

apunts

MEDICINA DE L'ESPORT

www.apunts.org



SPECIAL ARTICLE

Immunomodulators for inflammation and muscle injury due to exercise

Alfredo Córdova

Escuela de Fisioterapia, Departamento de Bioquímica, Biología Molecular y Fisiología, Campus Universitario, Soria, Spain

Received on May 17, 2010; accepted on June 10, 2010

KEYWORDS

Ergogenic aids;
Exercise;
Delayed onset of
muscular soreness;
Immunomodulators;
Glutamine

Abstract

Ergogenic (pharmacological and nutritional) aids in sport, such as immunomodulators would be useful for reducing the harmful effects of muscle injury and inflammation, as well as in states of fatigue. These aids, on accelerating the recovery process, could be important for improving performance by preventing damaging responses to exhausting exercise and modulating the homeostatic adaptation processes which lead to recovery and remodelling. With the use of these aids, the increase in training load that could be tolerated by athletes, which would also be very beneficial for their performance, is also an important aspect to consider, as well as mechanisms to preserve the health of the athlete.

Finally, remember that these extra requirements should be evaluated and recommended by a suitable professional.

© 2010 Consell Català de l'Esport. Generalitat de Catalunya. Published by Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE

Ayudas ergogénicas;
Ejercicio;
Daño muscular
acumulado;
Inmunomoduladores;
Glutamina

Los inmunomoduladores frente a la inflamación y daño muscular originados por el ejercicio

Resumen

La utilización de ayudas ergogénicas (farmacológicas y nutricionales) en el deporte, como los inmunomoduladores, está indicada para reducir los efectos nocivos del daño muscular y la inflamación producidos por el ejercicio intenso, acompañados de un estado de fatiga. Estas ayudas, al acelerar el proceso de recuperación, son importantes para mejorar el rendimiento mediante la prevención de las respuestas perjudiciales frente a ejercicio extenuante modulando los procesos homeostáticos de adaptación que conducen a la recuperación y remodelación muscular. Con el uso de estas ayudas, se produciría un aumento de la carga de entrenamiento que podría ser tolerado por los deportistas. Esto, además de ser beneficioso para su rendimiento competitivo, también es un elemento

importante a considerar como mecanismos para preservar la salud del deportista. Por último recordar que estos requerimientos extras deberán ser evaluados y recomendados por un profesional idóneo.

© 2010 Consell Català de l'Esport. Generalitat de Catalunya. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

Exercise-induced muscle damage and its clinical corollary (delayed onset on muscular soreness, DOMS) often occur due to the predominance of eccentric exercise. The injury itself is a mechanical disturbance of the sarcomeres provoked by an inflammatory response¹⁻⁶. PGE2 is the direct cause of the pain, whereas leukotrienes increase the vascular permeability and attract neutrophils to the site of the damage. Together, these two factors result in the feeling of inflammation felt by the sportsperson after a hard training session⁷. In contrast, the other type of muscle inflammation commonly found in high performance sportspeople, which results from cumulative muscle damage, occurs 1-2 days after a heavy exercise session and/or competition, particularly those exercises with a high eccentric component in the muscle action, or as a result of muscle overuse, is related to DOMS^{1,7,8}.

The effects of exercise on immune function

Intense and acute physical exercise is accompanied by responses which are in many ways very similar to those induced by infection, sepsis or trauma⁷. The size of the increase in the number of circulating leukocytes (mainly lymphocytes and neutrophils) which occurs is related to both the intensity and length of the exercise. Increases are also found in the plasma concentrations of various substances which affect the function of leukocytes, including inflammatory cytokines such as TNF- α , the inflammatory

macrophages protein-1 and IL-1, the anti-inflammatory cytokines IL-6 and IL-10 and IL-1 receptor antagonist (IL-1ra), as well as acute-phase proteins, including C-reactive protein (CRP). Indeed, it has been shown that even a relatively small increase in the plasma levels of IL-6 leads to an increase in the levels of the anti-inflammatory cytokines IL-1ra and IL-10 and in CRP. The increase in IL-6 levels during exercise precedes that of these two cytokines, thereby suggesting that IL-6 may initiate this response (Figure 1).

