Case Reports and Reviews

Review Article

Viral Infection in Athletes

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Abstract

Most epidemiological and clinical studies suggest that systematic physical activity increases the body's immune capacity against infections. On the contrary, much evidence suggests that prolonged vigorous exercise training favors the development of infections, particularly viral ones. This two-way exercise effect is described as a “paradox” of exercise. Some theories have been developed about these adverse effects of exhaustive exercise on cellular and humoral immunity, such as open window theory, the J-curve, and the S-curve. However, some questions remain regarding the prevalence of these mechanisms, and the level of the exercise that leads to immunosuppression. Other factors favoring the onset of viral infections in athletes are stress, climatic conditions, incorrect nutrition, crowding, etc. The most common infections are viral infections of the upper respiratory tract, influenza, infection from the Epstein Barr virus. There is no information available to correlate the volume of physical stress with COVID-19 infection. The best preventive measures are to avoid exercising during a febrile infection, vaccination, adequate nutrition, and reduce stress..

Introduction

It is well known that moderate, regular physical training causes beneficial effects in health, including, for example, cardiovascular preventive adaptations, metabolic benefits, and possibly an increased immunity, especially to upper respiratory tract infections [1,2]. On the contrary, many reports supported that strenuous endurance exercise is followed by temporary functional immunodepression [2,3]. However, the idea that any kind of strenuous exercise can be assessed as 'immunosuppressive' has recently been challenged, and the theory of an "open window" has been questioned [3-5]. Thus, inquiries such as if athletes are more susceptible to viral infection (mainly of the upper respiratory tract) than the general population, if the exercise alone is sufficient to negatively affect the immunity, and the usefulness of specific biomarkers to evaluate immune health, remain unquestionable. The purpose of this review article is to describe the mechanisms reported so far about the positive and negative effects of competitive exercise on the immune system, to discuss the doubts that arise in the recent literature, and to refer to the most common viral infections in athletes briefly.

Many studies supported that athletes are more vulnerable to infections than non-athletes [6,7]. The most common contamination amongst athletes is the viral upper respiratory tract infection [6]. The reasons behind this are that the athletes frequently live in groups and are in close contact with many others during sports events and competitions. Moreover, they are often forced to train or compete in an environment conducive to the growth of microorganisms and the transmission of infections, e.g., swimming pools and, also, because they have strenuous and prolonged exercise overload, which inhibit the humoral and cellular immunity of athletes [8]. On the contrary, it is well known that mild to moderate physical activity increases the immunity against diseases [1,2]. For example, at least 30 minutes a day of moderate-intensity exercise increases the immunity capacity, while the continuous high volume of training, such as super marathon training or triathlon, increases the sensitivity to infections [4,9]. Improving body defence through exercise rehabilitation also appears to be in patients with chronic diseases with impaired immune function, such as patients with chronic renal failure [10]. This controversial effect of exercise on the immune system has been characterized as an "exercise paradox" [11].

Mechanisms of increased sensibility

Exercise leads to an acute immune response, the degree of which depends on the nature of the exercise. This response is directly related to the neurohormonal and metabolic responses that co-occur [3]. These moderate exercise responses lead to protective effects for health, but in intense exercise can lead to harmful results. However, the red line that separates the beneficial from the harmful level of exercise for immune health has not yet been quantified. Various theories were developed on the impact of physical activity on the body's defence, such as the J-curve, the "open window" theory, and the S-curve [2,12]. Most observations led to the "open window" hypothesis (Figure 1), which is a decrease in the protection of the immune system for some time after intense the following days [12,13]. Some controvert the existence of this mechanism

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during exercise. However, the information provided for denial of the "open window" concept is not yet adequately cogent [4,5]. Also, it was supported that the relationship between upper respiratory tract infections and exercise intensity and duration is "J" shaped (Figure. 2), with a higher risk of infections in high-level athletes [5,13]. However, many questions remain about this immunity-exercise relationship, especially when the athlete exercising over weeks and months [4,14]. Campbell et al. [5] suggested that other factors such as circadian rhythm, metabolic and endocrine changes could, in principle, affect aspects of immune function. The main mechanisms that supported the reduction of immune capacity during or after exercise are: (a) the acute effect of vigorous exercise transiently lowers IgA immunoglobulin levels in salivary glands, and therefore increases the risk for an upper respiratory tract infection, and (b) after strenuous exercise, a decrease in peripheral blood defence cells (leukocytes and especially lymphocytes) is observed, leading to a period of immunosuppression [15-17]. Nieman et al. [17], supported that acute exercise (moderate-to-vigorous intensity, less than 60 min) is a severe immune system adjuvant to enhance recirculation of immunoglobulins, anti-inflammatory cytokines, and immune cells between the circulation and tissues.

