ACUTE EFFECTS OF EXERCISE ON IMMUNITY

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Several studies have shown that exercise has either a positive or a negative effect on immunity. These effects depend on the nature, intensity and duration of exercise[1-3].

Heavy training schedules or endurance competitions such as marathons or long-distance cycling are examples of extreme physical stress and can lead to immunodepression in athletes, which is associated with increased susceptibility to infection especially upper respiratory tract infections (URTI)[3,4].

This risk of illness in response to exercise has been modelled as a 'J-shaped Curve'[5]. This model suggests that individuals engaging in moderate physical activity are at lower risk of illness compared with sedentary individuals. Conversely, excessive volumes of strenuous endurance exercise may suppress immune function, thereby increasing the risk of illness[5-7].

For example, a five-fold increase in risk of infection was observed in the 2 weeks following a competitive ultra-endurance running event[8].

In a study on athletes who took part in the Los Angeles marathon, it was shown that 13% of the participants suffered from infections of the upper airways in the week after the event. In athletes who intended to participate in the marathon but were unable to for reasons other than illness, the incidence of respiratory infections was only 2%[9].

Peters and Bateman[10] studied the incidence of URTI following a running endurance event (distance of 56 km) in 150 randomly selected participants and compared them to 124 age-matched controls. During the 2 weeks after the race, 33.3% of the runners reported symptoms of URTI, compared to 15.3% in the control group.

In addition, it has been revealed that a high weekly training load (>65 km in runners) could lead to more URTI symptoms compared with a lower weekly training distance/load. These initial findings have been confirmed by a number of other studies[11-13].

In general, post-exercise immune function impairment is highest when the exercise is continuous, prolonged (>1.5 hours), of moderate to high intensity (70% to 77% maximum oxygen uptake (VO_2 max)) and performed without food intake[14].

After an excessive amount of prolonged, high-intensity exercise there is a general decrease in immunity for a certain amount of time, termed the 'open window' theory. The open window phase has a variable duration, depending on the studies and the parameters taken into consideration. It may last between 3 and 72 hours. During this open window of immune dysfunction viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical upper airway infection.

THE IMMUNE SYSTEM AND IMMUNO-SUPPRESSION

The mechanisms behind immuno-suppression after an excessive amount of prolonged, high-intensity exercise (>70 to 75% VO_2 max) are complex, multifactorial and include neuro-endocrinological and metabolic factors that affect innate and

