The Clinical Pharmacology of Sport and Exercise
T. Reilly and M. Orme, editors

Overtraining, Immunosuppression, Exercise-Induced Muscle Damage and Anti-Inflammatory Drugs

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Key words: Anti-inflammatory, immunity, infection, muscle damage, overtraining.

1. INTRODUCTION

Athletes engaged in heavy training programmes, particularly those involved in endurance events, appear to be more susceptible than normal to infection [1-3]. For example, sore throats and flu-like symptoms are more common in athletes than in the general population, and once infected, colds may last for longer in athletes. There is some convincing evidence that this increased susceptibility to infection arises due to a depression of immune system function [4-6].

2. IMMUNOSUPPRESSION IN ATHLETES

The main component of the immune system comprises the white blood cells (leucocytes), whose numbers and functional capacities may be decreased by repeated bouts of intense prolonged exercise [4-6]. The reason why immune function can be deleteriously affected by exercise is still unclear, but is probably related to increased levels of stress hormones during exercise [7-8]. Some very recent research suggests that falls in the blood concentration of glutamine, an amino acid that is essential for the optimal functioning of leucocytes, may also be implicated in causing the immunosuppression associated with heavy training [9,10]. Muscle damage may be another factor [11,12].

An acute bout of physical activity is accompanied by responses that are remarkably similar in many respects to those induced by infection [1,4-6]: there is a substantial increase in the number of circulating leucocytes (mainly lymphocytes and neutrophils), the magnitude of which is related to both the intensity and duration of exercise. There are also increases in the plasma concentrations of various substances that are known to influence leucocyte functions, including interferon-α, tumour necrosis factor, interleukins 1, 2 and 6 [13], acute phase proteins like C-reactive protein [14] and activated complement fragments [15]. Hormonal changes also occur in response to exercise, including rises in the plasma concentration of several hormones (e.g. adrenaline, cortisol, growth hormone and prolactin) that are known to have immunomodulatory effects [7]. Acute exercise temporarily increases the phagocytic

activity of neutrophils and macrophages and increases natural killer (NK) cell lytic activity, but has been shown to diminish the proliferative response of lymphocytes to mitogens [1, 4-6]. During recovery from exercise, NK cell numbers and activity fall below pre-exercise levels, and if the exercise bout was of high intensity, the number of circulating lymphocytes may be decreased below pre-exercise levels for several hours after exercise and the T lymphocyte CD4+/CD8+ (helper/suppressor) ratio is decreased. Following prolonged strenuous exercise the production of immunoglobulins (antibodies) by B lymphocytes is inhibited [5,6,12]. These changes during early recovery from exercise would appear to weaken the potential immune response to pathogens and have been suggested to provide an "open window" for infection representing the most vulnerable time period for athletes in terms of their susceptibility to contracting an infection [12].

Exercise training also modifies immune function, with most changes on balance suggesting an overall decrease in immune system function, particularly when training loads are heavy. Circulating numbers of leucocytes are generally lower in athletes at rest compared with sedentary people (Table 1), and increases in the leucocyte count during exercise (at the same absolute or relative intensity) are lower after training. Phagocytic activity of blood neutrophils has been reported to be markedly lower in trained cyclists compared with age and weight-matched sedentary controls [16]. Levels of secretory immunoglobulins such as salivary IgA are lower in well trained subjects [17], as are T lymphocyte CD4+/CD8+ ratios and *in vitro* mitogen-stimulated lymphocyte proliferation responses [6].

Table 1
Mean ± S.D. circulating leucocyte counts (x 10^9 cells/l) in trained cyclists and age- and weight-matched untrained controls.

		Total leucocytes	Neutrophils	Lymphocytes
Trained	(n=8)	4.36 ± 1.15 *	2.46 ± 0.87 *	1.36 ± 0.20 *
Untrained	(n=8)	6.62 ± 0.87	3.83 ± 0.86	2.02 ± 0.27

Data from Blannin *et al.* [16]; * $P<0.01$: significant difference between trained and untrained.