Local inflammatory responses

Eccentric contraction-induced muscle damage attracts leukocytes to the site of the injury. Neutrophils invade the skeletal muscle over several hours (4 h) and remain present for up to 24 h post-exercise^{2,9-11}. The neutrophils and macrophages help to degrade the damaged muscle by releasing reactive oxygen and nitrogen species¹², although they may also produce proinflammatory cytokines^{11,12}. The proinflammatory cytokines interleukin (IL)-1 β and tumour necrosis factor (TNF)- α are expressed in the muscle for up to 5 days post-exercise^{13,14}. IL-1 β and TNF- α play a role in initiating the destruction of the damaged muscle tissue^{13,14}. Other cytokines, such as IL-6 and transforming growth factor (TGF)- β 1, and inflammatory antigens, such as leukemia inhibitory factor (LIF) and hypoxia-inducible factor (HIF)-1 β are also expressed in muscle in the days following eccentric exercise^{13,15}. The local inflammatory response in skeletal muscle after eccentric exercise is therefore mainly proinflammatory.

Systemic inflammatory responses

Numerous studies have analysed the changes in the concentration of systemic cytokines after eccentric exercise, therefore here we will only summarise the findings as regards the response of systemic cytokines to various types of eccentric exercise^{16,17}. Running at an intensity of $\geq 75\%$ $\text{VO}_{2\text{max}}$ results in a greater increase in the plasma concentrations of IL-6, IL-1 and IL-1ra than other forms of eccentric exercise. This difference appears to be related to the intensity and length of the exercise and possibly to the temperature increase at the site of the muscle damage^{9,17}.

Furthermore, it should also be noted that a strong anti-inflammatory immune reaction, which affects the concentration of both pro- and anti-inflammatory cytokines, occurs after eccentric exercise^{9,18}. Anti-inflammatory cytokines, such as IL-4, IL-13, IL-1ra and IL-10, and soluble

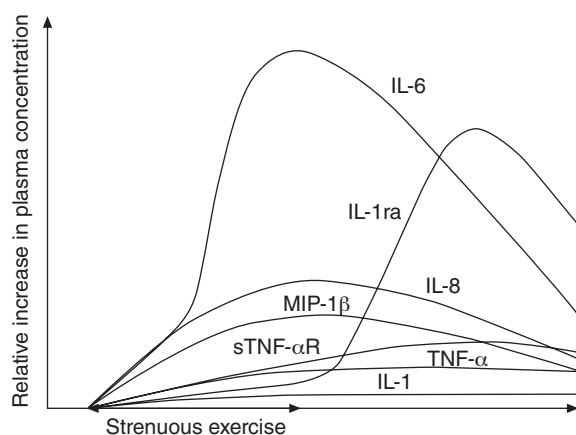


Figura 1 Cytokine response to exercise.

TNF- α receptors appear to be produced in the immune system's mononuclear cells^{19,20}. Thus, although the proinflammatory responses occur within the muscles after eccentric exercise, the release of proinflammatory cytokines into the bloodstream also appears to be inhibited. The mechanism governing this inhibition is not yet clear, although a study by Petersen et al²⁰ appears to suggest the involvement of IL-6. Thus, these authors suggest that IL-6 acts indirectly to restrict the inflammation by stimulating the production of anti-inflammatory cytokines, including IL-1ra, IL-10, cortisol and soluble TNF- α receptor²⁰. The plasma concentrations of TNF- α (2.3 \times), IL-1 β (2.1 \times), IL-6 (128 \times) and IL-10 (27 \times), for example, increase immediately after running a marathon, whereas the increases in soluble TNF- α receptor (\sim 2 \times) and IL-1ra (39 \times) concentration occur 1-1.5 hours later²¹. Eccentric exercise therefore also results in an increase in circulating anti-inflammatory cytokines in response to the local production of proinflammatory cytokines to limit the systemic inflammation.

