Excessive Exercise and Immunity: The J-Shaped Curve

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Abstract

Exercise modulates the innate and specific arms of the immune system with a marked intensity-dependent response. This response might be influenced by sex differences and other factors including age, nutrition status, and overall level of psychological stress.

Exercise immunology is the field that studies this area. In the 1990s, Dr. Nieman formulated the controversial "J-shaped hypothesis" to describe the relationship between exercise intensity and the risk of acquiring upper respiratory tract infections (URTI). This hypothesis suggests that moderate exercise has the ability to improve immune function above sedentary levels while high intensity exercise depresses the immune system. However, some methodological problems exist in studies of the J-curve which makes evidence more anecdotal than evidence-based regarding the role of moderate and intense exercise in the incidence of URTI. These limitations are presented in the chapter.

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24.1 Learning Objectives

After completing this chapter you should be able to:

1. Understand the J-Shaped curve model.
2. Describe the effects of moderate and intense exercise on immune system.
3. Understand the possible mechanisms of exercise-induced change in immunosurveillance.
4. Distinguish most important sex differences in the immune system.

5. Describe the effects of some dietary supplements on the immune system function.
6. Realize the limitations in this research field.
7. Know the expertise recommendations to perform exercise training during and after upper respiratory tract infection (URTI).

24.2 Introduction

Exercise modulates the innate and specific arms of the immune system with a marked intensity-dependent response that might be influenced by sex differences [1] and other factors including age, nutrition status, and overall level of psychological stress.

Exercise immunology is the field that studies this area. This is a brand new scientific discipline that has experienced increased growth in the last decade with more than 80 % of articles published from 1990 onward [2]. One of the factors underlying the fast growth of this discipline is the commonly held belief that the frequency of URTIs is high in elite athletes after a single bout and/or during periods of intense training [3, 4]. On the other hand, URTIs, usually described as the common cold, are the most frequent occurring illness among humans worldwide. More than 200 viruses cause URTI with influenza, rhinovirus, and coronaviruses being the most common [5].

Despite preventive efforts, influenza epidemics are responsible for substantial morbidity and mortality every year in the United States. A huge economic burden, as described by Molinari et al., includes outpatient visits, hospitalization, and mortality, as well as time lost from work; indeed, estimated costs are $87.1 billion annually [6].

The first epidemiological study in the 1980s documented a twofold to sixfold increase in the risk of developing respiratory symptoms by participants in a marathon [3, 7]. This observational study motivated Nieman in the 1990s to formulate the controversial "J-shaped hypothesis" to describe the relationship between exercise and URTI. The term J-curve is used in several fields, which, in our case, describes the relationship between exercise intensity and susceptibility to infections [8, 9]. This hypothesis suggests that moderate exercise has the ability to improve immune function above seden-
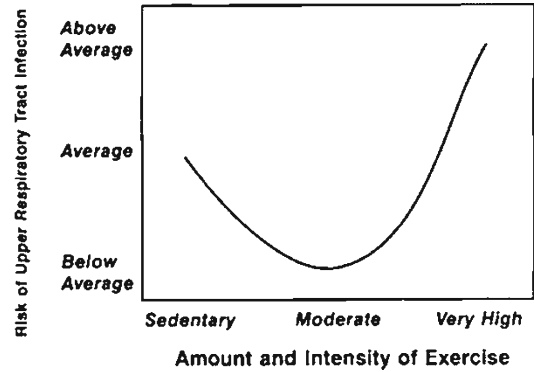

Fig. 24.1 "J"-shaped model of relationship between varying amount of exercise and risk of URTI. This model suggests that moderate exercise may lower risk of respiratory infection, while excessive amounts may increase the risk. Reproduced from Nieman D.C: Exercise, infection and immunity. International Journal of Sports Medicine 1994 15: S131–S141, with kind permission of Georg Thieme Verlag

tary levels while high intensity exercise depresses the immune system [4, 10, 11] (Fig. 24.1).

