

# Dosing and Efficacy of Glutamine Supplementation in Human Exercise and Sport Training<sup>1,2</sup>

Michael Gleeson\*

School of Sport and Exercise Sciences, Loughborough University, Loughborough LE11 3TU England

## Abstract

Some athletes can have high intakes of L-glutamine because of their high energy and protein intakes and also because they consume protein supplements, protein hydrolysates, and free amino acids. Prolonged exercise and periods of heavy training are associated with a decrease in the plasma glutamine concentration and this has been suggested to be a potential cause of the exercise-induced immune impairment and increased susceptibility to infection in athletes. However, several recent glutamine feeding intervention studies indicate that although the plasma glutamine concentration can be kept constant during and after prolonged strenuous exercise, the glutamine supplementation does not prevent the postexercise changes in several aspects of immune function. Although glutamine is essential for lymphocyte proliferation, the plasma glutamine concentration does not fall sufficiently low after exercise to compromise the rate of proliferation. Acute intakes of glutamine of ~20–30 g seem to be without ill effect in healthy adult humans and no harm was reported in 1 study in which athletes consumed 28 g glutamine every day for 14 d. Doses of up to 0.65 g/kg body mass of glutamine (in solution or as a suspension) have been reported to be tolerated by patients and did not result in abnormal plasma ammonia levels. However, the suggested reasons for taking glutamine supplements (support for immune system, increased glycogen synthesis, anticatabolic effect) have received little support from well-controlled scientific studies in healthy, well-nourished humans. J. Nutr. 138: 2045S–2049S, 2008.

## Introduction

L-Glutamine is a naturally occurring nonessential neutral amino acid. It is important as a constituent of proteins and as a means of nitrogen transport between tissues (1). It is also important in acid-base regulation, gluconeogenesis, and as a precursor of nucleotide bases and the antioxidant glutathione. Glutamine is the most abundant free amino acid in human muscle and plasma. In adult humans, following an overnight fast, the normal plasma glutamine concentration is 550–750  $\mu\text{mol/L}$  and the skeletal muscle glutamine concentration is ~20 mmol/kg wet weight (2). Skeletal muscle is the major tissue involved in glutamine synthesis and is known to release glutamine into the circulation at ~50 mmol/h in the fed state. Its alleged effects can be classified as anabolic and immunostimulatory. Glutamine is utilized at high rates by

leukocytes (particularly lymphocytes) to provide energy and optimal conditions for nucleotide biosynthesis and hence, cell proliferation (3). Indeed, glutamine is considered important, if not essential, to lymphocytes and other rapidly dividing cells, including the gut mucosa and bone marrow stem cells. Unlike skeletal muscle, leukocytes do not possess the enzyme glutamine synthetase, which catalyses the synthesis of glutamine from ammonia ( $\text{NH}_3$ ) and glutamate, and therefore leukocytes are unable to synthesize glutamine (3). Consequently, leukocytes are largely dependent on skeletal muscle glutamine synthesis and release into the blood to satisfy their metabolic requirements.

Prolonged exercise is associated with a decrease in the intramuscular and plasma concentrations of glutamine and it has been hypothesized that this decrease in glutamine availability could impair immune function (4). Periods of very heavy training are associated with a chronic reduction in plasma concentrations of glutamine and it has been suggested that this may be partly responsible for the immunodepression apparent in many endurance athletes (4). The intramuscular concentration of glutamine is known to be related to the rate of net protein synthesis (5) and there is also some evidence for a role for glutamine in promoting glycogen synthesis (6). However, the mechanisms underlying these alleged anabolic effects of glutamine remain to be elucidated.

Based on an uncritical evaluation of the scientific literature, various manufacturers and suppliers of glutamine supplements claimed that they have the following effects that may benefit athletes: nutritional support for the immune system and prevention

<sup>1</sup> Published in a supplement to *The Journal of Nutrition*. Presented at the conference "The Seventh Workshop on the Assessment of Adequate and Safe Intake of Dietary Amino Acids" held November 2–3, 2007 in Tokyo. The conference was sponsored by the International Council on Amino Acid Science (ICAAS). The organizing committee for the workshop was David H. Baker, Dennis M. Bier, Luc A. Cynober, Yuzo Hayashi, Motoni Kadowaki, Sidney M. Morris Jr, and Andrew G. Renwick. The supplement coordinators were David H. Baker, Dennis M. Bier, Luc A. Cynober, Motoni Kadowaki, Sidney M. Morris Jr, and Andrew G. Renwick. Supplement coordinator disclosures: all of the coordinators received travel support from ICAAS to attend the workshop.