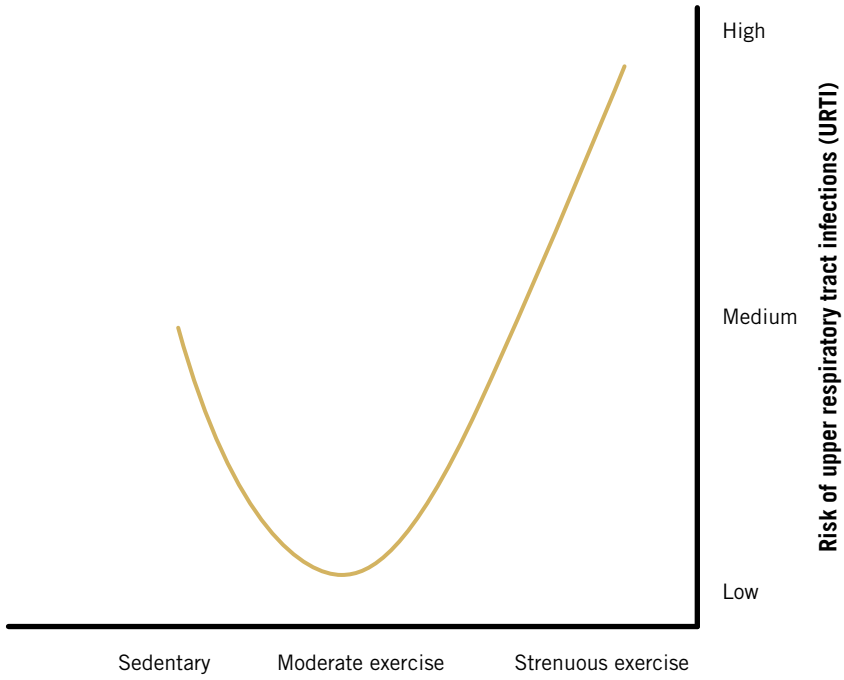

Figure 1: Risk of illness in response to exercise. Strenuous endurance exercise (>70 to 75% VO_2 max) increases the risk of illness. Conversely, moderate physical activity decreases the risk of illness compared with being sedentary.

adaptive immunity. The immune system is the collection of cells, tissues and molecules that protects the body from numerous pathogenic microbes and toxins in our environment. This defense against microbes has been divided into two general types of reactions: reactions of innate immunity and reactions of adaptive immunity.

The innate immune system comprises the cells and mechanisms that defend the host from infection by other organisms. The cells of the innate system recognise and respond to pathogens in a generic way, but unlike the adaptive immune system, it does not confer long-lasting or protective immunity to the host. The innate branch of the immune system includes both soluble factors and cells. Soluble factors include proteins which mediate phagocytosis, control inflammation and interact with antibodies, interferon α/β (which limits viral infection) and anti-microbial peptides which limit bacterial growth. Major cells of the innate immune system include neutrophils which are first line defenders against bacterial infection, dendritic cells which serve to orchestrate immune responses, macrophages which perform important phagocytic, regulatory and antigen presentation functions, and natural killer cells (NK) which recognise altered host cells (e.g. virally infected or transformed).

Acquired immunity (also known as adaptive or specific immunity) is designed to combat infections by preventing colonisation of pathogens and destroying invading micro-organisms. The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B-cells and T-cells are the major types of lymphocytes.

B-cells are small white blood cells whose primary role is to make antibodies – molecules which bind to various types of antigens such as bacteria and viruses and mark them out for destruction by phagocytes and other cells of the immune system.

T-cells attack those cells which have become infected by viruses or which have become cancerous. They can determine whether a cell has been infected and, if so, they instigate a process of self-destruction, thereby killing the viruses inside in the process. A subset of T-cells, called T-helper cells, do not attack infected cells directly, but secrete cytokines which draw other immune cells to the site of the infection. The convergence of immune cells causes the swelling, inflammation and redness we typically associate with a cut or other injury.

Although partitioning the immune system into innate and adaptive systems makes it easier to understand, these branches are in fact inextricably linked with each other. For example, the innate immune system helps to develop specific immune responses through antigen presentation, whereas cells of the adaptive system secrete cytokines that regulate innate immune cell function.

What happens to innate immunity after an excessive amount of prolonged, high-intensity exercise?

An excessive amount of prolonged, high-intensity exercise induces a transient depression of the innate immune system, a decrease of phagocytic activity for many hours, a reduced oxidative burst of granulocytes in particular neutrophils and a reduction in the blood values of monocytes, neutrophils and basophils[15-19].

> ***The risk of illness in response to exercise has been modelled as a 'J-shaped curve'***

It has been acknowledged that phagocytic neutrophils play a critical role in the first line of defence against pathogens. They rapidly migrate to the infection site, ingest the pathogens and release reactive oxygen species to kill the pathogens[20].

Phagocytic neutrophils appear to be activated by an acute bout of exercise, but show a diminished responsiveness to stimulation by bacterial lipopolysaccharides (including reduced oxidative burst and diminished degranulation responses) after exercise, which can last for many hours.

Moreover, there is increased cellular oxidative stress, which is able to stimulate neutrophil apoptosis[21-22]. Apoptosis is a highly regulated and controlled process of programmed cell death, which confers advantages during an organism's lifecycle.