Intense exercise-induced immunodepression has a multifactorial origin. This includes (1) increased number of neutrophils with decreased number of lymphocytes in the blood; (2) impaired phagocytosis and neutrophil function; (3) decreased oxidative burst activity; (4) decreased natural killer cell cytolytic activity (NKCA); and (5) diminished immunoglobulin levels [8]. However, none of these functions reflect immune function as whole, and the immune system has multiple functions to protect the human body against pathogens. Therefore, measurements of blood leukocyte subtypes (e.g., Europhiles, lymphocytes) by number and function (e.g., natural killer cell activity) may not reflect the immunocompetence as a whole. Also, the host immune system is sensitive to many factors such as age, gender, nutrition state, and stress; consequently, it is difficult to predict the overall effects of small to moderate changes on immune parameters on host resistance. For this reason, the incidence of URTI is the most useful outcome from a clinical point of view [8].

Some methodological problems exist in studies of the J-curve, which makes evidence more anecdotal than evidence-based as to the role of moderate and intense exercise in the incidence of URTI [4]. A recent systematic review conducted

by Moreira et al. identified 162 relevant publications using the key search terms of URTIs and exercise. From these, only 30 were categorized as high quality observational studies that used the Newcastle-Otawa scale "star system," and studies using multiple doses of exercise are limited. As a result, the "J" curve hypothesis has been built based on a combination of results from observational and case series surveys [8]. Herein lies the controversy of this hypothesis.

24.3 Research Findings

24.3.1 Moderate Exercise and Risk of URTI

The evidence suggests that moderate regular exercise may be beneficial to diminish the risk of URTI. However, research in this field is scarce compared to the evidence documented regarding heavy exercise and URTI [8]. When the "J-shaped curve" hypothesis was first proposed, little had been published about moderate exercise-induced alteration in immune system. Activity in this field has emerged in recent years in response to an increasing interest to find factors that may lessen influenza's incidence and severity and/or improve influenza's vaccine efficacy [12].

Most epidemiological studies support the notion that moderate levels of physical activity reduce URTI incidence [13]. However, important methodological limitations have been described and will be discussed later in this chapter.

A study performed in mice by Lowder et al. showed a protective effect of moderate treadmill exercise at 65–70 % of their maximal oxygen uptake (VO_{2max}) in mice who exercised 3 days after influenza virus inoculation yet before the onset of flu symptoms. Meanwhile, prolonged exercise (2.5 h) led to increased morbidity and decreased survival, and moderate exercise significantly decreased mortality rates, even when compared with sedentary controls; specifically, 83 % survived in moderate when compared with 43 % survived in the control group [12].

The American Colleague of Sport Medicine's (ACSM) physical activity guidelines for healthy adults recommend that most adults should engage in moderate-intensity cardiorespiratory exercise training for ≥30 min/day on ≥5 day/week for a total of ≥150 min/week (see Chap. 20). The effects of a moderate bout of 30 min brisk walking on the immune system function were investigated by Nieman et al., in healthy non-obese women. Results showed that walking between 60 and 65 % of VO_{2max} compared with the same participant sitting as a non-exercise control induced discrete and short-lived increases primarily in Natural Killer cells (NK) and neutrophils [14].

Mitogen-induced leukocyte proliferation has been observed immediately after walking due to an increase in serum T cells. Furthermore, IL-6 cytokine showed a small yet significant increase, while cortisol levels, salivary IgA or plasma IL-1ra concentration remained unchanged. These changes are inconsistent with those reported during prolonged and intensive exertion such as large increases in leukocyte, neutrophil and monocytes counts, plasma cortisol concentration, plasma IL-6 and IL-1ra concentration, and extensive postexercise decline in IgA secretion rate, NK count and activity, and mitogen-induced lymphocyte proliferation [14, 15]. Several findings support the stance that moderate exercise induces favorable changes in immunosurveillance [16–21], yet the mechanisms underlying exercise reduced URTI risk have not been fully identified [14, 22]. One study revealed that lung macrophages play an important role in mediating the beneficial effects of moderate exercise on susceptibility to respiratory infections. Specifically, mice were assigned to one of four groups: exercise and resting control with and without clodronate encapsulated liposomes (CL_2MDP-lip) (a substance used to deplete tissue macrophages). The results showed that regular moderate exercise decreased morbidity by 36 %, mortality by 61 %, and symptom severity score. Davies et al., however, demonstrated in another study with mice that alveolar macrophage antiviral resistance is suppressed after exercise until fatigue, and also after 30 min of a single bout of exercise. Mice were virus inoculated after the exercise session with suppression after 30 min of

exercise lasting for 3 h, and then resolved after 8 h. Increased mortality rate was only observed in mice that exercised to the point of fatigue. At first glance, these in vitro results may appear to contradict findings of Murphy et al., yet the different results could be explained by differences in immune system regulation between a single acute bout of moderate exercise and a regular moderate bout of moderate exercise performed at least 6 days before inoculation.

