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Magnesium Influence on Stress and Immune Function in Exercise

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Magnesium (Mg) may enhance physical activity through a number of associated mechanisms: all phosphotransfers, a cofactor to over 325 enzymatic reactions, protein synthesis, and electrolyte balance [1,2]. About 60% of adults in the United States do not consume the estimated average requirement of Mg, yet widespread pathological conditions attributed to Mg deficiency have not been reported [3]. That a significant Mg deficiency has not been recognized may be attributed to only 1% of Mg is in the serum, therefore, a lack of sensitivity of serum Mg. Low dietary intakes, coupled with exercise-induced urinary losses, may eventually lead to an Mg deficiency. A deficiency of the mineral therefore has many physiological and exercise performance implications.

Further, clinical studies have described Mg influence on immune function and inflammation; with low magnesium stimulating immunopathological changes that are related to the initiation of a sequential inflammatory response. Low serum and dietary magnesium levels are strongly correlated with low grade systemic inflammation [5-8]. Experimental Mg deficiency produces a clinical inflammatory syndrome with leukocyte and macrophage activation, inflammatory cytokines released, and excessive production of free radicals. Results from animal studies have been corroborated in human responses, with Mg deficiency upregulating markers of inflammation and oxidative stress [5,9]. Mg deficiency elicits a systemic pro-inflammatory/pro-oxidant state, involving multiple tissues/organs.

Hypomagnesemia promotes low-grade inflammation as demonstrated by elevated concentrations of C-Reactive Protein (CRP) and TNF-α [10,11]. Low Mg is independently associated with elevated hsCRP levels [11,12]. Subjects who consume less than 75% of RDA were 1.94 times more likely to have elevated serum CRP levels than consuming above the RDA [13] and, in another study, the number of subjects with CRP > 3 mg·L^{-1} significantly decreased from the lowest to the highest tertile of dietary Mg [14]. Adults who consumed less than the Mg RDA were 1.48-1.75 times more likely to have elevated CRP than adults who consumed more than the RDA [7]. Additionally, low Mg induces increases in circulating substance P that stimulates systemic inflammatory stress [15,16].

There are various mechanisms that may explain the role of Mg in modulating immune function. Mg potentiates iron–transferrin binding, an important contribution to offsetting oxidative stress [17]. Mg reduces oxidative stress through stabilization of DNA. [18]. However, Mg acts as a natural calcium antagonist and the molecular basis for the inflammatory response is most likely strongly linked to the modulation of the intracellular calcium concentration [19]. Potential mechanisms include priming of phagocytic cells, opening of calcium channels, activation of N-Methyl-D-Aspartate (NMDA) receptors, and activation of the renin-angiotensin system [20]. Mg deficiency induces a systemic stress response through activation of the neuroendocrine axis. Mg has a strong influence on both nonspecific and specific immune responses, and research shows it is related to inadequate cellular and humoral immune responses. The mechanism is postulated to be the role of Mg deficiency that leads to the initiation of a sequential inflammatory response. Further studies are still needed to better elicit the role of Mg in human immune responses.

The specific mechanisms of the inflammatory response in Mg deficiency have not been elucidated. However, Mg deficiency results in a stress effect and increased susceptibility to physiological damage produced by stress. Stress activates the sympathetic nervous system and renin-angiotensin-aldosterone axis resulting in increased oxidative stress. Aldosteronism is immunostimulatory, as is commonly seen in congestive heart failure . The inflammatory syndrome induces mechanisms dependent on cytosolic calcium activation. These interrelationships support that the Mg effect on intracellular calcium homeostasis may be a common link between stress and inflammation [21].

Stressors include exercise; especially extreme physical activity of any type which may have implications for the immune system. Physical exercise may deplete Mg, which together with a marginal dietary Mg intake may impair immune function [4]. Strenuous exercise induces immunodepression that is multifactorial in origin. Aspects of immune function can be depressed temporarily by either a single bout of very severe exercise or a longer period of excessive training. Depressed immunity may allow an episode of infection, particularly upper respiratory tract infections. Thus, the ability to perform physical work may be compromised.