<sup>2</sup> Author disclosures: M. Gleeson, the ICAAS paid the author's travel expenses to attend the meeting.

\* To whom correspondence should be addressed. E-mail: m.gleeson@lboro.ac.uk.

of infection; improved gut barrier function and reduced risk of endotoxemia; improved intracellular fluid retention (i.e. a volumizing effect); more rapid water absorption from the gut; stimulation of muscle glycogen synthesis; stimulation of muscle protein synthesis and muscle tissue growth; reduction in muscle soreness and improved muscle tissue repair; and enhanced buffering capacity and improved high intensity exercise performance.

Most manufacturers recommend the ingestion of 1000 mg/d glutamine in the form of a supplement to obtain some of the benefits claimed above. The evidence for these effects is reviewed below.

### Glutamine supplements and immune function

In humans, glutamine has been shown to influence *in vitro* lymphocyte proliferation in response to mitogens in a concentration-dependent manner with optimal proliferation at a glutamine concentration of  $\sim 600 \mu\text{mol/L}$  (7). It is the requirement of glutamine for both energy provision and nucleotide synthesis in immune cells that has led to the hypothesis that a decrease in the plasma glutamine level below  $\sim 600 \mu\text{mol/L}$  will have deleterious effects on immune function. It has been speculated that failure of the muscle to provide sufficient glutamine could result in a depressed rate of lymphocyte proliferation in response to antigens and so might impair immune defense to viral infection (8). Intense physical exercise might decrease the rate of glutamine release from skeletal muscle and/or increase the rate of glutamine uptake by other organs or tissues that utilize glutamine (e.g. liver, kidneys), thereby limiting glutamine availability for cells of the immune system (8).

### Acute exercise effects on plasma glutamine

The effects of acute exercise on plasma glutamine concentration appear to be largely dependent on the duration and intensity of exercise (9). Studies have shown an increase (10,11) or no change (12) in plasma glutamine levels following short-term ( $<1$  h) high intensity exercise in humans. For example, Babij et al. (10) observed an increase in glutamine concentration from  $575 \mu\text{mol/L}$  at rest to  $734 \mu\text{mol/L}$  during exercise at 100% of maximum oxygen uptake ( $\dot{V}\text{O}_2 \text{ max}$ )<sup>3</sup>. It has been speculated (11) that the increase in plasma glutamine levels during short-term high intensity exercise may be due to glutamate acting as a sink for  $\text{NH}_3$  in the formation of glutamine from glutamate during enhanced intramuscular  $\text{NH}_3$  production in high intensity exercise (the  $\text{NH}_3$  is predominantly derived from the deamination of adenosine monophosphate).

In contrast to the data for high intensity exercise, there is a consistent body of evidence showing that the plasma glutamine levels fall substantially after very prolonged exercise. Plasma glutamine concentration decreased from  $557 \mu\text{mol/L}$  at rest to  $470 \mu\text{mol/L}$  immediately after 3.75 h of cycling at 50%  $\dot{V}\text{O}_2 \text{ max}$  (5). The plasma glutamine concentration reached a minimum of  $391 \mu\text{mol/L}$  after 2 h of recovery and remained depressed at  $482 \mu\text{mol/L}$  after 4.5 h of recovery. Large declines in plasma glutamine level following a marathon race from  $592 \mu\text{mol/L}$  (prerace) to  $495 \mu\text{mol/L}$  immediately posttrace were reported in 24 club standard athletes (4). Continuous cycling at 55%  $\dot{V}\text{O}_2 \text{ max}$  for 3 h in 18 healthy males resulted in a decrease in plasma glutamine concentration from  $580 \mu\text{mol/L}$  preexercise to  $447 \mu\text{mol/L}$  after 1 h recovery. However, continuous cycling to exhaustion at 80%  $\dot{V}\text{O}_2$

max (mean endurance time was 38 min) in the same subjects did not alter the plasma glutamine concentration compared with preexercise (12). The decline in plasma glutamine concentrations after prolonged exercise is probably due to increased hepatic uptake of glutamine for gluconeogenesis and synthesis of acute-phase proteins and/or to increased kidney glutamine uptake in an attempt to buffer acidosis (9). Increased glutamine uptake by activated leukocytes may also contribute to the fall in plasma glutamine levels after prolonged exercise, although limited evidence is available to support this suggestion (13).