Data from animal studies have been difficult to apply to human participants, but, in general, are consistent with the finding that heavy exercise bouts after virus inoculation may lead to high morbidity and mortality rates [12, 22–24]. Nevertheless, data in this area are still insufficient [24].

In a large epidemiological study conducted in 641 healthy nonathlete adults, moderate exercise was found to decrease the risk of URTI in 20–30 %—especially during the summer and fall. Unfortunately, the use of self-report methods to assess URTI and physical activity, as well as the absence of a formally validated tool to assess URTI, limits the reliability of these findings [13]. Additionally, no differences were reported between exercise and sedentary control groups in an intervention study where 50 moderate fit young adults reported severity and duration of Rhinovirus. Specifically, the exercise group trained 10 days at 70 % of heart rate reserve during 40 min sessions, beginning the first day of virus inoculation. This well-designed control intervention study did not find any difference in the self-reported outcomes of severity and duration of the virus infection between exercise and sedentary control participants [25]. These results indicate that exercise may be safe during virus infection if the exercise is performed at moderate intensity.

Additionally, several case–control studies regarding the chronic effect of exercise training performed in elderly participants have been conducted. Specifically, comparison between active and sedentary subjects showed that the latter have a greater risk of developing URTIs [8]. These findings suggest that moderate regular exercise may protect the host against URTIs.

24.3.2 Exhaustive Exercise and Risk of URTI

Epidemiological research suggests that athletes engaged in strenuous exercise (e.g., a marathon) or an intense training period, such as near a competition, are at greater risk of URTI. After prolonged or intensive exercise bouts, many components of the immune system reflect physiological stress and immunodepression. This period commonly lasts 3–72 h, and commonly is known as the "Open window."

Nieman, a recognized researcher in the field, conducted an epidemiologic survey-based study of Los Angeles Marathon (LAM) participants to investigate the relationship between self-reported infectious episodes, previous training performed, and the intensity at which the race was run. Results showed that runners under heavy training—defined as more than 97 km/week—may be at double risk of infectious episodes compared with those who trained equal to or less than 32 km/week. Also, runners who participated in the LAM race experienced a greater incidence of URTI compared to runners who did not run in the race [26]. These data suggest that other than exercise intensity, cumulative training affects URTI risk. This is consistent with findings from other studies [27, 28].

A recent epidemiological study conducted by Ekblom et al., did not show any relationship between training volume 6 months previous to the Stockholm Marathon in Sweden and the increase to acquire an infection in the weeks following this competition [27]. Specifically, the rate of URTI was 16 % before the competition, which remained stable 3 weeks afterwards in the runners without URTI symptoms before competition. The researchers did suggest that exercise stress may play an important role in virus reactivation for those participants who had a virus 3 weeks before competition; this is because they showed a 33 % risk of URTI following competition [27]. Also, faster finishing time in relation to prerace fitness seems to be a risk factor, especially in younger runners.

Cross-sectional study compared immune function and infections rates in nonathletic females vs. female's elite rowers [29]. Findings showed

significantly higher phytohemagglutinin-induced lymphocyte proliferation and NKCA in the elite rowers. However, the numbers of days with URTI symptoms during the spring season did not differ between both groups [29]. Also, another study of 12 national-level swimmers under intense exercise training showed that neutrophil oxidative activity was significantly lower compared to sex-matched sedentary participants. Nevertheless, URTI rates did not show differences between the swimmers and the control group [30]. In sum, findings are not consistent in this area. Indeed, Moreira et al. suggest that the risk of URTI may be dependent upon each participant and not solely on exercise intensity [8].

The results do suggest that although exercise induces changes in immune functions, these not always are associated with risk of URTI [30, 31].

24.3.3 Effects of Exercise on Innate Immune Cell Count and Function

This section will focus primarily on the influence of acute exercise on cellular components of innate immunity due to regular exercise training, which does not appear to alter peripheral blood leukocyte counts [4]. General information as to the influence of chronic exercise also will be discussed.