Physical exercise therefore affects both the cellular and humoral functions of the immune system. Physical exercise also results in an increase in the number of T and B lymphocytes, and a decrease in the T helper/T suppressor (CD4/CD8) ratio⁷. The changes to the NK cells depend on the intensity and duration of the exercise, and are more pronounced after long periods of exercise than after shorter ones¹².

In this scenario of cell demand and stress, an attraction between inflammatory cells in them muscle tissue occurs (Figure 2). Due to the global nature of the immune system, these localised changes have significant repercussions on the lymphocytes and accessory cells outside the muscle tissue²², characterising the exercise-induced inflammatory response and resulting in leukocyte infiltration and the production of proinflammatory cytokines^{9,23}. Furthermore,

in a broader manifestation of the systemic effects of exercise-induced muscle damage and inflammation, it should be noted that a state of immunosuppression known as "open window", which is characterised by a decrease in natural killer (NK) cell activity, neutrophil function, T and B lymphocytes and the concentration of IgA in saliva, and which can last for up to 24 hours after completion of the exercise, is produced after an intense and prolonged exercise session²⁴⁻²⁸. The seriousness of the damage and the length of time during which the symptoms persist depend on the specific characteristics of the exercise and factors inherent to the individual.

Immunomodulators

Ergogenic aid is defined as any substance or phenomenon which improves performance. In this review we concentrate on the role of immunomodulatory drugs such as glycoposphopeptical (AM3) and a nutritional factor known to play an immunomodulatory role, namely glutamine.

Exercise-induced muscle damage and inflammation lead to changes and imbalances in the immunological system along with an "acute phase response". As discussed above, the level of proinflammatory cytokines increases both during and after intense exercise. These and other cytokines mediate a wide range of metabolic events which affect all organ systems in the body^{9,20,21,29}.

The immunomodulators considered to be active in the prevention of, or recovery from, the immune system alterations associated with competitive sporting activity include immunoglobulins, glycoposphopeptical and glutamine, a non-essential amino acid which is nevertheless important for muscle recovery and regeneration^{7,8,30,31}.