Prolonged exercise is known to cause an elevation in plasma cortisol concentration, which stimulates not only protein catabolism and glutamine release but also increases gluconeogenesis in the liver, gastrointestinal tract, and kidneys (14). Increased hepatic, gastrointestinal, and renal uptake of glutamine could place a significant drain on plasma glutamine availability after prolonged exercise. Similar changes in plasma stress hormones occur after starvation, surgical trauma, sepsis, burns, and prolonged exercise, and all of these states of catabolic stress are characterized by lowered plasma glutamine concentrations, depressed cellular immunity, and increased gluconeogenesis (8). In conditions of metabolic acidosis, the renal uptake of glutamine increases to provide for ammoniogenesis. Diet-induced metabolic acidosis with a high-protein (24% of energy):high-fat (72% of energy) diet for 4 d led to a  $\sim 25\%$  reduction in the concentrations of glutamine in both plasma and muscle (15). In this situation, it seems likely that release of glutamine from muscle may have increased, along with renal uptake, in an attempt to maintain acid-base balance. Walsh et al. (9) have suggested that a common mechanism may be responsible for depletion of plasma glutamine after prolonged exercise, starvation, and physical trauma, namely, increased hepatic and gastrointestinal uptake of glutamine for gluconeogenesis at a time when muscle release of glutamine remains constant or falls.

### Endogenous glutamine concentrations, overtraining, and infection

The resting plasma concentrations of glutamine have been reported to be lower in over-trained (chronically fatigued) athletes compared with healthy well-trained athletes and sedentary individuals (4,16). For example, 1 study (4) reported values of  $503 \mu\text{mol/L}$  for plasma glutamine in over-trained athletes compared with a concentration of  $550 \mu\text{mol/L}$  for healthy control athletes (a 9% difference). A 23% reduction in resting plasma glutamine concentration has also been observed after 2 wk of intensified training in elite swimmers (13). Among chronically fatigued, elite athletes, resting plasma glutamine levels of  $330\text{--}420 \mu\text{mol/L}$  have been reported; those suffering from an infection did not differ from those who were not (16). According to the glutamine hypothesis, over-trained athletes with decreased plasma glutamine concentration would be predicted to exhibit impaired immune function and suffer a greater number and severity of upper respiratory tract infections (URTI). However, to date, there has been no direct evidence to our knowledge supporting a causal link between low plasma glutamine, impaired immune function, and increased susceptibility to infection in athletes. Although lower plasma glutamine levels in athletes reporting URTI symptoms have been reported (17), others have found no relationship between low plasma glutamine concentration and the occurrence of URTI in track and field athletes (16) or trained swimmers (13). Surprisingly, URTI was more common among well-trained swimmers (with 23% higher plasma glutamine) compared with over-trained swimmers.

<sup>3</sup> Abbreviations used: bm, body mass; URTI, upper respiratory tract infection;  $\dot{V}\text{O}_2 \text{ max}$ , maximum oxygen uptake.