Leukocytosis (increase in leukocyte number) in peripheral blood is noticed during an exercise bout. Leukocytosis depends on exercise type, intensity, duration, and is attenuated by exercise training [4, 11]. Exercise up to 30 min leads to an increased leukocyte cell count, which then returns to baseline levels within 10–30 min after exercise. This period of leukocyte level returning to baseline may be longer if exercise duration is longer [1]. Researchers originally attributed this leukocytosis to hemoconcentration. Nonetheless, this theory was rejected because the fluid loss from plasma during exercise does not fully explain the large increase in peripheral blood leukocytes, which may be more than double at maximal aerobic exercise [32]. A biphasic response characterized this leukocytosis. A redistribution

of leukocytes from marginal pools has been proposed to explain this sharp increase that occurs in the first phase. At least two factors have been postulated to be responsible for this redistribution: (1) the increase in cardiac output that induces a greater mechanical force that drags leukocytes from blood vessels walls; and (2) catecholamine release that might be responsible for a down regulation of leukocytes and/or endothelial cells adherence capacity [4, 11, 32]. However the second increment also called "delay leukocytosis" is present only in extensive aerobic exercise (>1 h) and 2–4 h after a short bout of exercise. This occurs almost exclusively due to an increased number of neutrophils that are released from bone marrow [11]. This increase in neutrophils, moreover, likely is mediated by an increase in granulocyte colony stimulating factor (G-CSF) rather than from epinephrine or cardiac output [1]. Previous studies in which cortisol was infused in healthy participants demonstrate that increments in cortisol plasma levels seem to be responsible for the delayed leukocytosis. Therefore, recent evidence shows that short bouts of intense exercise may cause this delay in the release of neutrophils from the bone marrow [11, 33]. Exercise intensity of less than 50 % of VO_{2max} does not elevate plasma cortisol levels.

Monocytes and macrophages cells seem to be affected by patterns similar to neutrophils. Indeed, research has demonstrated that counts of neutrophils and monocytes circulating in blood may increase by about 90 % after an intensive bout of exercise [32, 33]. Neutrophils are the predominant circulating leukocytes with importance in the nonspecific immune function by phagocyte bacteria, virus, and protozoa, which is followed by intracellular digestion mediated by granular hydrolytic enzymes and reactive oxygen species. Moderate intensity exercise may enhance neutrophils' respiratory burst activity, mediated by increase in inflammatory cytokine IL-6 [11]. Degranulation appears to be mediated by exercise because a postexercise plasma elevation in concentrations of elastase and myeloperoxidase has been found [11]. Prolonged and acute exercise do not appear to provoke neutrophil degranulation changes during exercise, yet a great

reduction of elastase release per neutrophils has been observed 2.5 h postexercise in response to bacterial stimulation. Also, intense or long duration exercise may suppress the production of reactive oxidants via elevated circulating concentrations of epinephrine (adrenaline) and cortisol [34]. In principle, improved responsiveness of neutrophils to stimulation following exercise of moderate intensity could mean that individuals participating in moderate exercise may have improved resistance to infection. On the other hand, competitive athletes undertaking regular intense exercise may be at greater risk of URTI. To investigate the long-term effect of endurance training (>10 years) on immunity, a study assessed phagocytic activity of circulating neutrophils at rest and after a submaximal bout of exercise in well-trained cyclists (VO_{2max} 61.0 ml/kg/min) and sedentary age-matched controls (VO_{2max} 37.4 ml/kg/min). Results showed that circulating neutrophil phagocytic capacity was approximately 70 % lower in trained individuals at rest compared to that of control participants. Therefore, prolonged periods of endurance training may lead to increased susceptibility to opportunistic infections by diminishing immune function at rest [35]. Table 24.1 reflects the incidence of different types of exercise on neutrophil function [11, 15, 34]. Moreover, the effects of exercise on the neutrophil function have been discussed in detail by Peake [34].