Acute exercise temporarily increases the number of circulating NK cells, but following exercise NK cell counts drop to less than half of normal levels. Normal resting values are usually restored within 24 hours. NK cell cytolytic activity falls after exercise and if the activity is both prolonged and strenuous the decrease in NK cell counts and cytolytic activity may begin during the exercise session[23].

In one recent study, increased URTI incidence during 4 week of intense military training was significantly correlated with decreased numbers of circulating NK cells[24]. Several studies have reported a higher incidence of viral infection after marathon running[25].

Ultra-endurance exercise causes oxidative stress, which can persist for 1 month depending on the specific biomarker examined. These results suggest that ultra-endurance events are associated with a prolonged period of reduced protection against oxidative stress. In particular, ultra-endurance exercise results in the formation of reactive oxygen species[26]. The extent of this production has the potential to overwhelm antioxidant defences, causing oxidative stress. Oxidative stress is associated with damage to proteins, lipids, and DNA and has been causally related to ageing, development of cancer and cardiovascular disease[27]. Exercise may cause protein carbonylation, lipid peroxidation and damage to DNA. It also may cause a reduction in whole-blood growth stimulating hormone (GSH) concentration. All parameters would return to baseline levels within 28 days of the marathon race. GSH is a molecule that is key in cellular redox status regulation. Prolonged GSH depletion may compromise immunity. For example, lower GSH is associated with decreased lymphocyte proliferation and increased viral reactivation[28].

As well as the risks that DNA damage might confer, damage to lymphocytes might inhibit cell-mediated immunity after exercise, which corresponds with reports of increased infection risk after endurance exercise events[29].

What happens to acquired immunity after an excessive amount of prolonged, high-intensity exercise?

It has been demonstrated that there is increased lymphocyte apoptosis after endurance exercise of different duration and intensity such as marathon runs, intensive treadmill running and cycle ergometer exercise. Apoptosis induction was only observed after exceeding a specific intensity of exercise, whereas no effects were demonstrated after moderate or low intensity exercise programmes[30].

When an exercise bout is strenuous and very prolonged (>1.5 hours), the number of

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circulating lymphocytes may be decreased below pre-exercise levels for several hours after exercise[31]. There are several mediators of exercise-induced lymphocyte apoptosis. It has been suggested that a change of extra- or intracellular pH levels regulates apoptosis in different cell types[32]. Intensive exercise is followed by increased lactate production and decreased blood pH, which may affect lymphocyte apoptosis[33]. Furthermore, intensive exercise induces a systemic inflammatory response accompanied by an increase of acute-phase proteins and cytokines.

There are also increases in the plasma concentrations of various substances that are known to influence lymphocytes functions:

- inflammatory cytokines, such as tumour necrosis factor-α, macrophage inflammatory protein-1, and interleukin-1 (IL-1),
- anti-inflammatory cytokines, such as IL-6, IL-10 and IL-1-receptor antagonist (IL-1ra),
- acute phase proteins, such as C-reactive protein.

The large increase in plasma IL-6 concentration observed during exercise can be entirely accounted for by the release of this cytokine from contracting muscle fibres[34]. An important action of IL-6 is the suppression of the production of tumour necrosis factor-α, which is a potent activator of inflammation.

In accordance with elevated IL-6, IL-10, and IL-1ra circulation, strenuous exercise decreases the percentage of T-cells in circulation. As T-cells promote cell-mediated immune responses, which primarily provide protection against viruses, exercise which increases muscle-derived IL-6 may decrease virus protection in the host and thus may account for why athletes appear to be more prone to acquiring URTI.

Following prolonged, strenuous exercise, the production of immunoglobulins by B-lymphocytes is inhibited. Levels of secretory immunoglobulins, such as salivary immunoglobulin A (s-IgA), vary widely between individuals and, although some early studies indicated that s-IgA concentrations are lower in endurance athletes compared with sedentary individuals, the majority of more recent studies indicate that s-IgA levels are generally not lower in athletes compared with non-athletes, except when athletes are engaged in periods of very heavy training[35,36].