## Glutamine supplementation, immune function, and infection

If a decrease in plasma glutamine concentration were a causal factor in the transient postexercise depression of immune function, then preventing the fall in plasma glutamine by supplementing glutamine orally should prevent the associated immune impairment. A study with a rat model indicated that glutamine supplementation of 1000 mg/kg body mass (bm) by gavage increased the phagocytic capacity of neutrophils and the production of reactive oxygen species and abolished the decrease in nitric oxide production induced by exercise (18). However, several glutamine feeding intervention studies in humans suggest that glutamine supplementation before and after exercise has no detectable effect on exercise-induced changes in immune cell functions. In a randomized, cross-over, placebo-controlled study, Rohde et al. (19) had subjects perform 3 successive bouts of cycle ergometer exercise at 75%  $\dot{V}O_2$  max for 60, 45, and 30 min with 2 h rest between each bout. Subjects were fed glutamine (0.1 g/kg bm) 30 min before the end of each exercise bout and 30 min after each exercise bout. The arterial plasma glutamine concentration declined from  $508 \pm 35 \mu\text{mol/L}$  (preexercise) to  $402 \pm 38 \mu\text{mol/L}$  at 2 h after the last exercise bout in the placebo trial and was maintained above preexercise levels in the glutamine supplementation trial. Although glutamine feeding prevented the fall in the plasma glutamine concentration, it did not prevent the fall in lymphocyte proliferation 2 h after each bout or the fall in activity of lymphokine-activated killer cells at 2 h after the final bout of exercise. Using similar glutamine treatments, other recent studies have also shown that glutamine supplementation (sufficient to prevent any fall in the plasma glutamine concentration) during and after 2 h of cycling did not prevent the decrease in the activity of natural killer cells (20) or in the concentration of immunoglobulin-A in saliva (21). In another study, subjects ingested 3 g of glutamine every 15 min during the final 30 min of a 2-h exercise bout and every 15 min during a subsequent 2-h recovery period (total intake of 30 g) with no effect on the exercise-induced transient decrease in bacteria-stimulated neutrophil degranulation (22).

Castell et al. (17) have provided the only evidence to date for a prophylactic effect of oral glutamine supplementation on the occurrence of URTI in athletes. In a randomized, double-blinded, placebo-controlled study, ultra-marathon and marathon runners participating in races were given either a placebo or a glutamine beverage (5 g glutamine in 330 mL water), which was ingested immediately after and 2 h after the race. The runners were given questionnaires to self-report the occurrence of symptoms of URTI for 7 d after the race. In those receiving the glutamine drink ( $n = 72$ ), 81% experienced no URTI episodes in the week following the race, whereas in those receiving the placebo (maltodextrin) drink ( $n = 79$ ), only 49% experienced no URTI episodes in the week following the race. Although the reporting of URTI symptoms increased following the race in both groups, it was concluded that the provision of the glutamine supplement in the 2 h following the race decreased the incidence of infection in the week after the event. However, it is unlikely that the glutamine dose given was actually sufficient to prevent the postexercise decline in the plasma glutamine concentrations. Indeed, in another study by the same group, plasma glutamine concentration decreased similarly in placebo and glutamine-supplemented groups when glutamine was supplemented (5 g glutamine in 330 mL water) immediately after and 2 h after a marathon (23). Another glutamine feeding study showed that an oral dose of 0.1 g/kg bm ( $\sim 7$  g) increased plasma glutamine concentration by  $\sim 50\%$  within 30 min and

glutamine concentration returned to baseline within 90–120 min (24). Thus, doses in excess of 5 g need to be ingested at frequent intervals (e.g. every 30–60 min) to sustain a moderate elevation of the plasma glutamine concentration over several hours.

## The glutamine immune boosting hypothesis: conclusions

The glutamine hypothesis is that a decrease in plasma glutamine concentrations, brought about by heavy exercise and training, limits the availability of glutamine for cells of the immune system that require glutamine for energy and nucleotide biosynthesis. Thus, the glutamine hypothesis provides a mechanism to explain exercise-induced immune impairment and increased susceptibility to infection in endurance athletes. The time course of the decrease in plasma glutamine concentrations after prolonged strenuous exercise coincides with the decreases in many immune parameters (25,26); in addition, it is prolonged moderate-high intensity exercise that most often results in the greatest immune impairment and this type of exercise also results in the greatest reduction in plasma glutamine concentration. The glutamine hypothesis is based predominantly on *in vitro* work by Parry-Billings et al. (8), which showed that mitogen-stimulated lymphocyte proliferation is enhanced by glutamine in a concentration-dependent manner with optimal proliferation at glutamine concentrations between 100 and 600  $\mu\text{mol/L}$ . Evidence showing that the provision of glutamine-supplemented, total parenteral nutrition to severely ill surgical patients improves T lymphocyte mitogenic responses also provides further support for the 'glutamine hypothesis' (27). However a reevaluation of the glutamine requirement for lymphocyte proliferation by Blanchard (28) indicated that lymphocyte proliferation in culture was only depressed significantly when the glutamine concentration in the medium was  $<100 \mu\text{mol/L}$ . Thus, lymphocytes function equally well when cultured at a glutamine concentration of 300–400  $\mu\text{mol/L}$  (equivalent to the lowest plasma glutamine concentration measured postexercise), as when cultured at normal resting levels of  $\sim 550$ – $750 \mu\text{mol/L}$  (29). Even during severe catabolic conditions, such as severe burns, plasma glutamine concentration rarely falls below 200  $\mu\text{mol/L}$ .