Monocytes/macrophages make up around 10–15 % of leukocytes, and their main function is phagocytic and to kill pathogens. Additionally, they play an important role in mediating the acquired immune system response to an antigen presenting cell. Basically, an antigen presenting cell is responsible for displaying a fragment of the antigen that is bound to a class II MHC molecule on their membrane. Specifically, this is accomplished by either phagocytosis or receptor-mediated endocytosis. This way, a T cell can recognize and react to the antigen; however, T cells can only recognize antigens that have been processed and presented by cells via an MHC molecule. After a prolonged bout of intense exercise, the expression of some Toll-like receptors (TLR) on monocytes decreases. TLRs are receptors that

recognize molecules, which are broadly shared by pathogen that allow antigen presenting cells to recognize pathogens [11]. The decrease of TLR 1, 2, 4 was described by Lancaster et al. [36]. Further studies are needed to clarify whether this decrease is real or merely reflects a decrease in monocytic count. A decrease in IL-6, IL-1α, and TNF-α production also has been associated with a reduction in TLR expression [4].

24.3.4 Role of NK Cells in Immunosurveillance

The mechanism underlying moderate exercise-induced decreases in URTI has not been identified completely; however, improved NKCA may play a role. NK cells are a heterogeneous sub-population of lymphocytes that are the most responsive immune cells to acute exercise. They are part of innate immunity and their main function is to destroy virus and tumor cells. Two main NK cell subtypes have been described; that is, NK cells bright (CD56^{bright}) and NK cells dim (CD56^{dim}). NK cells dim are the expressed high level of CD16 and are the most cytotoxic subtype. NK cells bright express absent or low levels of CD16 resulting from high levels of cytokine production. They appear to play an important role in early immune challenge by coordinating the action between the innate and adaptive arms of the immune system. The decision to lyse a target cell is made by these cells via a complex signal system in which activating and inhibiting signals or the Killer immunoglobulin-like receptor (KIR) is involved. NK cell activating signals should dominate over inhibiting signals to lyse the target cell. If an NK cell is engaged with a major histocompatibility complex (MHC) class 1 molecule, the inhibitory KIR is activated, and the presenting signal prevents NK cells from killing host cells (non-MHC restricted) [37]. In response to an aerobic or anaerobic exercise, NK cells are mobilized faster into the peripheral blood circulation. A review published by Timmons et al. in 2008 states that this mobilization is associated with improved the immune system function, which reduces the risk

Table 24.1 Effect of acute and chronic exercise on neutrophils functions

Neutrophils function	Acute moderate exercise	Acute exhaustive exercise	Chronic exercise at rest	Description
Chemotaxis	↑	↕	↕	Ability to migrate to other tissue guided by chemical signals
Adherence	↕	↕		First stage of diapedesis
Phagocytosis	↑	→	→	Action to engulf the pathogen
Neutrophils degranulation	↑	→	↕	Digestion of microorganism by releasing granular lytic enzymes
Oxidative burst activity	↑	↕	→	Digestion of microorganism by generating reactive oxygen species (ROC)

Increase, ↑; decrease, ↓; no change, →; ↕

References: Gleeson et al. [11]; Walsh et al. [4, 10]; and Pedersen and Hoffman-Goetz [15]

of virus acquisition [37]. However, a biphasic response in the NK cell function has been described after intense exercise. This NK cell cytolytic response may result from an exercise-induced imbalance in Th1/Th2 lymphocytes. Research shows that Th1 lymphocytes are suppressed after intense exercise due to corticosteroid effect. IL-2, mainly secreted by Th1 lymphocytes, is an important cytokine responsible for stimulating NKCA [11, 38, 39]. This NKCA reduction appears to make the host more susceptible to invasion by microorganisms—especially to viruses [40, 41]. Moderate regular exercise has been found to increase NK cell function in both sedentary individuals and cancer patients [39, 42, 43]. A study conducted in obese women showed that 6 weeks of walking for 45 min, 5 days/week, produced a 57 % increase in NKCA compared with the 3 % increase found in the control group [44]. A marked increase in NK cell count, generally, is documented at the end of exercise, which may be due to a catecholamine-mediated demargination of cells. The opposite occurs several hours after exercise; specifically, the NK cell counts drops about 50 % compared with normal levels. In general, the normal resting value is restored in a couple of hours or within 24 h, except in prolonged intense and stressful exercise which might take longer. Also if activity is both prolonged and vigorous, the decrease in NK cell counts and NKCA may begin during the exercise session [39]. This decrease in NK cell number and cytolytic activity seems to be irrelevant for recreational participants, but becomes more important in athletes who might experience this immunosuppression several times per week.

