

Exercise, magnesium and immune function

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Abstract. Physical exercise may deplete magnesium, which together with a marginal dietary magnesium intake may impair energy metabolism, muscle function, oxygen uptake and electrolyte balance. Consequently, the ability to perform physical work may be compromised. Many aspects of immune function can be depressed temporarily by either a single bout of very severe exercise or a longer period of excessive training. Although the disturbance is usually quite transient, it can be sufficient to allow a clinical episode of infection, particularly upper respiratory tract infections. However, regular and moderate exercise has been reported to improve the ability of the immune system to protect the host from infection. Magnesium also has a strong relation with the immune system in both non specific and specific immune responses and magnesium deficit has been shown to be related to impaired cellular and humoral immune function. Magnesium deficiency leads to immunopathological changes that are related to the initiation of a sequential inflammatory response. Although in athletes magnesium deficiency has not been investigated regarding alterations in the immune system, the possibility exists that magnesium deficiency could contribute to the immunological changes observed after strenuous exercise.

Key words: magnesium, exercise, immunity, inflammation

Magnesium and exercise

Magnesium is a deficit frequently found in the industrialised countries. Several studies have reported that athletes may be deficient in magnesium [1, 2]. The studies of Klepping and co-workers [3] showed that the food intake of both athletes and sedentary subjects is very similar, apart from significant energy values in the intake of athletes. Adequate magnesium levels are required in order to sustain an appropriate performance level, because of its key role in the use of energy rich compounds, in muscular contraction and in the maintenance of the membrane properties [4].

During exercise, compartmental shifts of magnesium have been observed, but data to demonstrate magnesium variations induced by exercise are inconsistent. Partially, such heterogeneity can be attrib-

uted to differences in experimental designs and work intensity and duration. Moreover, the timing of blood sample and the different analytical protocols have to be taken into account [5].

With respect to blood extracellular magnesium, various authors have indicated that high intensity exercise leads to hypermagnesemia as a consequence of the decrease in plasma volume [6-9]. These changes may depend on the relative contribution of anaerobic metabolism to the total energy expended during exercise [10]. On the other hand, submaximal exercise has been reported to be accompanied by hypomagnesemia [9, 11-16]. Prolonged strenuous exercise, especially under hot conditions, may lead to hypomagnesemia [11, 17-20]. Low plasma magnesium levels have been explained by several mechanisms: redistribution of magnesium to red blood cells, adipocytes or myocytes [21]; loss in urine due to increases in aldosterone, antidiuretic hormone, thyroid hormone and acidosis that reduce the tubular reabsorption of magnesium [10] or increased lipoly-

Presented in part at the European Meeting on Magnesium, EuroMag, Paris, May 15-17, 2008.

sis due to raises in catecholamines levels induced by exercise [22-24]. Hyperexcretion in sweat only acquires real importance in the case of intense activity undertaken in conditions of a damp atmosphere and high temperature [25].

A transient shift of magnesium to the intracellular space during exercise is a probable explanation for a large proportion of the hypomagnesaemia. However, regarding magnesium variations with exercise in red blood cells (RBC), dissimilar findings are reported. The magnesium levels in RBC were reported to be increased after several exercises [1, 6, 10, 26] and were related to the increased metabolic activity during exercise, which would induce a shift of the cation from the plasmatic compartment. Conversely, the magnesium levels of RBC were reported to be decreased [15, 27-29]. Golf and co-workers [29] postulated that as the exercise duration increases, magnesium would shift from the erythrocyte reservoir into the plasma and then into the working muscles. An increased ionised magnesium (Mg^{2+}) efflux may be involved in the reduction of total magnesium content of erythrocyte particularly in magnesium deficient conditions [30]. With prolonged exercise (more than one hour) hypomagnesaemia may occur as a result of the depletion of the erythrocyte reservoir. Several studies suggest that low magnesium levels in red blood cells may persist during a season of training [31-33].

Ionised magnesium concentration is supposed to be a more sensitive parameter than total magnesium and so it should give more reliable information about the status and regulation of major, mobilizable magnesium pools in the body. However, only limited information about the effects of exercise on the metabolically and regulatory fraction of Mg^{2+} is available [34]. Recently, Mooren and co-workers [35] showed that, at the end of a treadmill ergometer test, both total blood and serum Mg^{2+} and serum total magnesium decreased. In contrast, in both thrombocytes and erythrocytes Mg^{2+} increased but total magnesium was unchanged, making a Mg^{2+} shift between the intra and extracellular blood compartment unlikely. This study also showed opposite changes of the ratio $[Mg^{2+}]/[total\ Mg]$ in the intracellular and the extracellular compartment after anaerobic exercise. In *in vitro* experiments, similar changes of Mg^{2+} in the two blood compartments could be mimicked by application of weak acids like lactic and propionic acid. These authors concluded that changes in the fraction of Mg^{2+} should be enough to influence intracellular signalling and metabolic processes.