Finally, as described above, the majority of studies have found no beneficial effects of maintaining plasma glutamine concentration, with glutamine supplements during exercise and recovery, on various immune responses after exercise. Collectively, the evidence does not support a role for decreased plasma glutamine concentrations in the etiology of exercise-induced immune depression. More research is required to elucidate the mechanism(s) by which oral glutamine supplements may have prophylactic effects in long-distance runners (17). Although a direct effect of decreased glutamine availability for immune cells is unlikely, glutamine may have an indirect effect on immune function and infection incidence through preservation of the antioxidant glutathione or maintenance of gut barrier function (30).

## Glutamine and water transport

Glutamine is not included in commercial sports drinks mainly because of its relative instability in solution. Water transport from the gut into the circulation is known to be promoted by the presence in drinks of glucose and sodium (31). This is because water movement is determined by osmotic gradients and the cotransport of sodium and glucose into the gut epithelial cells is accompanied by the osmotic movement of water molecules in the same direction. Glutamine is transported into gut epithelial

cells by both sodium-dependent and sodium-independent mechanisms and the addition of glutamine to oral rehydration solutions has been shown to increase the rate of fluid absorption above that of ingested water alone (32). However, the potential benefits of adding glutamine to commercially available sports drinks have not been adequately tested and any additional benefit in terms of increased rate of fluid absorption and retention is likely to be very small indeed.

### Glutamine and acid-base balance in exercise

One study (33) has reported that the plasma bicarbonate concentration was increased by 2.7 mmol/L (an ~10% increase above baseline) 90 min following oral ingestion of 2 g glutamine (16–36 mg/kg bm). However, a placebo-controlled study that investigated the effects of glutamine supplementation (30 mg/kg bm) on extracellular buffering capacity and high intensity exercise performance (34) did not find any beneficial effects on blood acid-base balance or time to fatigue in cycling at 100%  $\dot{V}O_2$  max.

### Glutamine supplements and muscle anabolic processes

Muscle protein breakdown occurs in the fasted state. Recent research indicates that resistance-exercise reduces the extent of this protein catabolism, but an anabolic (muscle growth) response requires an intake of essential amino acids (dietary protein) in the recovery period after exercise (35). This promotes amino acid uptake into muscle and increases the rate of synthesis of tissue protein without affecting the rate of protein breakdown. Provided that the ingested protein contains the 8 essential amino acids, taking supplements of individual nonessential amino acids at this time is unlikely to provide any additional benefit (36). There is some evidence for an effect of glutamine supplements in promoting glycogen synthesis in the first few hours of recovery after exercise: 8 g of glutamine in addition to 61 g of glucose polymer ingested after a glycogen-depleting bout of exercise resulted in a 25% increase in whole body glucose disposal in the h 2 of recovery compared with glucose polymer alone (6). However, further research using optimal carbohydrate feeding after exercise needs to be undertaken to substantiate this finding and to give it practical relevance. The ingestion of 61 g of carbohydrate is a suboptimal amount; amounts in excess of 100 g are needed to achieve the maximum rate of muscle glycogen synthesis over a 2-h postexercise period (31). Thus, a postexercise meal consisting of predominantly carbohydrate (~100 g) with some protein (~20 g) would seem to be the best strategy to promote both glycogen and protein synthesis in muscle after exercise (31,37).

One study (33) has reported that the plasma concentration of growth hormone was increased 4-fold 90 min following oral ingestion of 2 g glutamine. However, 1 h of moderate to high intensity exercise can result in a 20-fold increase in plasma growth hormone concentration, so this is not a reason for athletes engaged in exercise training to take glutamine supplements.