24.3.5 Possible Mechanisms Underlying Immune Suppression Through Intensive Exercise

The role that intense exercise plays in the risk of URTI has multiple potential explanations. Commonly a temporary drop in circulating NK cells is observed after a vigorous exercise bout, which generally lasts for several hours. At first sight, this period of time seems to allow easier access to infected microorganism and is commonly known as "open window." NK cells count and activity typically have been described as being depressed for only a few hours. The new technology has revealed that high intensity exercise does not destroy NK cell. Instead, high intensity exercise is responsible for catecholamine secretion that increases the activation of adhesion molecules; therefore, NK cells are redistributed to reservoir sites such as walls of peripheral veins [4]. Information about the role of NK cells and moderate exercise was reviewed earlier in this chapter.

Changes in salivary IgA (s-IgA) immunoglobulin concentration and secretion rates have been postulated as the only consistent immune measures to date responsible for the increase in upper respiratory symptoms (URS) [3, 4, 11, 32]. The immunoglobulin-A is the predominant Ig in mucosal secretions that, in concert with innate mucosal defenses, provide the "first line of defense" against pathogens and antigens presenting at the mucosa [45]. Meanwhile, research has shown that prolonged high intensity exercises provoke a fall in s-IgA concentration, while short and moderate exercise increases it [45–52]. Decreased secretion rate of s-IgA have been implicated as risk factors for subsequent episodes of URTI and URS in athletes and non-athletes [4]. The mechanism underlying exercise-induced modifications in s-IgA remain unclear. Furthermore, adrenaline seems to be partially responsible. Chronic stress, like intensive training, is associated with diminished functioning of the hypothalamic–pituitary–adrenal axis (HPA), suppressed effects on IgA synthesis, and/or transcytosis (process by which various macromolecules are transported across the interior of a cell) [4].

In 2011, a group of highly recognized researcher in the field announced by consensus that high incidence of infections are reported in individuals with selective deficiency of s-IgA very low saliva flow rates. Also, decreases in s-IgA may occur during intensive periods of training. The main limitation in the field is that

most of the studies were conducted in military populations. Military intensive training introduces a wide range of bias because this intensive training usually is accompanied with dietary energy deficiency, sleep deprivation, and psychological stress. The majority of these factors also may alter the immune response. These stressful factors appear to amplify the exercise-induced alteration.

24.3.6 Role of Exercise on the Acquired Immune System

The T- and B lymphocytes are part of the acquired immune system and play an important role in the control of viral infection. Lymphocytes express a high density of β_2-adrenergic receptors, and the density of these receptors increase due to exposure to exercise or catecholamines. The NK cells are the lymphocytes that express most of the density of these receptors followed by Lymphocytes cytotoxic T cells (CD8$^+$) and Lymphocyte B cells (CD19$^+$); and Lymphocyte T helper cells (CD4$^+$) express the least amount. For that reason NK cells are more sensitive to exercise modulation, while CD4$^+$ shows the lowest response to exercise. Lymphocytosis was observed during and immediately after an acute bout of exercise followed by decreased below resting levels during early stages of recovery. The decrease is largely observable in T lymphocytes, especially Th1 subtype, while B lymphocyte showed a lesser effect. The extent of exercise mobilization is primarily dependent on exercise intensity and duration [53]. Adrenaline seems to be responsible for this biphasic response. It is not clear as to whether the decrease is due to apoptosis or redistribution. Also, the decrease in Th1 T lymphocytes count alone does not necessarily imply reduced host immunosurveillance.

The position Stand (2011) concludes that acute intensive exercise produces a depression of acquired immune system function. This depression is usually short-lived and will resolve within 24 h unless insufficient recoveries between exercise sessions cause chronic depression of acquire immunity [4]. Also, the combined effect of small

detrimental changes in several aspects of host defense may compromise resistance to minor illness such as URTI [4].

24.4 Contemporary Understanding of the Issues

24.4.1 Methodological Problems that Limit the Quality of Research

Abundant anecdotal and survey data exist supporting the J-shaped curve hypothesis [23]. The limitations in this research field come from many factors that include the following: the use of self-report data, nonclinically diagnosed URTI, poorly defined exercise intensity, and lack of control over important research variables [24].