Several studies have estimated the impact of long-term training on systemic and mucosal immunity. The results indicated significant depression of resting

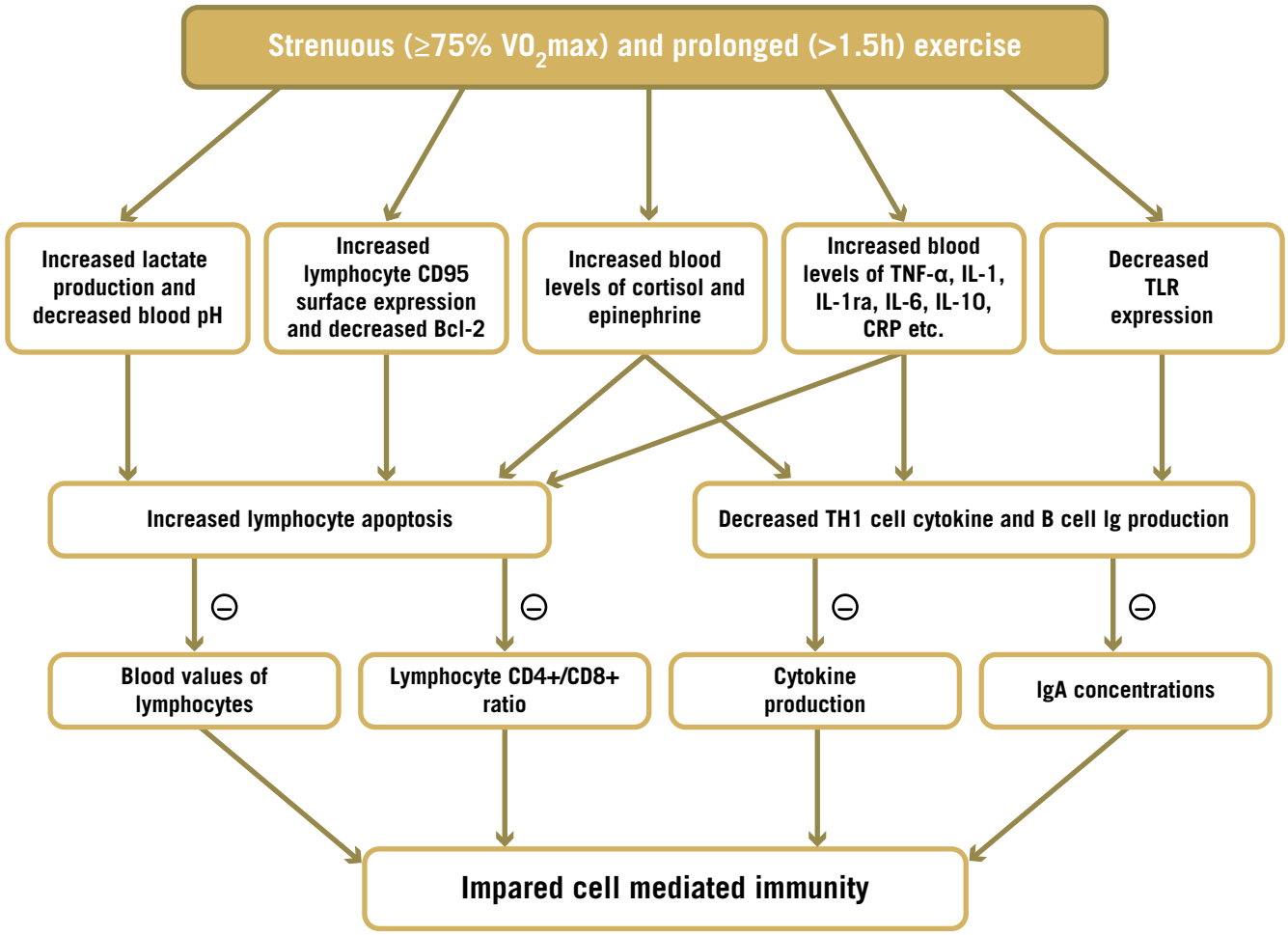

Figure 2: Possible mechanisms by which strenuous exercise impaires cell mediated immunity. CD=cluster of differentiation, Bcl-2=B-cell lymphoma 2, TNF-α=tumour necrosis factor alpha, IL=interleukin, CRP=C-reactive protein, TLR=toll-like receptors, TH1=Type 1 T-helper cells, Ig= immunoglobin.