Eccentric exercise-induced muscle damage does not affect plasma glutamine concentrations (38). There is no scientific evidence for a beneficial effect of oral glutamine supplementation on muscle repair after exercise-induced damage and no evidence of reduced muscle soreness when consuming glutamine compared with placebo (38).

### Glutamine intakes in the athletic population

The normal daily intake of glutamine from dietary protein is ~3–6 g/d (assuming a daily protein intake of 0.8–1.6 g/kg bm for

a 70-kg individual). Supplements currently available are in the form of L-glutamine tablets or capsules (250, 500, and 1000 mg) or as a powder. Other dietary sources of glutamine for athletes may include protein supplements such as whey protein and protein hydrolysates (39). Glutamine is thought to be relatively safe and well tolerated by most people, although administration of glutamine to people with kidney disorders is not recommended. No adverse reactions to short-term glutamine supplementation in amounts of 20–30 g within a few hours (22) have been reported in healthy athletes. Doses of up to 0.65 g/kg bm of glutamine (in solution or as a suspension) have been reported to be tolerated by pediatric cancer patients and do not result in abnormal plasma ammonia levels (40). Although higher doses resulted in ammonia levels above the acceptable limit (>150  $\mu$ mol/L), the suspension of glutamine necessary to give such high levels is not palatable (39). In the only relatively long-term, repeated high-dose glutamine supplementation study in athletes (41), 4 women and 9 men of high fitness consumed 0.1g/kg bm of L-glutamine 4 times daily (average intake of 28 g/d) for 2 wk. No ill effects were reported, but even this high glutamine intake did not prevent a decrease in the plasma glutamine concentration over 9 d of intensive training (blood samples were taken 8 h after the last glutamine dose).

An inadequate dietary intake of protein impairs host immunity with particularly detrimental effects on the T-cell system, resulting in increased incidence of opportunistic infections (42). Although it is unlikely that athletes would ever reach a state of such extreme malnutrition, the impairment of host defense mechanisms is observed even in moderate protein deficiency. Dietary protein is also required to promote muscle protein synthesis after exercise. Interestingly, there is some evidence that an additional intake of 20–30 g/d protein can restore depressed plasma glutamine levels in over-trained athletes (16). Hence, ensuring an adequate intake of protein is important for athletes but consuming glutamine supplements is not.

Consuming glutamine supplements is unlikely to be of substantial benefit in terms of fluid balance restoration or preventing immunodepression after exercise, although there are some suggestions of a possible role for glutamine in stimulating anabolic processes, including muscle glycogen and protein synthesis. The available evidence at present is not strong enough to warrant a recommendation for an athlete to use a glutamine supplement.

Other articles in this supplement include references (43–52).

### Literature Cited

1. Watford M. Glutamine metabolism and function in relation to proline synthesis and the safety of glutamine and proline supplementation. *J Nutr.* 2008;138:2003–7.
2. Jonnalagadda SS. Glutamine. In: Driskell JA, editor. *Sports nutrition: fats and proteins*. Boca Raton (FL): CRC Press; 2007. p. 261–77.
3. Ardawi MS, Newsholme EA. Glutamine metabolism in lymphocytes of the rat. *Biochem J.* 1983;212:835–42.
4. Parry-Billings M, Budgett R, Koutedakis Y, Blomstrand E, Brooks S, Williams C, Calder PC, Pilling S, Baigrie R, et al. Plasma amino acid concentrations in the overtraining syndrome: possible effects on the immune system. *Med Sci Sports Exerc.* 1992;24:1353–8.
5. Rennie MJ, Edwards RH, Kryawych S, Davies CT, Halliday D, Waterlow JC, Millward DJ. Effect of exercise on protein turnover in man. *Clin Sci.* 1981;61:627–39.
6. 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.