There are several possible causes of the diminution of immune function associated with heavy training. One mechanism may simply be the cumulative effects of repeated bouts of intense exercise with the consequent elevation of stress hormones, particularly glucocorticoids, causing temporary immunosuppression [7]. When exercise is repeated frequently there may not be sufficient time for the immune system to recover fully. Furthermore, following exercise-induced muscle damage, plasma cortisol levels can be chronically elevated for several days [18,19].

Plasma glutamine levels can change substantially after exercise and may become severely depressed after high intensity interval training [9]. Repeated bouts of high intensity training appear to induce a sustained fall in the plasma glutamine concentration. Glutamine is essential for several functions of leucocytes including their ability to undergo cell division, to produce antibodies and to destroy bacteria by ingestion and digestion [10]. Skeletal muscle is thought to be the main source of glutamine released into the bloodstream and this release may play an important role in delivering glutamine to the cells of the immune system. In addition to exercise, other forms of stress such as trauma, surgery and

infection are known to cause increased release of glutamine from skeletal muscle, increase glutamine requirements by other organs, and decrease plasma glutamine levels [20], which may account for the impaired immune function associated with these stress states.

Yet another possible cause of immunosuppression during periods of heavy training could be a gradual depletion in the functional capacity of neutrophils [16,21]. These normally constitute 60-80% of peripheral blood leucocytes and are responsible for ingesting bacteria and damaged tissue. They represent an important first line of defence against invading pathogens which are killed by proteolytic and free-radical generating enzymes released from granules contained within neutrophils. Neutrophils seem to be activated during a bout of exercise, as there are elevated levels of their enzymes in the blood plasma after exercise [22] - which indicates that the neutrophils have undergone degranulation - the process of enzyme release from their granules. A similar response is observed when neutrophils are exposed to bacteria. However, the repeated activation of neutrophils by regular bouts of exercise could result in a depletion of their enzyme content or a reduced reaction to subsequent exposure to bacteria [21] as neutrophils have been reported to desensitize to a repeated stimulus [23]. This could reduce the ability of the neutrophils to respond appropriately to microorganisms that are able to penetrate the body's natural defences and enter the circulation. It seems that muscle-damaging exercise provides an increased stimulus to neutrophil activation [24] and this could bring about a more rapid or potent depletion of their function. Complement activation also occurs during exercise [15] and a diminution of the serum complement concentration with repeated bouts of exercise, particularly when muscle damage is incurred, could also contribute to decreased non-specific immunity in athletes; well trained individuals have a lower serum complement concentration compared with sedentary controls [6].

3. OVERTRAINING

Athletes can also suffer from overtraining, a condition in which under-performance is experienced despite continued or even increased training. Although improvements in athletic performance hinge on increasing the training load or "over-loading", overtraining - a vicious circle of more training producing lower performance and chronic fatigue - seems to be a stress response to training too hard too often, with insufficient recovery time between exercise bouts.

The reasons why some athletes become overtrained while others do not are unclear, and the consequences range from altered muscle function to motivation. The pathophysiology of overtraining can include muscle soreness and weakness, cytokine actions, hormonal and haematological changes, mood swings and psychological depression and nutritional problems such as loss of appetite and diarrhoea [25,26]. In some cases the underlying cause could be a persistent viral infection, similar to glandular fever; several types of virus are known to infiltrate skeletal and cardiac muscle. A marked fall in the blood leucocyte count is often indicative of a chronic viral infection. Athletes suffering from overtraining syndrome are often reported to be immuno-suppressed. Plasma glutamine could also be implicated here, as some studies have reported that overtrained athletes have low plasma glutamine levels, even in the resting state, and that these can remain low for several weeks, with recovery only taking place when the training load is markedly reduced [9,27]. Alternatively, declines in plasma glutamine concentration may actually be caused by an infection: falls in plasma glutamine concentration have been observed in humans following exposure to viral stress [28].

3.1. Muscle damage involvement

The under-performance may be the result of exercise-induced muscle damage - many athletes that have been diagnosed as suffering from overtraining have reported that their muscles feel sore - which causes a loss of muscle strength [11,25,26]. The consequences of exercise-induced muscle damage include muscle pain, soreness and stiffness; reduced range of motion; higher than normal blood lactate

concentration and perceived exertion during exercise, loss of strength and reduced maximal dynamic power output that can last 5-10 days [11,18].