On the contrary, in strenuous competitive exercise, in combination with the physiological, metabolic, and psychological stress, transient immune changes, inflammation, oxidative stress, muscle damage, and increased illness risk were found [17]. Heavy exercise influences immune function mainly via activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Extreme body workload increases immunoregulatory hormones, like epinephrine, norepinephrine, cortisol, beta-endorphin, and ACTH and changes the leucocyte subpopulations [11,16]. It was found that after an exhaustive workout, the production of pro-inflammatory and anti-inflammatory cytokines increases sharply [11,17]. It is unknown whether increased production of oxidants during exhausting athletic activity, as seen by the production of free oxidizing radicals, e.g., production of ROS, also predisposes to infections [18]. There is also insufficient evidence whether the administration of antioxidants is required. It was suggested that prophylactic administration of antioxidants not only prevents similar situations but may also adversely affect performance since oxidative processes are, to some extent, part of the body's normal metabolic functions in exercise [19]. Most studies refer to immune disorders in endurance athletes (marathon, skiing, cycling), while there is no corresponding information for intense strength training sports. Even though many studies refer to the beneficial results of moderate exercise in the body's defenses, especially against upper respiratory viral infections, there are no clear views in the literature on the corresponding chronic effect of participation in intense sports activities. Prominent risk factors are described for virus infections such as exercise training in the winter, overtraining syndrome, lack of sleep, long-haul travel and jet lag, inappropriate diet, high levels of psychological stress, anxiety, and depression [3,4].

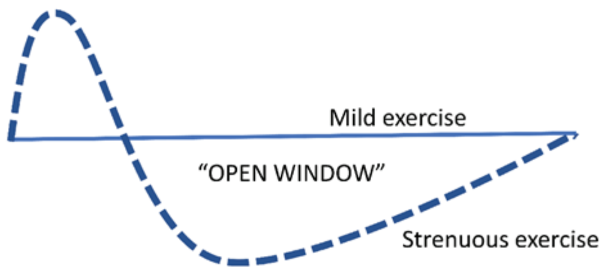

Figure 1. *Design of the "open window" theory.*

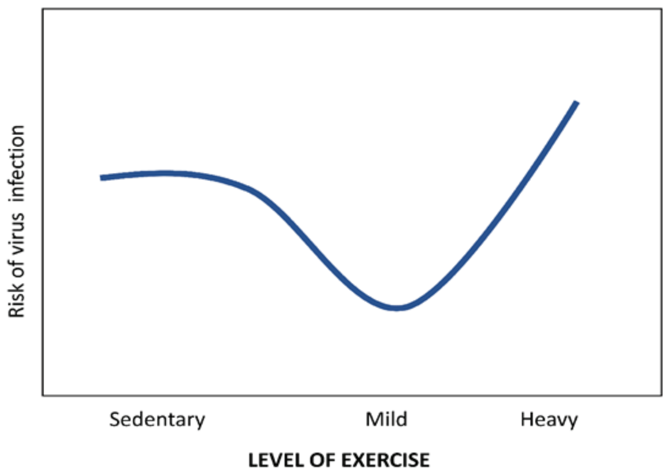

Figure 2. *The j-shaped model of relationship between the exercise level and the risk of virus infection.*

The effects of exercise on cellular immunity

Moderate-intensity exercise improves the immune response of peoples [1,2]. Increases in the neutrophils, lymphocytes, and the activity of natural killer cells (NK) after moderate exercise have been reported [17,20]. In contrast, a high- intensity or prolonged acute exercise seems to have the opposite effect on the cellular immune response [3,17,20]. A biphasic change of lymphocytes in a strenuous exercise has been described [21]. At the peak of the effort, a significant decrease in the frequency of lymphocytes in the bloodstream was found. This change was maintained 1-2 h post-exercise; then, lymphocyte returns to pre-exercise levels within 24 h.