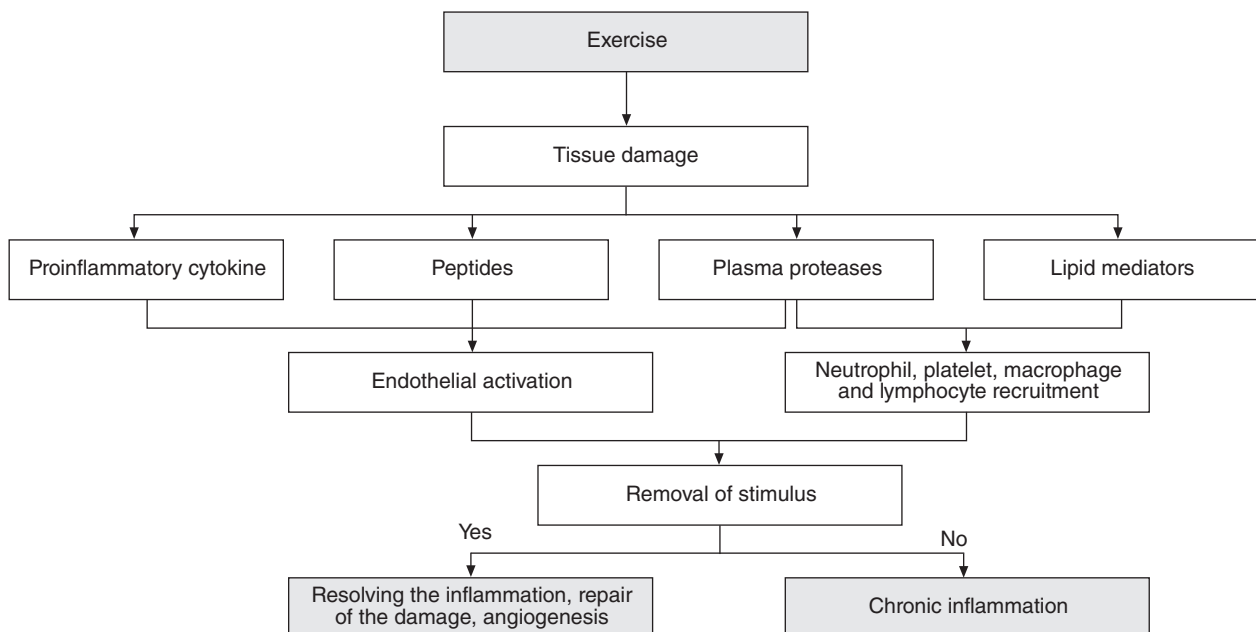


Figure 2 Mechanisms in the inflammation triggered by exercise.

Glycophosphopeptical (AM3)

AM3 is a commercially available immunomodulator with a low toxicity profile whose active ingredient is a polysaccharide with a complex structure, namely purified *Candida utilis* protein, which has a wide range of regulatory effects on innate and adaptive immunity in both mice and humans^{32,33}.

AM3 partially inhibits the production of tumour necrosis factor (TNF- α) and modulates the production of regulatory cytokines (IL-1, IL-2, IL-12)³². Taken together, these alterations result in an overall anti-inflammatory effect. We have recently shown that AM3 can also reduce and normalise the blood concentration of muscle enzymes during intense and prolonged competitive sport^{8,31}. This biochemical effect is associated with a reduction in proinflammatory cytokine levels. AM3 also has other immunomodulatory effects, such as stimulating macrophages and NK activity, both of which could be beneficial in elite sportspeople, who are more susceptible to infection as a result of chronic exercise- and stress-related immunosuppression^{30,31,33}. Our study clearly showed that AM3 can prevent exercise-induced increases in blood IL-6 levels (cycle race, measured 4 hours after the race)³¹. Furthermore, training prior to competition is associated with a reduction in soluble TNF receptor levels, whereas the competition itself generated a significant increase in these levels, albeit with no concomitant increase in TNF- α . This immunomodulator could therefore be important for prevention of the immunological imbalances and tissue damage associated with intense sporting activity. The use of these drugs could therefore limit the metabolic, muscular and immunological alterations associated with prolonged and intense physical exercise (Figure 3 A and B).

Glutamine

Glutamine is a non-essential amino acid which promotes muscle growth and reduces exercise-induced immunodepression³⁴. Skeletal muscle is the tissue most involved in glutamine production, which affects glutamine supply to the immune system, therefore skeletal muscle activity can directly affect the immune system. Glutamine levels in plasma increase after short-term exercise but decrease after prolonged and demanding exercise^{35,36}, thus suggesting the hypothesis that this reduction in glutamine availability could damage immune function. Glutamine is one of the main stimulators of *heat shock protein* (HSP), a complex which protects cells against certain types of damage³⁷. Indeed, a recent review by Wischmeyer³⁸ proposed several interesting concepts regarding HSP, especially that glutamine could regulate these cell-protection proteins.

Very intense and prolonged training periods are associated with a chronic decrease in the plasma concentration of glutamine, and it has been suggested that this reduction could be partly responsible for the immunodepression found in many resistance athletes³⁷. The intramuscular concentration of glutamine is known to be related to the net protein synthesis rate³⁹. However, the mechanisms underlying these purported anabolic effects of glutamine remain to be determined. It is believed that glutamine reduces and attenuates the cytokine response, probably via

