, hepcidin levels increase, leading to a decrease in ferroportin and suppression of iron transport. Conversely, when iron is needed, hepcidin expression decreases, allowing ferroportin to promote iron transport. Under normal conditions, blood iron levels are regulated. However, when excess iron is administered or during inflammation, hepcidin is overproduced, leading to a state of

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functional iron deficiency where stored iron cannot be utilized. Measuring blood hepcidin concentration is important for determining whether iron metabolism is normal[12].

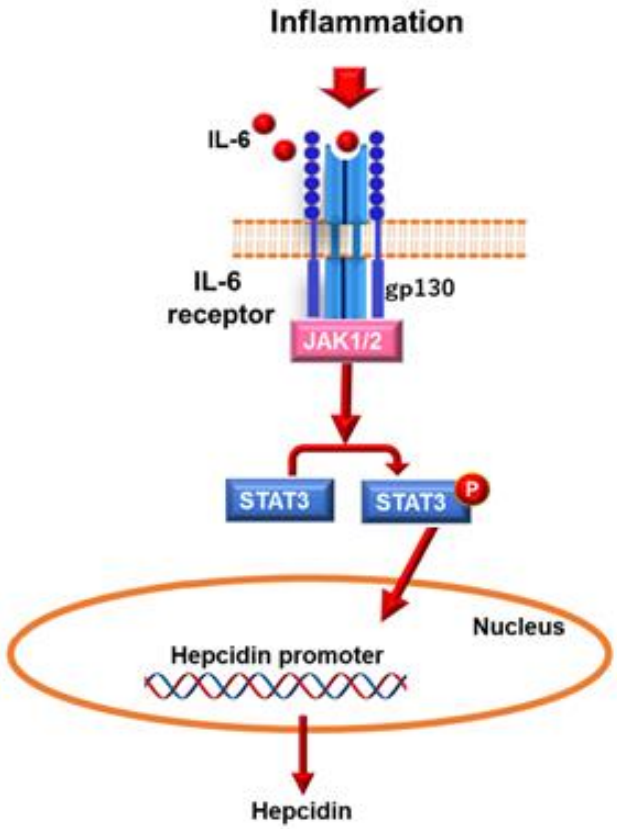

Figure 1: Regulation of hepcidin expression. In the inflammatory pathway, IL-6, which is produced during inflammation, binds to the IL-6 receptor and gp130. This activates JAK1/2. This process results in the phosphorylation of STAT3, which then translocates into the nucleus and binds to the hepcidin promoter, thereby activating transcription[11].

(2) HEPCIDIN EXPRESSION DRIVEN BY IL-6

Inflammation increases hepcidin synthesis. IL-6 is required for hepcidin induction during inflammation, and the cytokine itself can rapidly induce iron-deficiency anemia[13]. The signal transduction and activator of transcription 3 (STAT-3) and BMP/SMAD pathways induced by IL-6 have been identified. For example, SMAD binding sites on the hepcidin promoter have been reported to be important for IL-6-mediated hepcidin expression[14], and hepcidin is less responsive to IL-6 in liver-specific Smad4 gene knockout mice[15]. Another important transcription factor that has been reported to control ferritin expression is CCAAT enhancer-binding protein alpha (C/EBPα). The hepcidin promoter contains binding sites for STAT-3 and C/EBPα, allowing these two signaling pathways to interact.

Exercise and iron

(1) IRON AND NUTRIENTS

Recently, the impact of carbohydrate and energy intake on the hepcidin response in athletes has been investigated[16]. Decreased muscle glycogen content has been shown to increase exercise-induced IL-6[17]. McKay et al. found that both low energy availability (LEA) and low carbohydrate intake increased the hepcidin response. They also noted that acute and long-term carbohydrate restriction had different effects on the hepcidin response and iron status[18]. Moreover, they concluded that while acute effects may influence the hepcidin response, the long-term approach is highly dependent on the athlete's initial iron intake and not on their long-term carbohydrate intake. While the ferritin study results

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may be recent, the importance of the carbohydrate intake for muscle protein synthesis has been known for some time. As early as 1986, Henderson et al. reported an increased utilization of glucose as an energy source in iron-deficient rats[19]. More research on this topic is needed[20].

In recent years, in addition to iron deficiency anemia, the relative energy deficit in sport (RED-S) has become a concern[21]. RED-S occurs in both males and females, resulting in decreased endurance, increased risk of injury, and decreased glycogen stores. Low energy availability (LEA) is commonly observed during daily training in endurance athletes[22] and may increase the risk of iron deficiency[23]. It has also been suggested that severe energy deprivation may worsen hepcidin levels, even in the absence of inflammation[24]. Therefore, it can be said that nutritional deficiencies may indirectly affect iron status via increased hepcidin activity.

Decreased energy intake (EI) and/or increased exercise energy expenditure (EEE) have been reported to cause LEA, which in turn has been linked to a number of undesirable conditions. These include decreased resting energy expenditure and disruption of various hormonal, metabolic and functional properties[25]. However, the effects of LEA during endurance exercise on iron metabolism, particularly hepcidin levels, during endurance exercise, remain unknown.

Several studies have examined total energy intake in athletes and have associated LEA with an increased hepcidin response[26]. Hennigar et al. found that athletes experiencing energy deprivation had an increased hepcidin response after exercise in comparison to those with normal energy intake, resulting in reduced iron absorption[26]. Barney et al. observed that in runners with low iron stores, prolonged running increased hepcidin levels and decreased dietary iron absorption in comparison to resting[27]. This suggests that maintaining an adequate energy balance may prevent the exercise-induced increase in hepcidin response and decrease dietary iron absorption[28].