Nevertheless, unclear views remain regarding the changes of cytotoxicity and cytolytic activity of NK cells during different modes of exercise [17,20]. Exhaustive exercise training leads to a slight decrease in naïve T cells and an increase in memory T cells [5,22]. Maybe that due to the re-activation of latent viruses and operated by exercise-induced adrenergic activity, oxidative stress, and inflammatory cytokines. Campbell et al. [5] reported a reduction in the frequency and function of lymphocytes (and other immune cells) in peripheral blood following vigorous exercise; however, they suggested that these changes did not reflect proper immune suppression. Others supported that the systematic physical activity may be prevented or delay the immunological 'aging' by limiting the accumulation of CD4+and CD8+ antigen-experienced memory T cell clones and proliferating blood with antigen-inexperienced naïve T cells [23,24]. Phagocytosis also improves with moderate-intensity exercise and decreases with high-intensity exercise [25].

The effects of exercise on humoral immunity

Less information is available on acute and chronic intense exercise on the humoral aspect of immunity. Some authors argue that there are no changes in immunoglobulin and supplement levels [4,5]. Some others, however, observed after prolonged exercise a transient decrease in IgA and IgM immunoglobulins [15]. Nieman et al. [26] supported that ultramarathon running may lead to higher and longer-lasting reductions in serum immunoglobulin levels than following the exercise of shorter duration. It seems that strenuous exercise training causes a decrease in the salivary IgA levels and an increased susceptibility to upper respiratory tract infection [17,27]. Tomasi et al. [9] reported that IgA was reduced by 20% after 2-3 h of cross-country skiing. Mackinnon et al. [15] supported that these changes were transient: salivary IgA concentrations decreased immediately after two hours of intensive cycling but returned to normal levels within 24 h. Strenuous exercise increases the production of several pro-and anti-inflammatory cytokines (IL-6, IL-8, IL-11), endogenous cytokine inhibitors, and chemokines [3,13]. On the contrary, a slight decrease in interleukins after moderate exercise was reported [28,29]. It appears that the environment can affect some hormone levels and the humoral aspect of immunity [30].

The clinical meaning of virus infections in athletes

The clinical meaning of virus infections, specifically the upper respiratory tract infections, which affect young, healthy athletes, remains questionable. In most common infections, such as upper respiratory tract infection, influenza, and, more recently, the coronavirus epidemic, the course of the disease in young, healthy athletes is mild, without complications. On the other side, there are case reports of death in young athletes after or during vigorous exercise in the course of their acute viral illness [31]. Recently, unpublished data (from Outlook magazine) showed a list of athletes engaged in different sports who died from the coronavirus. In a study of 78 sudden deaths during or immediately after vigorous exercise, Jokl et al. [32] reported five sudden death in athletes with a history of recent upper respiratory tract infection. Cases of myocarditis and or pericarditis, leading to arrhythmias or sudden death after Coxsackie virus infections in young people, and especially athletes, have also been reported [33]. It was supported that athletes who stress themselves with exhaustive physical activity during viral upper respiratory tract infections have an increased risk of developing cardiomyopathy, causing irreversible heart failure [34]. In general, during international competition events has been reported that 2%-18% of elite athletes involvement with infection episodes, with more frequent infections of females and those who participate in endurance sports [17]. During a common cold infection, the person may be exercising.

Nevertheless, the decrease in exercise performance after a viral upper respiratory tract infection can last 2-4 days [17,35]. On the contrary, during the febrile period of an infection and a few days after, exercise should be interrupted [22]. It is claimed that following a viral infection, returning to the playing field should only be allowed as many days as the fever has been maintained. Intense exercise during a virus infection can worsen symptoms or cause the recurrence of the infection or even the appearance of complications in the various systems [22,34]. So, athletes should avoid stress during the febrile phase of an acute viral infection. The International Olympic Committee has established rules to protect the health of athletes against infections and their complications related to hygiene, cessation of exercise, and return to training [36].

Interestingly, few shreds of evidence support that regular intermittent exposures to environmental stress (as intermittent hypoxia training) lead to enhanced immune function [37]. Most sports medicine doctors strongly recommended the application of vaccination in athletes, which, if correctly managed, constitute a powerful, costly and long-lasting tool [38,39]. Sometimes a respiratory infection is diagnosed without being accompanied by safe laboratory findings. In many of these cases, especially if the symptoms persist for a long time, a differential diagnosis from other conditions such as bronchial asthma or sinusitis should be made. Also, extra-competitive factors such as over-flying flights, climatic conditions, sleep disruption, altered diet, dehydration, and psychological stress may be associated with immune disorders than the exercise itself [3,5]. There is a link between malnutrition in carbohydrates and proteins with the manifestation of immune dysfunction [40,41]. Carbohydrate reinforcement during prolonged exercise, chicken or bovine soup intake, judicious use of antioxidants, adequate iron intake, probiotics, zinc, and vitamin intake A, D, E, B6, and B12 are essential for maintaining immune function [40,42].