serum and salivary immunoglobulin concentrations in athletes, associated with long-term training at an intensive level[37-40]. A negative relationship between s-IgA concentration and incidence of URTI has also been reported[41].

In summary, ultra-endurance exercise such as a marathon causes a transient and generalised depression of immune function and impairs the body's defences against infection. Specifically, this condition increases the risk of URTI. In the post-exercise period IgA levels in the mucous membranes of the upper airways decreases as does the serum concentration and activity of T-cells and NK cells.

Immediately after a race, contact with the fans and press or other runners in the changing room, steam in the showers and air conditioned environments all expose the athlete to higher risk of coming into contact with pathogens, in particular viruses. If a virus is able to penetrate into the airways, it comes across a weakened immune system in which the defensive barrier of IgA is impaired and the ability to eliminate virus-infected cells is deficient. This makes it more likely the virus will penetrate the cells of the upper airways, replicate and develop a symptomatic infection.

Although there is no single method that completely eliminates the risk of conracting an infection, there are several effective ways to reduce the number of infectious episodes associated with the open window phase. One possible means to reduce infection risk is to use appropriate immune-nutritional support. Various nutritional agents have been tested for their capacity to attenuate immune changes and inflammation following intensive exercise.

Regular ingestion (0.5 litres/hour) of a 6 to 8% complex carbohydrate (CHO) solution (long-chain maltodextrins) during ultra-durance exercise and ingestion of high glycaemic index CHO solution (1.2g CHO/kg body mass) immediately after prolonged strenuous exercise. Glucose is, in fact, an important fuel substrate for lymphocytes, neutrophils and macrophages. An adequate CHO availability and stable blood glucose concentration may help to attenuate exercise-induced changes of stress hormone levels, leukocyte cell counts and cytokine changes[42,44].

Taking a 700 mg cystine and 280 mg theanine supplement several days before and during prolonged and intensive training can also help to counteract exercise-induced immunosuppression[45]. Cystine is a dipeptide of the sulphur amino acid cysteine, it is a precursor of glutathione – responsible for the anti-oxidative response inside the body – and its supply is limited in the synthesis of glutathione. Theanine is an amino acid abundant in green tea and is known to be metabolised to glutamic acid and ethylamine within the intestinal tract and liver. Oral administration of cysteine and theanine reinforce GSH synthesis and antigen-specific antibody production after antigen stimulation[45].

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Another compound that is essential for the homeostasis of leukocytes and therefore important for the correct functioning of the immune system is vitamin C. It has been proven that doses of vitamin C are able to reduce the incidence and duration of infections (especially respiratory) in ultra-endurance athletes[46]. It appears that the intake of even a low dose (150 to 200mg/day) of vitamin C is important to protect athletes from infectious diseases during the open window phase[47,48].

Echinacea is another compound that has proved to be effective in reducing the incidence and duration of infections of the upper airways in athletes. This is a plant native to North America, whose active principles favour immunostimulant action (confirmed by experimental tests) such as increased phagocytosis and the production of IgA and various interleukins including IL-10, which plays an important role in the regularisation of lymphocyte activation and proliferation. Echinacea also enhances the activity of phagocytes and the cytolytic activity of NK cells[49].

Supplementation with branched chain amino acids, (6 grams/day for 30 days and an additional 3 gram dose 30 minutes before prolonged strenuous exercise) suppresses changes in inflammatory response and prevents a decrease in immune function (e.g. exercise-induced neutrophilia and lymphocytopenia)[50,51].