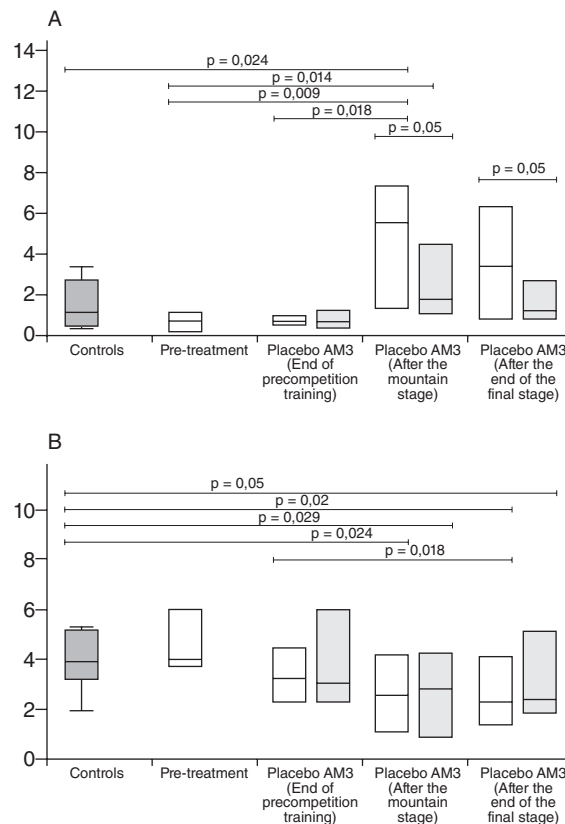


Figure 3 A) Changes in IL-6; B) TNF- α after a mountain stage in professional cyclists treated with AM3 for 90 days.

NF- κ B, in other words it modulates the inflammatory stimulus.

Intense physical exercise can reduce the release of glutamine from skeletal muscle and/or increase the absorption of glutamine by other organs or tissues which use it (liver, kidneys), thereby limiting the availability of glutamine for immune system cells⁴⁰. Glutamine neutralises the catabolic, or cell-tissue destruction, effect caused by stress. Stress, particularly exercise-induced stress, results in an increase in blood cortisol levels, which causes proteolysis of the muscle proteins and increased glutamine release⁴⁰. Glutamine plays a key role in muscle recovery, increase of muscle mass, force and recovery⁴¹. Furthermore, an increase in L-alanine, L-citrulline, L-histidine and L-arginine levels has been observed after the administration of L-glutamine as well as an increase in branched-chain amino acids (BCAAs), which facilitates absorption by the muscles and the recovery and growth of new muscle fibres⁴². Parry-Billings et al⁴³ have shown (in vitro) that a reduction in glutamine levels to below 600 mmol/L is associated with a reduction in the synthesis of RNA, the production of IL-2, the synthesis of immunoglobulin and in the proliferative response of lymphocytes to mitogens, as well as a reduced rate of phagocytosis in macrophages.

In light of the above, and in order not to prolong the discussion of this topic, it appears clear that glutamine helps to maintain a good state of health (Table 1). The consumption of glutamine supplements could therefore be

Table 1 Reasons why it is important to provide glutamine

- Maintains or moderates the decrease in its intracellular concentration in the muscle
- Improves protein synthesis and nitrogen balance
- Improves immunological parameters with a decrease in the risk of infections
- Maintains the integrity of the intestinal mucosa with prevention and /or reduction in bacterial translocation
- Modifies the endogenous inflammatory response
- Significantly promotes hepatic glutathione synthesis, regardless of dose and is able to recover the measured endogenous glutathione levels
- Decreases post-exercise inflammation complications
- There is a lot of evidence that it improves the recovery of the athlete

beneficial in preventing post-exercise immunodepression and for its possible role in promoting anabolic processes, including muscular glycogen and protein synthesis, although Antonio et al⁴⁴ have reported that short-term glutamine intake does not improve performance in trained male weightlifters, thus suggesting its long-term indication. However, there is ample evidence to show that prolonged periods of intense exercise result in decreased blood glutamine levels, which are associated with fatigue, overtraining and other catabolic states. In this sense, Agostini and Biolo⁴⁵ have reported that the reduced post-exercise bioavailability of glutamine could mean that glutamine can be considered to be a marker of overtraining. An appropriate availability of glutamine could reduce inflammation and increase the health benefits associated with optimal training. Glutamine supplementation could therefore improve systemic immunocompetence.