The reliability of the data collected from survey-based epidemiology studies may have been influenced by several variables of the experimental design: the participants may have been aware of the objective of the survey and consequently altered their responses; also, recall information over a long period of time may have produced potential error due to participant's boredom [11].

Most of the studies did not clinically confirm URTI infections. This is a common bias in this field of research. Therefore a sore throat reported as a URTI symptom would be the consequence of a noninfectious airways inflammation due to drying of the mucosal surfaces and or/inhalation of pollutant or dry air [4, 8, 11].

Most human studies in the exercise immunological field are limited to immune measures derived from the blood, and immunosurveillance is not fully represented by serum measures. Therefore, it is difficult to determine the impact of changes on the human immune system's ability to fight against infections [4].

Studies with athletes or those who describe the effect of acute bouts of exercise-induced change in the immune system rarely report an objective measure of exercise intensity (e.g., intensity assessed by heart rate, lactate or VO$_{2max}$ percentage) [8]. This makes the comparison of

result among studies much more difficult. Also, control of other important variables such as nutrition status, overall level of stress, and the use of nutritional supplement among others were rarely performed [8, 24].

24.4.2 Role of Nutrition in Diminishing the Risk of URTI

A healthy and balanced diet may supply all the required nutrients for non-athletes engaging in moderate physical activity. However, athletes might benefit from immunonutritional support to enhance immunity during heavy training periods [10].

Some studies have investigated the efficacy of vitamin C supplementation in decreasing the risk of URTI after an ultra marathon race. Peters et al. found that the consumption of 600 mg of vitamin C supplement 21 days before the race enhanced runners' resistance to post race URTI infections, a common occurrence in these competitive runners. During 14 days after the race, a significant difference was revealed with 68 % of the placebo control group reporting URTI symptoms vs. 32 % of runners who had received vitamin C supplementation [54]. Another study conducted by the same author showed that supplementation of more than 500 mg of Vitamin C supplementation least 3 weeks before a race was effective in diminishing URTI symptoms in 90 km ultra marathon runners. The ratio of URTI infections after vitamin C supplementation alone, or in combination with Vitamin E or beta-carotene, was almost halved [55].

Vitamin C (ascorbic acid) has been described as an antioxidant responsible in part for mediating free radicals neutralization. In simple terms, a reactive and possibly harmful free radical can interact with vitamin C. The reactive free radical is reduced, and the ascorbyl radical formed in its place is less reactive. This process is called free radical scavenging or quenching [56]. It is known that free radical cause inhibition of chemotaxis, phagocytosis, proliferation of T and B lymphocytes, and cytotoxic activity of natural killer cells. But the data in this area are scarce and inconclusive because other studies failed to show significant differences in the risk of URTI after a

marathon by Vitamin C supplementation by runners [57]. Also, a recent publication regarding immune health by a panel of world-leading experts [10] did not recommend the use of vitamin E or Vitamin C as a supplement to improve immunosurveillance in athletes during exertive training phases. The researchers explained that vitamin E might be pro-oxidative in heavy exertion, and also, that the existing data have not shown vitamin C to be consistently different from placebo effects.

Another area where consensus is lacking is the consumption of carbohydrate beverage to attenuate immunosuppressive effect of prolonged exercise [55]. Maintaining blood glucose levels during exercise appears to diminish the secretion of stress hormones, which therefore diminishes the immune inflammatory response [10]. In terms of practical application, experts recommend to ingest up to 60 g of carbohydrate per hour of heavy exertion exercise.

Glutamine and amino acid supplement also are not recommended due to the suggestion that large glutamine body store can easily exceed exercise-lowering effects.

A recent research interest in the field of exercise immunology involves the effects of dietary polyphenols (such as quercetin) in immune system modulation because of their antioxidative, anti-inflammatory, anti-pathogenic, anticarcinogenic, and mitochondrial stimulatory activities. Forty trained male cyclists were randomized to quercetin ($N=20$) or placebo ($N=20$) groups and, under double-blind procedures, received 3 weeks quercetin (1,000 mg/day) or placebo before, during, and for 2 weeks after a 3-day period in which subjects cycled for 3 h/day at approximately 57 % Watts max. Results showed less incidence of URTI during the 2-week postexercise period in quercetin group vs. the placebo group. Although quercetin vs. placebo ingestion did not alter exercise-induced changes in several measures of immune function, it significantly reduced URTI incidence in cyclists during the 2-week period following intensive exercise. Thus, initial data appears to support the use of quercetin supplementation in athletes. Some foods rich in quercetin include black and green tea, capers, apples,

red onion, tomato, broccoli, and other leafy green vegetables.