A glutamine supplement (5 grams of glutamine in 330 ml of water after prolonged strenuous exercise) can also be useful to combat exercise-induced immunosuppression. Glutamine is a major fuel for leukocytes and lymphocytes, and plays an important role in protein synthesis, cytokine production and macrophage function. Prolonged exercise is associated with decreased plasma glutamine concentration and it has been hypothesised that such a substantial drop may lead directly to immunodepression and a higher risk of URTI. It has been reported that a significantly lower incidence of URTI symptoms (32%) occurred in the 7-day period following a marathon-type event in a glutamine-supplemented group of runners compared with a placebo group[52].

Furthemore polyphenol resveratrol, present in grapes and Polygonum cuspidatum (commonly known as Japanese knotweed), has shown to have an effective

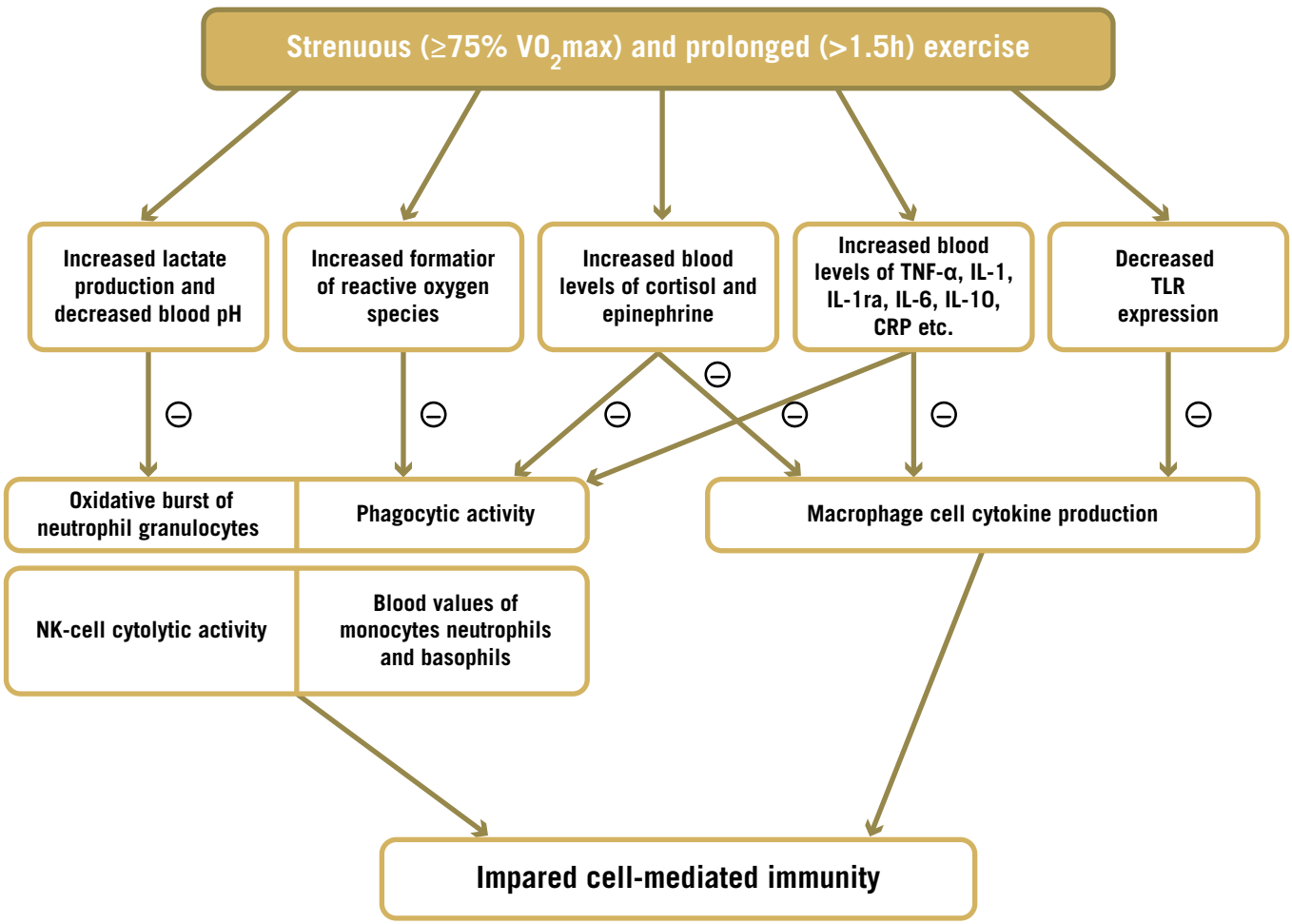

Figure 3: Measures against exercise-induced immuno-depression. Possible mechanisms by which strenuous exercise impaires innate immunity. TNF-α=tumour necrosis factor alpha, IL=interleukin, CRP=C-reactive protein, TLR=toll-like receptors, NK=natural killer.

One possible means to reduce infection risk is to use appropriate immune-nutritional support

anti-inflammatory, antioxidant and immunostimulant action. Several studies have shown a possible antiviral effect of this substance. For example, it has been observed that this compound is able to inhibit the replication of the influenza A virus[53].

Lactoferrin is another compound effective in reducing infectious episodes. It is a glycoprotein with antimicrobial, antioxidant and immunomodulatory properties[54]. The antimicrobial properties of lactoferrin are mainly due to its effect on lipopolysaccharides in the outer layers of the cell membrane of some Gram-negative bacterial species.

Beta-glucans are polysaccharides occurring in the bran of cereal grains (barley and oats and to a much lesser degree rye and wheat about 7%, 5%, 2% and less than 1%, respectively). Beta-glucans can also be found in the cell walls of yeast in bread and many types of fungi. A growing number of discoveries indicate that beta-glucans can improve health, especially beta-1.3-glucans, which improve the body's immune defence system against external pathogens, boosting the ability of macrophages, neutrophils, T-lymphocytes and NK-cells to respond and fight attacks from bacteria, viruses, fungi and parasites[55,56].