References

- Pacheco L, Garcia-Tirado JJ. Sobre la aplicación de estiramientos en el deportista sano y lesionado. *Apunts Med Esport*. 2010;166:109-25.
- Servicios Médicos Fútbol Club Barcelona. Guía de práctica clínica de las lesiones musculares. Epidemiología, diagnóstico, tratamientos y prevención. Versión 4.5 (9 de febrero de 2009). *Apunts Med Esport*. 2009;164:179-203.
- Cheung K, Hume P, Maxwell L. Delayed onset muscle soreness: treatment strategies and performance factors. *Sports Med*. 2003;33:145-64.
- MacIntyre DL, Reid WD, McKenzie DC. Delayed muscle soreness. The inflammatory response to muscle injury and its clinical implications. *Sports Med*. 1995;20:24-40.
- Warren GL, Hayes DA, Lowe BM, Prior BM, Armstrong RB. Materials fatigue initiates eccentric contraction-induced injury in rat soleus muscle. *J Physiol*. 1993;464:477-89.
- Gleeson MJ, Almey S, Brooks R, Cave A, Lewis, Griffiths H. Haematological and acute-phase responses associated with delayed-onset muscle soreness in humans. *Eur J Appl Physiol*. 1995;71:137-42.
- Córdova A, Alvarez de Mon M. *Inmunidad y deporte*. Madrid: Gymnos; 2001.
- Córdova A, Martin JF, Reyes E, Alvarez-Mon M. Protection against muscle damage in competitive sports players: the effect of the immunomodulator AM3. *J Sports Sci*. 2004;22:827-33.
- Peake J, Nosaka K, Suzuki K. Characterization of inflammatory responses to eccentric exercise in humans. *Exerc Immunol Rev*. 2005;11:64-85.
- MacIntyre DL, Reid WD, Lyster DM, McKenzie DC. Different effects of strenuous eccentric exercise on the accumulation of neutrophils in muscle in women and men. *Eur J Appl Physiol*. 2000;81:47-53.
- Stupka N, Tarnopolsky MA, Yardley NJ, Phillips SM. Cellular adaptation to repeated eccentric exercise-induced muscle damage. *J Appl Physiol*. 2001;91:1669-78.
- Nguyen HX, Tidball JG. Interactions between neutrophils and macrophages promote macrophage killing of rat muscle cells in vitro. *J Physiol*. 2003;547:125-32.
- Hamada K, Vannier E, Sacheck JM, Witsell AL, Roubenoff R. Senescence of human skeletal muscle impairs the local inflammatory cytokine response to acute eccentric exercise. *FASEB J*. 2005;19:264-6.
- Cannon JG, St Pierre BA. Cytokines in exertion-induced skeletal muscle injury. *Mol Cell Biochem* 1998;179:159-67.
- Malm C, Sjödin TL, Sjöberg B, Lenkei R, Renstrom P, Lundberg IE, et al. Leukocytes, cytokines, growth factors and hormones in human skeletal muscle and blood after uphill or downhill running. *J Physiol*. 2004;556:983-1000.
- Peake JM, Suzuki K, Wilson G, Hordern M, Yamaya K, Nosaka K, et al. Exercise-induced muscle damage, plasma cytokines and markers of neutrophil activation. *Med Sci Sports Exerc*. 2005;37:737-45.
- Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. *Exerc Immunol Rev*. 2002;8:6-48.
- Smith L, Anwar A, Fragen M, Rananto C, Johnson R, Holbert D. Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise. *Eur J Appl Physiol*. 2000;82:61-7.
- Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol*. 2003;285:433-7.
- Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol*. 2005;98:1154-62.
- Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *J Physiol*. 1999;515:287-91.
- Bousquet J, Chanez P, Mercier J, Prefaut C. Monocytes, exercise, and the inflammatory response. *Exerc Immunol Rev*. 1996;2:35-44.
- Marqueste T, Decherchi P, Messan F, Kipson N, Grélot L, Jammes Y. Eccentric exercise alters muscle sensory motor control through the release of inflammatory mediators. *Brain Res*. 2004;1023:222-30.
- Pedersen BK, Bruunsgaard H, Jensen M, Toft AD, Hansen H, Ostrowski K. Exercise and the immune system-influence of nutrition and ageing. *J Sci Med Sport*. 1999;2:234-352.
- Nieman DC, Pedersen BK. Exercise and immune function. Recent developments. *Sports Med*. 1999;27:73-80.
- Akerstrom TC, Pedersen BK. Strategies to enhance immune function for marathon runners: what can be done? *Sports Med*. 2007;37:416-9.
- Nieman DC. Marathon training and immune function. *Sports Med*. 2007;37:412-5.
- Gleeson M. Can nutrition limit exercise-induced immunodepression? *Nutr Rev*. 2006;64:119-31.