A practical index of muscle damage in athletes performing heavy training is elevation of muscle proteins (e.g. myoglobin, creatine kinase, lactate dehydrogenase and myosin heavy chain fragments) in the blood plasma [29,30]. The damaged muscle tissue can cause an initial activation of the immune system, as white blood cells are attracted to the damaged muscles to begin breakdown of damaged muscle fibres and initiate the repair process [31]. However, increased levels of stress hormones such as cortisol also appear in the blood [18,19] and these can have quite a potent depressing effect on the white blood cells [7]. While this might be seen as the body's natural response to prevent excessive damage of the muscles by the immune system, it may also weaken the immune response to invading bacteria and viruses, rendering the unfortunate athlete more susceptible to infection.

Athletes are always loathe to stop training, and with good reason, because the physiological adaptations to training begin to be lost within a few days of stopping. However, continuing to undertake strenuous exercise with already damaged muscles may make the situation even worse by preventing tissue repair and maintaining a state of inflammation with chronically elevated levels of immunosuppressive stress hormones. Another practical problem is that 3-6 days after a muscle-damaging bout of exercise, athletes can no longer perceive that their muscles are still weak, so they may exercise too hard too soon [11].

Another detrimental effect of exercise-induced muscle damage is that it impairs the restoration of muscle glycogen stores [32]. Stores of glycogen become depleted after prolonged exercise. Damaged muscle has an impaired ability to take up glucose from the blood which is required to resynthesize glycogen in the muscle [33]. This would be expected to result in decreased endurance performance in subsequent exercise bouts.

Low muscle glycogen stores induced by a combination of exercise and a diet low in carbohydrate have also been associated with falls in the intramuscular and plasma concentrations of glutamine [34], the amino acid mentioned previously, that is needed by leucocytes in order to enable them to carry out their functions in destroying bacteria and viruses. Thus, exercise-induced muscle damage could be expected to result in decreased athletic performance and make the athlete more prone to infection.

3.2. Pharmacological treatment of muscle soreness

Potential pharmacological treatments for exercise-induced muscle damage have focused on reducing the inflammation, or oedema, consequent to tissue damage. Other strategies including stretching, cold application, ultrasound, transcutaneous electrical nerve stimulation, massage and light exercise have also been tried. Although some success has been reported by a few authors using stretch, ultrasound and transcutaneous electrical nerve stimulation to reduce muscle soreness, the majority of studies indicate that no effective way has yet been found to reduce substantially the soreness once it has occurred. Various pharmacological agents have been administered in order to eliminate or minimize muscle soreness following eccentric exercise-induced muscle damage. Administration of the antioxidant vitamins C and E appears to be completely ineffective in reducing soreness in comparison to a placebo-treated groups [35, 36]. Several non-steroidal anti-inflammatory drugs have also failed to reduce muscle soreness [37-39]. The steroidal anti-inflammatory agent, prednisolone had no effect on soreness scores or serum creatine kinase activity compared with a placebo group in a double-blind cross-over design experiment [40].

Pharmacological treatments that *have* proved to be effective in reducing, though not eliminating muscle soreness, include aspirin taken orally [41] and topically applied analgesic anti-inflammatory creams containing 10% triethanolamine salicylate [42,43]. Phenyl butazone is widely used in race horses to give permanent anti-inflammatory cover to tissue micro-traumas, but this drug can cause fluid retention, gastrointestinal disturbance and peptic ulceration and so should not be used casually [44]. In fact most of the anti-inflammatory preparations in use today cannot be recommended for indiscriminate high dosage or long-term use because of the very real danger of side-effects. The most

common of these, gastrointestinal upset, is aggravated by alcohol, so that athletes celebrating a win or drowning their sorrows in a mixture of anti-inflammatory agents and alcohol, will no doubt come to regret it!