Strenuous exercise induces pyrogenesis and suppresses cellular immunity leading to increased susceptibility to infections [22]. A common view is that Upper Respiratory Tract Infections (URTI) are increased in elite endurance athletes after single bouts of endurance exercise and during intensive training. The evidence is inconclusive, although exercise does alter the number and function of circulating innate immune cells [23]. Lymphocytosis is observed during and immediately after exercise, proportional to exercise intensity and duration, before returning to resting values normally within 24 h. Mobilization of T and B cell subsets is largely influenced by catecholamines. This apparent depression in acquired immunity appears to be related to exercise-induced elevated stress hormones. Salivary IgA underlying the alterations in mucosal immunity with acute exercise are probably under control of the sympathetic nervous system. There are numerous examples where exercise alters measures of immunity by 15-25% [23].

As with Mg studies, inflammatory markers escalate with strenuous exercise. CRP and TNFα increased significantly during the two weeks of exercise [24]. Four days of increased training load reduced running performance and altered the inflammatory response to high-intensity intermittent exercise [25]. CRP is higher is contact sport than noncontact [26] and in exercising females compared to males [27]. Differences in the immune responses to exercise between healthy and illness-prone athletes may explain the greater incidence of URTI. The relationship between resting CRP concentrations and the peak pro and

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anti-inflammatory responses to exercise supports involvement of CRP in the complex network regulating exercise-induced inflammatory disturbances [28]. Excessive cytokine release related to overtraining [29] may upset the balance between modulation of repair and development of inflammation and possible infections.

Other inflammatory markers are influenced by exercise, as well. Sprint intervals significantly increase inflammatory mediators, specifically IL-1 and IL-6 [30]. Endurance exercise lasting more than 12 hours showed that intensity, and not duration, is the main determinant of the IL-6 response [31]. Intense exercise game activity showed increases in serum cortisol and IL-6 and decreases in circulating T lymphocytes and natural killer cells, immediately post and 14 h after exercise until levels were restored [32].

Managing training to preserve immune health requires low to moderate volume and intensity [23] with gradual periodized increases in training volumes and intensity. Variety may limit stress; avoid excessively heavy training loads that could lead to exhaustion, illness or injury. Sufficient rest and recovery are essential and identification of performance deterioration and physical stress may ameliorate extreme immune changes. An appropriate exercise program may avoid high catecholamine levels [18,33] and lessen Mg perturbations. It is also recommended to give attention to nutritional countermeasures to exercise-induced immune perturbations [34]. In general, undernourishment is associated with impaired immunity and should be addressed.

Mg improves markers of inflammation and oxidative stress, but supplementation studies have yielded inconsistent results [14]. It appears that an optimal magnesium intake may also be essential for antioxidant protection and for regulation of related responses, although more research is needed to describe the underlying mechanisms and to identify sufficient magnesium for performance [35,36]. Recently, it was shown that dietary magnesium is correlated with strength and power outcome measures [37]. In a study that excluded subjects who used supplements but controlled for chronic infection or inflammatory disease, a decline of serum magnesium with concomitant increases in the inflammatory marker, IL-6, were noted after running a marathon compared to baseline [38]. The baseline Mg status is implicated in whether the athlete will respond to supplementation; but, Mg status is difficult to obtain easily as the plasma levels are intransigent except for profound deficiency [1]. If Mg levels were so low to elicit defined plasma Mg deficiency, there would be severe compromise of physical performance. Very few studies have been conducted on this topic of Mg, exercise, and immune function combination, to date. However, nascent evidence has been published recently that low dietary Mg is linked with increased immuno-inflammatory markers and associated with oxidative stress, as is intense exercise. Together with the similarities in outcomes of low Mg status and strenuous exercise, it is an area that warrants further inspection. Mg deficiency in athletes has not been robustly investigated regarding alterations in the immune system. The possibility exists that magnesium deficiency could contribute to the immunological changes observed after strenuous exercise [4].

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