29. Córdova A, Alvarez-Mon M. Behaviour of zinc in physical exercise: a special reference to immunity and fatigue. *Neurosci Biobehav Rev.* 1995;19:439-45.
30. Córdova A, Alvarez-Mon M. El sistema inmune II: importancia de los inmunomoduladores en la recuperación del deportista. *Arch Med Dep.* 1999;70:155-65.
31. Córdova A, Monserrat J, Villa G, Reyes E, Álvarez-Mon M. Effects of AM3 (Inmunoférón®) on increased serum concentrations of interleukin-6 and tumour necrosis factor receptors I and II in cyclists. *J Sport Sci.* 2006;24:565-73.
32. Alvarez-Mon M, Miravittles M, Morera J, Callol L, Alvarez-Sala JL. Treatment with the immunomodulator AM3 improves the health-related quality of life of patients with chronic obstructive pulmonary disease. *Chest.* 2005;127:1212-8.
33. Prieto A, Reyes E, Bernstein ED, Martinez B, Monserrat J, Izquierdo JL, et al. Defective natural killer and phagocytic activities in COPD are restored by glycoposphopeptical (Inmunoférón®). *Amer J Respir Critical Care Med.* 2001;163:1578-83.
34. Fiel CJ, Johnson I, Pratt VC. Glutamine and arginine: immunonutrients for improved health. *Med Sci Sports Exerc.* 2000;32:377-88.
35. Gleeson M. Dosing and efficacy of glutamine supplementation in human exercise and sport training. *J Nutr.* 2008;138:2045-9.
36. Agostini F, Biolo G. Effect of physical activity on glutamine metabolism. *Curr Opin Clin Nutr Metab Care.* 2010;13:58-64.
37. Kelly D, Wischmeyer PE. Role of L-glutamine in critical illness: new insights. *Curr Opin Clin Nutr Metab Care.* 2003;6:217-22.
38. Wischmeyer PE. Glutamine and heat shock protein expression. *Nutrition.* 2002;18:225-8.
39. Bowtell JL, Gelly K, Jackman ML, Patel A, Simeoni M, Rennie MJ. Effect of oral glutamine on whole body carbohydrate storage during recovery from exhaustive exercise. *J Appl Physiol.* 1999;86:1770-7.
40. Castell LM. Glutamine supplementation in vitro and in vivo, in exercise and in immunodepression. *Sports Med.* 2003;33:323-45.
41. Welbourne TC. Increased plasma bicarbonate and growth hormone after an oral glutamine load. *Am J Clin Nutr.* 1995;61:1058-61.
42. Kreider RB, Miriel V, Bertun E. Amino acid supplementation and exercise performance: proposed ergogenic value. *Sports Med.* 1993;16:190-209.
43. Parry-Billings M, Budgett R, Koutedakis Y, Blomstrand E, Brooks S, Williams C, et al. Plasma amino acid concentrations in the overtraining syndrome: possible effects on the immune system. *Med Sci Sports Exerc.* 1992;24:1353-8.
44. Antonio J, Sanders MS, Kalman D, Woodgate D, Street C. The effects of high-dose glutamine ingestion on weightlifting performance. *J Strength Cond Res.* 2002;16:157-60.
45. Agostini F, Biolo G. Effect of physical activity on glutamine metabolism. *Curr Opin Clin Nutr Metab Care.* 2010;13:58-64.