7. Parry-Billings M, Evans J, Calder PC, Newsholme EA. Does glutamine contribute to immunosuppression after major burns? *Lancet*. 1990;336:523–5.
8. Parry-Billings M, Blomstrand E, McAndrew N, Newsholme EA. A communicational link between skeletal muscle, brain, and cells of the immune system. *Int J Sports Med*. 1990;11 Suppl 2:S122–8.
9. Walsh NP, Blannin AK, Robson PJ, Gleeson M. Glutamine, exercise and immune function. Links and possible mechanisms. *Sports Med*. 1998;26:177–91.
10. Babji P, Matthews SM, Rennie MJ. Changes in blood ammonia, lactate and amino acids in relation to workload during bicycle ergometer exercise in man. *Eur J Appl Physiol Occup Physiol*. 1983;50:405–11.
11. Sewell DA, Gleeson M, Blannin AK. Hyperammonaemia in relation to high intensity exercise duration in man. *Eur J Appl Physiol Occup Physiol*. 1994;69:350–4.
12. Robson PJ, Blannin AK, Walsh NP, Castell LM, Gleeson M. Effects of exercise intensity, duration and recovery on *in vitro* neutrophil function in male athletes. *Int J Sports Med*. 1999;20:128–35.
13. MacKinnon LT, Hooper SL. Plasma glutamine and upper respiratory tract infection during intensified training in swimmers. *Med Sci Sports Exerc*. 1996;28:285–90.
14. Stumvoll M, Perriello G, Meyer C, Gerich J. Role of glutamine in human carbohydrate metabolism in kidney and other tissues. *Kidney Int*. 1999;55:778–92.
15. Greenhaff PL, Gleeson M, Maughan RJ. The effects of diet on muscle pH and metabolism during high intensity exercise. *Eur J Appl Physiol Occup Physiol*. 1988;57:531–9.
16. Kingsbury KJ, Kay L, Hjelm M. Contrasting plasma amino acid patterns in elite athletes: association with fatigue and infection. *Br J Sports Med*. 1998;32:25–33.
17. Castell LM, Poortmans JR, Newsholme EA. Does glutamine have a role in reducing infections in athletes? *Eur J Appl Physiol Occup Physiol*. 1996;73:488–90.
18. Lagranha CJ, de Lima TM, Senna SM, Doi SQ, Curi R, Pithon-Curi TC. The effect of glutamine supplementation on the functions of neutrophils from exercised rats. *Cell Biochem Funct*. 2005;23:101–7.
19. Rohde T, MacLean DA, Pedersen BK. Effect of glutamine supplementation on changes in the immune system induced by repeated exercise. *Med Sci Sports Exerc*. 1998;30:856–62.
20. Krzywkowski K, Petersen EW, Ostrowski K, Kristensen JH, Boza J, Pedersen BK. Effect of glutamine supplementation on exercise-induced changes in lymphocyte function. *Am J Physiol Cell Physiol*. 2001;281:C1259–65.
21. Krzywkowski K, Petersen EW, Ostrowski K, Link-Amster H, Boza J, Halkjaer-Kristensen J, Pedersen BK. Effect of glutamine and protein supplementation on exercise-induced decreases in salivary IgA. *J Appl Physiol*. 2001;91:832–8.
22. Walsh NP, Blannin AK, Bishop NC, Robson PJ, Gleeson M. Effect of oral glutamine supplementation on human neutrophil lipopolysaccharide-stimulated degranulation following prolonged exercise. *Int J Sport Nutr*. 2000;10:39–50.
23. Castell LM, Newsholme EA. The effects of oral glutamine supplementation on athletes after prolonged, exhaustive exercise. *Nutrition*. 1997;13:738–42.
24. Ziegler TR, Benfell K, Smith RJ, Young LS, Brown E, Ferrari-Baliviera E, Lowe DK, Wilmore DW. Safety and metabolic effects of L-glutamine administration in humans. *JPEN J Parenter Enteral Nutr*. 1990;14:137S–46S.
25. Gleeson M, Editor. *Immune function in sport and exercise*. Edinburgh: Elsevier; 2005.
26. Gleeson M. Immune system adaptation in elite athletes. *Curr Opin Clin Nutr Metab Care*. 2006;9:659–65.
27. O’Riordain MG, De Beaux A, Fearon KC. Effect of glutamine on immune function in the surgical patient. *Nutrition*. 1996;12:S82–4.
28. Blanchard M. Carbohydrate supplementation and high intensity exercise: glutamine metabolism and immune function in well trained athletes. PhD thesis, University of Queensland, Australia; 2002.