Undoubtedly, the best strategy is prevention by avoiding provocative modes and intensities of exercise that are known to induce muscle damage. Regular exercise reduces the incidence and magnitude of muscle soreness, but occasional excesses remain distressing. While there is a place for eccentric exercise, plyometrics and weight-lifting in the training programmes of many athletes, the frequency and intensity of these exercise modes should be carefully regulated and positively avoided in the weeks leading up to competition. Some individuals are far more prone to muscle soreness and stiffness than others, although there is no evidence to link this to any form of rheumatism or arthritis [44]. A thorough warm-up and slow stretching techniques applied both before and immediately after exercise can minimize subsequent stiffness.

4. SCREENING FOR THE ONSET OF OVERTRAINING

Reliable techniques for the detection of the onset of overtraining have not yet been established [11]. Possible markers are being studied, including blood levels of stress hormones, antibodies, cytokines and glutamine as well as the ability of leucocytes to respond to stimulation by antigens. Measures of these potential markers made in athletes undertaking their normal training and in others whose training loads have been markedly increased, as well as in athletes who are diagnosed to be currently suffering from overtraining syndrome may enable sports scientists to screen athletes for the onset of overtraining. Psychological profiling may also be undertaken to some effect using self-scored profiles of mood states; some scientists believe that the best gauge of overtraining is how the athlete feels: as training advances, athletes tend to develop dose-related mood disturbances with low scores for vigour and rising scores for negative moods such as depression, tension, anger, fatigue and confusion [45]. This may allow the identification of common factors among overtrained subjects in comparison with well trained athletes not suffering from under-performance and could permit appropriate intervention to prevent athletes from progressing to a more serious stage of the overtraining syndrome. Practical markers of overtraining would be ones that could be measured routinely in the laboratory and offered to athletes as part of their sports science and medical support.

5. NUTRITIONAL CONSIDERATIONS

The possible role of glutamine in modifying immune function and the effects of different intensities and durations of exercise on plasma glutamine concentration require further investigation. It is possible that a low level of plasma glutamine could provide a useful marker of the onset of overtraining and dietary glutamine supplementation may improve recovery of leucocyte function from exercise-induced stress and overtraining. Prolonged exercise, fasting, low carbohydrate diets, infection and physical trauma (e.g. surgery) are all associated with falls in the plasma glutamine concentration. After surgery the intravenous infusion of glutamine, corresponding to about 0.2 g glutamine/kg body mass/24 hours, preserves plasma and muscle glutamine concentration and diminishes the post-operative decline in skeletal muscle protein synthesis [46]. Glutamine can also be taken orally and as a 1.5% w/v aqueous solution is almost tasteless. Consumption of such glutamine drinks can raise the plasma glutamine concentration substantially for several hours (Figure 1) and so could be consumed by athletes during or after exercise in order to prevent falls in the plasma glutamine concentration. Adequate dietary intakes of micronutrients are important to preserve immune system status. Deficiencies of Vitamins A, B6 and C or of minerals including zinc and iron are known to be associated with impairment of immunity. However, excessive doses can be harmful. Consumption of a plant extract (*Eleutherococcus senticosus*, ES) has been reported to reduce the incidence of infection, and ES appears to increase the circulating numbers of lymphocytes and NK cells in healthy normal subjects [47]. The mechanism of

action is not yet resolved, but may be due to ES stimulated interferon production or macrophage activity: polysaccharides in ES may act as non-specific immune stimulants. Further well controlled studies are required to establish if ES could be used to bolster the immune system in athletes.

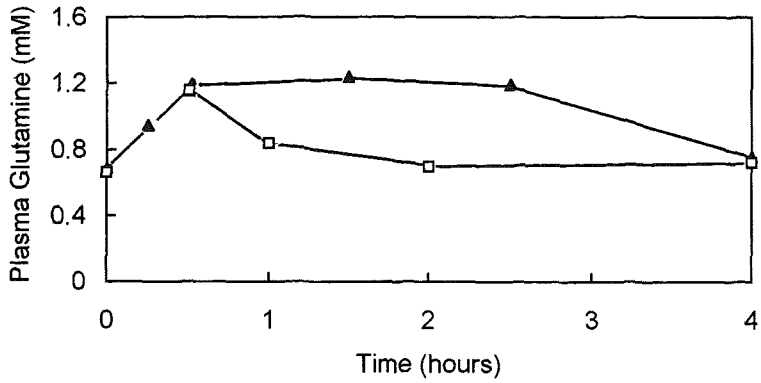

Figure 1. Effect of glutamine drinks (each 0.1 g/kg body weight) on plasma glutamine concentration at rest. □: single drink at Time = 0; ▲: drinks at Time = 0, 1 and 2 hours.