Omega-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid, found in oily fish and fish oils, are essential to an athlete's health and are known to be strong anti-inflammatory agents[57]. Despite these characteristics no beneficial effects of fish oil supplement on the immunological response to strenuous exercise have been shown.

Conversely, quercetin supplementation is recommended. Quercetin is a flavonoid widely distributed in nature that has anti-inflammatory, anti-oxidative and anti-pathogenic effects. Quercetin supplementation diminishes inflammation, oxidative stress and illness rates in exercise-stressed athletes with a strengthening of innate immune function. Supplementation with 1mg/day quercetin for 2 weeks before and an additional dose of 1mg/day for 1 week after prolonged strenuous exercise is recommended[58,59].

Furthermore, for prophylaxis of URTI it may be useful to use 7mg of lyophilised bacterial lysate of Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae, Klebsiella pneumoniae ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes and sanguinis, Moraxella (Branhamella) catarrhalis (corresponding to 36 billion bacteria). The regular ingestion of a capsule containing 7mg of lyophilised bacterial lysate for 10 consecutive days every month, for 3 months has proved to be effective in reducing URTI[60].

CONCLUSION

Control of the immune system of athletes has become an important part of the preparation for a competition, which also includes training, recovery, nutrition and psychological support. As interruptions in training due to illness can dramatically influence the preparation and competitive programme of a top-level athlete, a thorough plan of an athlete's preparation, including nutritional intervention, can enhance performance.

Even 'care' of the immune system through the use of food supplements, is fundamental to improve the body's natural defences and thus protect the athlete against infections.

An athlete with an adequate level of immunity is less susceptible to infectious episodes and ultimately more effective.

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