29. Hiscock N, Pedersen BK. Exercise-induced immunodepression: plasma glutamine is not the link. *J Appl Physiol*. 2002;93:813–22.
30. Castell LM. Glutamine supplementation *in vitro* and *in vivo*, in exercise and in immunodepression. *Sports Med*. 2003;33:323–45.
31. Jeukendrup AE, Gleeson M. *Sports nutrition: an introduction to energy production and performance*. Champaign (IL): Human Kinetics; 2004.
32. Silva AC, Santos-Neto MS, Soares AM, Fonteles MC, Guerrant RL, Lima AA. Efficacy of a glutamine-based oral rehydration solution on the electrolyte and water absorption in a rabbit model of secretory diarrhea induced by cholera toxin. *J Pediatr Gastroenterol Nutr*. 1998;26:513–9.
33. Welbourne TC. Increased plasma bicarbonate and growth hormone after an oral glutamine load. *Am J Clin Nutr*. 1995;61:1058–61.
34. Haub MD, Potteiger JA, Nau KL, Webster MJ, Zebas CJ. Acute L-glutamine ingestion does not improve maximal effort exercise. *J Sports Med Phys Fitness*. 1998;38:240–4.
35. Rasmussen BB, Tipton KD, Miller SL, Wolf SE, Wolfe RR. An oral essential amino acid-carbohydrate supplement enhances muscle protein anabolism after resistance exercise. *J Appl Physiol*. 2000;88:386–92.
36. Tipton KD, Ferrando AA, Phillips SM, Doyle D, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. *Am J Physiol*. 1999;276:E628–34.
37. Miller SL, Tipton KD, Chinkes DL, Wolf SE, Wolfe RR. Independent and combined effects of amino acids and glucose after resistance exercise. *Med Sci Sports Exerc*. 2003;35:449–55.
38. Gleeson M, Walsh NP, Blannin AK, Robson PJ, Cook L, Donnelly AE, Day SH. The effect of severe eccentric exercise-induced muscle damage on plasma elastase, glutamine and zinc concentrations. *Eur J Appl Physiol Occup Physiol*. 1998;77:543–6.
39. Manninen AH. Protein hydrolysates in sports and exercise: a brief review. *J Sports Sci Med*. 2004;3:60–3.
40. Ward E, Picton S, Reid U, Thomas D, Gardener C, Smith M, Henderson M, Holden V, Kinsey S, et al. Oral glutamine in paediatric oncology patients: a dose finding study. *Eur J Clin Nutr*. 2003;57:31–6.
41. Krieger JW, Crowe M, Blank SE. Chronic glutamine supplementation increases nasal but not salivary IgA during 9 days of interval training. *J Appl Physiol*. 2004;97:585–91.
42. Daly JM, Reynolds J, Sigal RK, Shou J, Liberman MD. Effect of dietary protein and amino acids on immune function. *Crit Care Med*. 1990;18:S86–93.
43. Taylor CL, Yetley EA. Nutrient risk assessment as a tool for providing scientific assessments to regulators. *J Nutr*. 2008;138:1987–91.
44. Hathcock JN, Shao A. Expanded approach to tolerable upper intake guidelines for nutrients and bioactive substances. *J Nutr*. 2008;138:1992–5.
45. Pencharz PB, Elango R, Ball RO. An approach to defining the upper safe limits of amino acid intake. *J Nutr*. 2008;138:1996–2002.
46. Phang JM, Jui Pandhare J, Liu Y. The metabolism of proline as microenvironmental stress substrate. *J Nutr*. 2008;138:2008–15.
47. Mitsubuchi H, Nakamura K, Matsumoto S, Endo F. Inborn errors of proline metabolism. *J Nutr*. 2008;138:2016–20.
48. Barbul A. Proline precursors to sustain mammalian collagen synthesis. *J Nutr*. 2008;138:2021–4.
49. Roth E. Nonnutritive effects of glutamine. *J Nutr*. 2008;138:2025–31.
50. Bertolo RE, Burrin DG. Comparative aspects of tissue glutamine and proline metabolism. *J Nutr*. 2008;138:2032–9.
51. Wernerman J. Clinical use of glutamine supplementation. *J Nutr*. 2008;138:2040–4.
52. Kimura T, Renwick AG, Kadowaki M, Cynober LA. The 7th workshop on the assessment of adequate intake of dietary amino acids: summary of general discussion. *J Nutr*. 2008;138:2050–2.