Although some explanations have been offered for the compartmental shifts of magnesium, the precise

mechanism remains to be clarified. It is important to evaluate whether there is only a transient fall in plasma magnesium concentration, or if the participation in sustained exercise may induce permanent alterations. Several studies indicate that there is a sustained fall in plasma magnesium after strenuous exercise and that hypomagnesaemia persists during a season of training [32, 33, 36-38].

So, exercise may increase the demand for magnesium and/or increase magnesium loss, potentially leading to magnesium deficit, which can result in muscle weakness, and neuromuscular dysfunction [17, 39].

Reports on magnesium supplementation are difficult to analyse. Frequently the magnesium status of the subjects prior to supplementation is not reported. So, supplementation with magnesium has been reported to increase muscle strength and power [40], and haemoglobin levels [41]. Conversely, marathon runners with adequate magnesium status exhibited no improvement in running performance or skeletal muscle function and no increase in muscle magnesium concentrations [42]. In spite of the discordant results, the findings suggest that magnesium supplementation *per se* does not illicit beneficial effect on physiological function or performance when magnesium status is normal [43].

Immune function related to exercise: possible roles of magnesium

Exercise, both high-intensity and prolonged, is a stress to the body that is proportional to the intensity and duration of the exercise, relative to the maximal capacity of the athlete. Exercise stress leads to a proportional increase in stress hormone levels like cortisol and catecholamines and concomitant changes in several aspects of immunity [44].

Many aspects of the immune function can be depressed temporarily by either a single bout of very severe exercise or a longer period of excessive training. Immuno-suppression has been attributed to decreased helper/suppressor T cells ratio and natural killer cell activity and elevated stress hormones [44, 45]. Although the disturbance is usually quite transient, it can be sufficient to allow a clinical episode of infection, particularly upper respiratory tract infections [46, 47]. However, regular and moderate exercise has been reported to improve the ability of the immune system to protect the host from infection [48, 49]. Resting levels of Natural Killer (NK) cells are enhanced as a result of training [50]. Leucocyte number is clinically normal and remains unchanged with training [48].

So, the response of the immune system to exercise is varied, with different behaviours for each cell type and dependent on the intensity and duration of the exercise test and on the training of the subject. Besides these factors, nutritional deficiencies alter immunocompetence and increase the risk of infection. Both heavy exercise and nutrition exert separate influences on immune function, appearing to be greater when acting synergistically [51]. Exercise training increases the body requirement for most nutrients. However some athletes adopt an unbalanced dietary regimen predisposing them to immunosuppression [51]. Several elements are known to exert modulatory effects on immune function including zinc, iron, selenium, calcium, copper and magnesium [44, 47, 52-56].

Several groups leading investigation in Nutrition and Immunology have shown evidence that magnesium plays a key role in the immune response: cofactor for immunoglobulin synthesis, C'3 convertase, immune cell adherence, antibody-dependent cytotoxicity, IgM lymphocyte binding, macrophage response to lymphokines, T helper-B cell adherence, binding of substance P to lymphoblasts and antigen binding to macrophage RNA [57-59]. Most of these studies have been designed in animal models, focussing on what happens in magnesium depleted animals.

The reason for assuming an association between magnesium and immune function was based on findings that magnesium deficiency leads to increased inflammation [60-63]. The appearance of clinical signs of inflammation is one of the early symptoms of magnesium deficiency in the rat. The activation of immune cells, such as monocytes, macrophages and polymorphonuclear neutrophils, that synthesise a variety of biological substances, some of which are powerful inducers of inflammatory events (cytokines, free radicals, eicosanoids), was also reported. High levels of circulating cytokines such as IL-6 could be detected early after initiating the magnesium deficient diet, leading to the release of the acute phase proteins by the liver.

Studies conducted in human populations are less extended than those using animal models. Bussi re and co-workers [64] observed *in vitro* that high magnesium concentrations of the medium decrease human leukocyte activation and suggested that extracellular magnesium can diminish leukocyte activation by its calcium antagonism, as magnesium counteracts calcium in many physiological and pathological processes. Inverse correlations between magnesium intake and C reactive protein plasma levels have also been observed [65-67].

Mooren *et al.* [68] observed that, after a two month period of magnesium supplementation, an exercise test till exhaustion induced an activation of the immune system as indicated by an increase in granulocyte count and a post-exercise lymphopenia. However, magnesium supplementation seems to have been unable to prevent any exercise-associated alterations in immune cell function in athletes with balanced magnesium status.

The similarities between exercise-induced alterations in immune function and the changes in immunity caused by the deficiency in magnesium are noteworthy. Prolonged, exhaustive exercise has been shown to be associated with temporary immunosuppression as well as to considerable magnesium decreases. Additionally, there is evidence that immunoregulation during and after intense physical exercise is influenced by transient or manifest deficiencies in magnesium. Therefore, although considerably more work needs to be done in this area, magnesium deficiency may amplify the decreased immune response induced by strenuous exercise.

Acknowledgments

The authors would like to thank Maria de F tima Raposo for her proficient technical assistance.

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