Clearly, athletes fail to perform to the best of their ability if they become infected, stale, sore or malnourished. Eliminating or minimizing these problems by providing advice and guidelines on training loads, recovery times, nutrition or pharmacological intervention based on sound science remains the ultimate goal of sports scientists.

ACKNOWLEDGEMENT

The senior author's work is supported by the Sports Council (UK)

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Discussion: Overtraining, Immunosuppression, Exercise-Induced Muscle Damage and Anti-Inflammatory drugs

A.J.M. Wagenmakers:

We also found that the plasma glutamine concentration is falling for a period of 6-7 hours after endurance exercise. The lowest concentration that we observed is about 450 micromolar. There is no evidence though that such a decrease in plasma glutamine concentration will hamper the immune system of the athlete *in vivo* and creates the so-called open time window of increased susceptibility to colds and infections. There is one *in vitro* study of Newsholme's group in which the proliferation rate of lymphocytes was investigated as a function of the glutamine concentration in the culture medium. At 450 micromolar the proliferation rate was reduced. However, the glutamine concentration was given at the start of the incubation, while the cells were cultured for 24 hours. If you start with 450 micromolar glutamine at zero time incubation, all glutamine theoretically may have disappeared in the next 24 hours and lead to lower proliferation rates than when the incubation is started with 650 micromolar glutamine or higher. This does not mean that the *in vivo* concentration of 450 micromolar is limiting lymphocyte proliferation *in vivo*.

M. Gleeson:

I agree entirely with that comment. Presently, we do not know how low plasma glutamine concentration would have to fall (or for how long) to become detrimental to while blood cell function.

F. Brouns:

In most studies, the changes observed in immune response parameters last only a few hours post-exercise. Can we say that this is representative of an impaired immune function? So far, I have not really seen good evidence that athletes have an increased frequency of illnesses, compared to normal trained people.

M. Gleeson:

There have been anecdotal reports that athletes were suffering recurrent infections, and when they got an infection, that it was hard to shake off or it lasted for longer than would be expected. There are also some epidemiological studies on the incidence of infection in athletes and non-athletes and also in athletes following marathon runs compared to subjects who did not take part in the runs. The general consensus from those is that there is an increased incidence in infection.

F. Brouns:

As far as I have understood, most of this research is based on questionnaires. Generally, athletes are more susceptible to feelings that they have some kind of cold because they may be disturbed by it than non-training people. Additionally, when you get the answer: "yes, I have a cold" there is no real control on this. Who checks that he really has an infected throat, for example? Such controlled data are not present, as far as I know the literature.

M. Gleeson:

No, you are right. There is no real clear cut evidence to say "yes or no". It is just a general feeling amongst athletes and their coaches that they do suffer from these sort of problems.

D.P.M. MacLaren:

Most of the data about glutamine refers to plasma glutamine and we are well aware that the red cell accumulates glutamine. The red cell is, in fact, a carrier of amino acids. Has anyone measured red cell glutamine levels when the plasma concentrations are low? Another question, are there any ergogenic aids other than glutamine that may alleviate immune suppression? I wonder whether by taking high carbohydrates or regular carbohydrates as ergogenic aids during exercise, one could actually attenuate the cortisol response and therefore, alleviate an immune suppression.

M. Gleeson:

Carbohydrates are important not only for the immune system, but for the actual performance of endurance exercise. You would expect that by giving carbohydrate supplementations, you would diminish both the catecholamine and the cortisol response to exercise. So by implication, you might expect that any suppressive effect on the immune system of such glucocorticoids would be diminished. Ways of boosting the immune system in athletes using drugs have not really been looked at in any well-controlled studies, to my knowledge.