Common viral infections

Common and febrile cold

Rhinovirus is the most common cause of common colds. It is transmitted either by inhalation of droplets or by contact with contaminated objects. Peters and Bateman [43] were found that one-third of 150 runners participating in the 1982 Two Oceans 56 km ultramarathon in Cape Town, South Africa, appeared upper respiratory tract infections in contrast with the control non-trained group, who reported only half the number of episodes. Engebretsen et al. [44] reported that 7% of the athletes who participated in the London Summer Olympic Games 2012 became ill. Of these, 41% developed an upper respiratory acute infection. Women suffered 60% more illnesses than men. Moreover, it was reported that approximately 7-10% of athletes competing in the London 2012 Paralympic Games report symptoms of viral infections during the competition weeks [45]. On the contrary, other epidemiological studies supported that the frequency of upper respiratory tract illness in sports activity communities was similar to the general population annually [4]. The limitation of the respective studies is since most diagnoses are based on questionable symptoms and not on laboratory findings [5].

Flu

The respiratory droplets easily transmit the influenza virus. In addition to timely vaccination with one of the available vaccines, which cover 80% of known viruses, prophylaxis is required in the event of epidemics: (a) avoidance to contact with a large number of people (b) avoidance of excessive physical stress and (c) adequate nutrition, good hydration and rest (46). In Italy, the seasonal influenza vaccine was actively offered in 75% of Serie A teams during the season 2015-2016 with a median coverage rate of 40% (47). In case of infection, it is recommended to lie down after the first symptoms appear and avoid exercise until healing, as in severe cases, it can cause severe complications.

Coxsackie infection

Coxsackieviruses are RNA viruses that may cause disease of muscles, lungs, and heart. Cardiac injuries (myocarditis, pericarditis) and fatal cases of cardiomyopathy were reported following Coxsackie infections [33,34,48]. In uncomplicated cases of virus myocarditis with normal left ventricular function during the acute phase and absence of late gadolinium enhancement, eligibility for sports could confirm three months following total clinical recovery [48]. However, suppose persistent pathological findings are remained, even after six months. In that case, recreational activities can only be recommended based on the course of the disease, left ventricular function, arrhythmias, a pattern of late gadolinium enhancement in cardiovascular magnetic resonance and cardiac computed tomography, because the risk for sudden cardiac death remains increased [33]. For all athletes, a follow-up examination should be performed yearly to determine of the intensity and volume of exercise performed during training and competition.

Chickenpox

Chickenpox is a highly contagious virus. It is transmitted by droplets of the athlete who is ill or by objects that have been recently infected. The athlete should stay at home for about two weeks, during which any exercise is prohibited. Chickenpox virus in childhood and adolescence may remain latent in the body and activate at an early age by various stimuli to produce herpes zoster [49]. The characteristic of the zoster is the appearance of pain and rash in a specific area of the body, usually a zoster area. Specific types of zoster are ophthalmic, genital, generalized, etc. A vaccine containing attenuated live chickenpox virus is available.

Mumps

Droplets mainly transmitted it. The swelling of the glands is the characteristic of the infection. Transmission occurs six days before and six days after the appearance of the parotid swelling; the athlete must be isolated for this period. During active infection, sports activity should be avoided [50]. Teenage athletes may develop complications from the genital system (orchitis), which can lead to neutering. Immunization with mumps vaccine has substantially reduced the incidence of an athlete's disease. The measles-rubella-mumps (M.M.R.) triple vaccine is available, containing live attenuated viruses and provides long-term protection against all three infectious diseases.

Infectious mononucleosis (Mono)

It is caused by the Epstein Barr virus, which mainly affects young people aged 15-30 years. It is usually transmitted by saliva, by direct contact (droplets, sexual intercourse). Hoffmann et al. [51] were reported lower EBV-specific IgG titers in winter sports athletes compared to controls. Therefore, they suggested a weaker immune function in competitive athletes regarding EBV infection. On the contrary, Blume et al. [13] did not find any direct relationship between training loads, clinical complaints, and EBV-specific immune responses in athletes. Athletes should avoid any physical activity for the first 21 days after the start of the symptoms. Then, slow, gradual re-activation is recommended, starting with low aerobic exercise and increasing the intensity or duration burden by 10% per week. The most severe complication of infectious mononucleosis in athletes is potential splenic rupture [52]. The return of the athlete to competitive sports is allowed after 2-3 months of infection. However, in some cases may be longer, especially when the spleen enlargement remains.