These findings suggest that, if appropriate for iron-deficient athletes, providing adequate energy and carbohydrates to meet training demands may be an important for optimizing an athlete's dietary iron status through diet.

(2) EXERCISE MOBILISES IRON

Gagne et al. observed a significant decrease in bone marrow iron in exercised rats in comparison to resting groups when they performed aerobic exercise (swimming), suggesting that the decrease in bone marrow iron is due to increased iron turnover, including the release of iron from cells and the rate of hemoglobin production[29]. Qian et al. reported that in animals that underwent intense exercise (swimming exercise), erythrocyte iron uptake in the bone marrow and hemoglobin synthesis increased, but tissue iron levels in the liver, spleen, kidney, and heart decreased[30]. The decrease in tissue iron levels has also been attributed to increased iron uptake into bone marrow cells for hemoglobin synthesis, suggesting that exercise may cause iron transfer from storage sites to bone marrow cells and promote hemoglobin synthesis[31,32]. In other words, hemoglobin, which is responsible for the transport of life-sustaining oxygen, is prioritized over the maintenance of tissue iron.

It has been observed that blood hemoglobin concentration is improved and maintained in resistance-trained rats without a decrease in tissue iron concentration in comparison to resting rats[33]. No significant differences in blood iron index or whole-body iron concentration were observed between the resistance exercise and resting rat groups. Furthermore, resistance exercise was observed to increase iron excretion in comparison to resting rats (Figure 2)[34]. Therefore, different types of exercise may have different effects on iron nutritional status.

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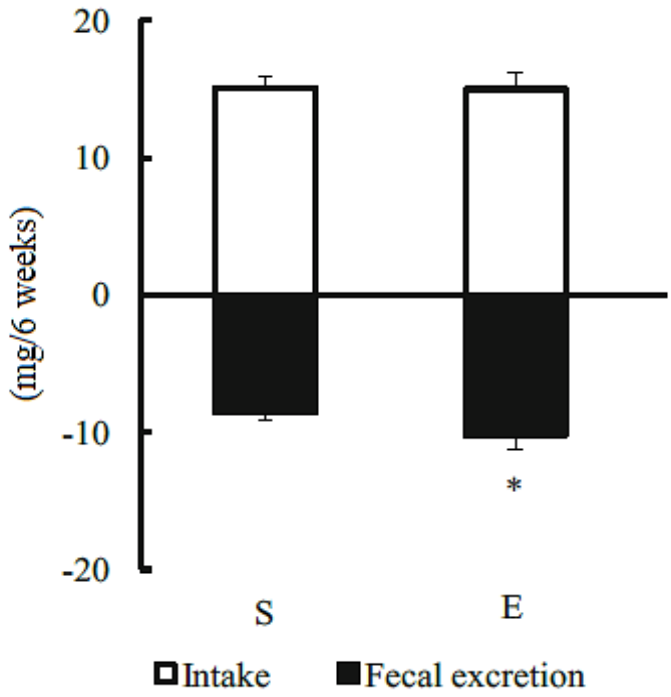

Figure 2. The dietary iron balance. The values are the means±SD for seven rats. *p<0.05, significantly different from the S group (Student's t test)

(3) INFLUENCE OF EXERCISE AND DIET TIMING ON IRON STATUS IN THE BODY

Fujii et al. investigated how meal timing affects the impact of resistance exercise on improving iron nutritional status in iron-deficient rats[35]. Rats were subjected to resistance exercise and maintained for 3 weeks in two groups: one group received a meal immediately after exercise; the other received a meal 4 h after exercise. The results showed an immediate increase in plasma iron after exercise, with no increase due to food intake. However, both plasma iron levels and bone marrow ALAD activity increased after exercise. Reports indicate that anemic subjected to resistance exercise show a significant increase in hemoglobin concentration in comparison to resting rats[36]. Plasma iron is reported to be used for hemoglobin synthesis[37]. The concurrent increase in bone marrow ALAD activity and plasma iron levels suggest that resistance exercise promotes hemoglobin synthesis and increases hemoglobin concentration[33,34].

McCormick et al. found that despite increased hepcidin concentrations after exercise, more iron is absorbed when a meal is eaten after morning exercise than when fasting at rest or from an evening meal[38]. While the physiological mechanisms promoting iron absorption after exercise remain unclear, this study suggests that overall iron absorption is influenced by cumulative responses to inflammation and hepcidin, in addition to transient physiological changes after exercise. Thus, they recommend that exercisers take or supplement iron immediately after morning exercise to enhance iron absorption. This recommendation is based on the fact that hepcidin levels increase 3 hours after exercise, regardless of whether it is performed in the morning or afternoon[39].

Conclusion

In this paper, we present evidence of the impact of exercise and diet on biological iron. Exercise induces an inflammatory response. The iron status of athletes should be monitored regularly throughout their training. It should be noted that exercise promotes iron excretion regardless of the type of training. Early detection of a decrease in biological iron stores may help maintain and improve athletic performance. However, further research is needed to reduce the burden of iron deficiency in athletes.

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The authors contributed equally to this work.

Disclosure statement:

No potential conflicts of interest were disclosed.

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