P.M. Clarkson:

The studies that show an activation of the immune response with muscle damage usually involve endurance-type exercise like downhill running or cycling. When one uses a model like the one I use that severely damages a local muscle group with non-endurance exercise (using high force eccentric exercise), creatine kinase (CK) can increase to 50,000 IU/l. For endurance-type exercise, if you get CKs of 1,000 IU/l and usually much less. We do not see the types of increases in white blood cells that you see after something like downhill running, yet our damage is much more extensive. Would you want to comment on that?

M. Gleeson:

The increase in circulating numbers of white blood cells that you get in response to exercise is not a response to damage. You get it in exercise that does not produce muscle damage. So the actual increase in the white blood cells -if that is what you define as the activation of the immune system- does not appear to occur with muscle damage. It is related to the intensity and also to the duration of the exercise performed, but not necessarily to whether muscle damage actually occurs or not. There is, of course, a very marked infiltration of damaged muscle by phagocytic neutrophils in the days following a bout of eccentric exercise.

P.M. Clarkson:

Are there any immune factors that you examined that can be tied directly to muscle damage?

M. Gleeson:

One of the things that has been measured in relation to muscle-damaging exercise has been the release of elastase from neutrophils. When it is measured in response to the same relative

intensity of exercise (in terms of the heart rate increase), doing eccentric work compared with concentric work, you get a larger increase in the plasma elastase concentration in the eccentric bouts compared with the concentric bouts. This suggests that there is an increased activation of the neutrophils in addition to the normal effect of exercise which could be mediated through actions of growth hormone, complement activation, or cytokines. When you damage muscle tissue as well, you get an additional activation of neutrophils.

P.M. Clarkson:

I would like to comment that we have done large clinical trials on naproxen as well as ibuprofen. We also found very small effects on alleviating muscle soreness, and this is with high concentrations of these drugs. It is very interesting that none of these drugs work (anti-inflammatory or analgesics) in preventing or reducing substantially the muscle soreness.

T.D. Fahey:

Articles in muscle magazines, often advise weight-athletes to treat specific symptoms of overtraining. For example, phosphatidyl serine is recommended for elevated cortisol and similar recommendation is the use of supplemental glutamine to treat immune disorders. I wonder if we could educate the athletes that these syndromes are much more complicated than treating a specific symptom, and that the ultimate cause of training problems relate to general stress responses.

B. Ekblom:

We do think that when you are moderately trained, you are better off (at least, if you think philosophically) against infections or whatever it is than if you are overtrained or untrained. But what part of the immune system would be called efficient in that respect?

M. Gleeson:

I have not seen any evidence to show that exercise is of any real benefit with immune function compared with being a coach potato.

B. Ekblom:

When we talk about concentrations in blood, it is always the balance between input and output but we seldom consider the possibility of different types of cells acting as stores, as it was mentioned in the case of glutamine.

M. Gleeson:

This is obviously important, in affecting not only substances like glutamine but the white blood cells themselves and what is actually happening to the turnover of those cells as a result of exercise, but, largely, those questions remain unanswered.

A. Miles:

I was just wondering whether there was any data that had looked at the effect of repeated bouts of exercise on glutamine plasma concentrations.

M. Gleeson:

I have no data from these type of studies. Trained individuals who are not overtrained and not suffering from muscle soreness seem to have pretty normal plasma glutamine levels at rest, in samples taken 12 hours or so after their last exercise. And this includes people who do exercise two or three times a day.

D.P.M. MacLaren:

Is there any evidence of an increased number of infections in cyclists from the Tour de France or in those who train to that level? And if there is not, could this be related to their higher carbohydrate intakes?

F. Brouns:

Cyclists are a very tough population and they never quit any race for any problem. They will not talk about their problems, even if they fall down and rip off the skin from their legs or their arms, they continue cycling. What we know though is that, if they are on high carbohydrate diets, they have a better or improved recovery on a day-to-day basis. Those who finish the Tour are generally without any infections. Those who get an infection mostly leave the Tour in silence.