Viral hepatitis

The disease is characterized by inflammation of the liver due to the viruses A, B, C, D, E, F, and G. Vaccination is recommended for athletes competing in countries endemic by hepatitis A. In contrast, the hepatitis B virus (DNA virus) is not transmitted by food, water, toilets, or social contact, but mainly by blood and sexual intercourse. Vaccination against hepatitis B (single or multiple vaccines), which is effective and safe, is recommended to prevent the disease. Resting during the acute phase of the disease is recommended for at least 30-45 days. Any sports activity should be stopped immediately. The return to the daily mild physical activity of the individual is progressive over the next 20-30 days [53]. In most cases of viral hepatitis, complete healing is completed within 6-12 weeks. Complete re-activation of the athlete is usually performed after three months of being clinically healthy [36,54]. Early repetition of athletic activities can cause recurrence of hepatic impairment and may favour the development of the disease in chronic hepatitis [53]. Serum (g-globin) administration is recommended as a precaution for athletes or individuals in the patient's immediate surroundings [55].

Acquired Immunodeficiency Syndrome (A.I.D.S.)

This syndrome is caused by infection with HIV or other related viruses. Patients with HIV and AIDS without severe complications encourage moderate aerobic and resistance exercise training programs [56]. Physical activity has beneficial effects on cardiorespiratory efficiency, increases muscle strength, and improves mood state, and quality of life. There are not adverse effects on disease progression. There are recommendations for the prevention of this syndrome on athletes during sports activities [57].

Coronavirus disease 19 (COVID-19)

It is an infectious disease caused by a severe acute respiratory syndrome coronavirus (2019-nCoV2). COVID-19 is transmitted in the same way as the seasonal flu and common cold by droplets from sneezing and coughing [58]. The usual symptoms of COVID-19 are fever, dry cough, and tiredness [59]. In children and young peoples, the symptoms begin gradually and usually are mild. Most people infected have mild symptoms and recover quickly. However, those with pre-existing health disorders or the elderly are most at risk of severe infection [60]. Also, COVID-19 infection has numerous direct and indirect effects on the heart, even in healthy athletes. A common COVID-19 myocardial injury is viral induced non-ischemic myocarditis, resulting in cardiac dysfunction, arrhythmias, and even death [61].

Mild-moderate exercise in healthy individuals is allowed during pandemics, as it offers undoubted benefits to physical and mental health and increases the body's defence against infections [62]. There is no data about the correlation between strenuous and prolonged physical activity and increased susceptibility to infection with coronavirus. However, recent articles reported the contribution of physical activity to mitigating the severe inflammatory response mediated by SARS-CoV-2 [63,64]. Hygiene rules should be followed very carefully. The athletes in competitive sports should follow unique protocols [65,66]. Phelan et al. [67] present a return-to-play algorithm for competitive athletes and highly active people. In COVID-19 negative athletes and in asymptomatic, no restriction need. In COVID-19 positive, uncomplicated athletes, after an initial period of rest during the active infection and for two weeks after symptom resolution, a slow resumption to activity, under the health care team's guidance, is allowed. In those with demonstrated evidence of myocardial involvement, extensive evaluation including biomarker testing, echocardiography, stress testing, rhythm monitoring, cardiac magnetic resonance imaging may be needed [67].

Conclusion

RIn conclusion, exhaustive exercise seems to result in humoral and cellular immunosuppression, while mild aerobic exercise induces immune-stimulation. However, there are not adequate evidence to support an immuno-suppressive effect of any high-level exercise type. Thus, further research is required to describe the immunological effects of different modes of endurance exercise training, as well as of heavy strength training. More studies should also need to clarify the red line that develops in the mechanisms of immunity between moderate exercise, that leads to protective health benefits in an individual, and intense exercise with which a competitive athlete train. Moreover, the interactions between exercise, nutrition, and immune function needs to be explored more clearly. In addition, insufficient information exists about the value of certain biomarkers to monitor immune health during or after exercise. The future of exercise immunology will focus on the wider use of techniques such as mass spectrometry and genetic testing technology, and in the microbiome field. Most viral infections in athletes, especially of the upper respiratory tract, do not cause complications. Nevertheless, when exercise occurs during the period of the febrile period of the infection or soon after this, it worsens immune function. Finally, in case of large-scale viral epidemic, athletes should be followed specific protocols carefully for the risk of contagion.

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