Multiple supplements have been studied. Please refer to Table 24.2 for a summary of findings on other supplements. More details about immunonutritional can be found in the Position stand: part two [10].

24.4.3 Sex Differences

Notable sex differences have been documented regarding immune function. At rest, females have (1) a higher percentage of activate neutrophils and macrophages circulating (studies in rats) [58, 59]; (2) greater T lymphocyte percentage (from the total pool of lymphocytes) [60]; and (3) higher Th2 cytokine in vitro production without differences along menstrual cycle. These differences might explain why females have a lower mortality rate than males for certain types of infections, and why females have higher rates of autoimmune disease [1].

As NK cells are the most responsive immune cell to exercise, IL-6 is the most responsive cytokine. Another recent study showed that this cytokine was secreted by muscles, had a potent anti-inflammatory effect due to the up-regulation of IL-1ra and IL-10 while avoiding TNF-α (alpha) release. Also, it has been shown to regulate fatty acid oxidation and glucose uptake [61]. The secretion of this interleukin is dependent upon exercise intensity (increased response) and fitness level (decreased response).

Overall, research shows that a significant difference in cytokine release between sexes. However, a study controlling for menstrual phase and oral contraceptive (OC) found a trend of increased IL-6 in women with and without consumption of oral contraceptive at follicular phase [62]. Previous studies have found an association of the follicular phase of the menstrual cycle with greater carbohydrates consumption during exercises (see Chap. 4). Also, a decrease in carbohydrates was associated with an increase in IL-6 release [1].

The majority of research conducted regarding sex differences in leukocyte response to exercise have not found any difference between the sexes.

However, important variables such as menstrual cycle, fitness level, and use of OC were not controlled. A study performed by Timmons et al. showed that after pedalling 90 min at 65 % of VO_{2max} females under OC treatment showed a greater increase of lymphocytes and neutrophils compared to males and females who did not use OC. No fluctuations due to menstrual cycle were experienced in females compared to non-OC users. However the response in the follicular and luteal phases seemed to affect exercise-induced changes in leukocytes. These results seem to indicate that sex hormones are not responsible for those changes. Rather, an increase in plasma levels in women under OC has been proposed to explain that [62].

In well-controlled studies, NK cell activity appears to be sex and menstrual phase dependant with greater response in women at the follicular phase. From animal studies, estrogens appear to inhibit the inflammatory response, which limits neutrophil infiltration by acting as a cell membrane stabilizer and antioxidant. When taking this into account, it makes sense that the greatest increase in neutrophils occurs during luteal phase when estrogens levels are lower [1].

It has been proposed that the highest amount of adipose tissue in females may be responsible for the greater IL-6 release in women compared to males. Previous research demonstrates the role of the adipose tissue in IL-6 release. Also the disparity in the leukocyte response between males and females might be explained by females presenting more β-2 adrenergic receptors than males.

Estrogens do not seem to be the primary factor responsible for many of the sex differences observed in research. Thus, more research is needed to clarify cytokine release differences between the sexes, while at the same time, controlling variables like menstrual cycle, OC use, fitness level, and exercise intensity.

24.4.4 Recommendation to Exercise During and After a URTI

Acute URTI is the most common medical condition affecting athletes at summer and winter Olympics games [10]. Heavy training

Table 24.2 Summary of rationale and findings for selected immunonutritional supplements

Immunonutritional supplement	Proposed rationale	Recommendation based on current evidence
Vitamin E	Quenches exercise-induced reactive oxygen species (ROS) and augments immunity	Not recommended; may be pro-oxidative with heavy exertion
Vitamin C	Quenches ROS and augments immunity	Not recommended; not consistently different from placebo
Multiple vitamin and minerals	Work together to quench ROS and reduce inflammation	Not recommended; not different from placebo; balance diet is sufficient
Glutamine	Important immune cell energy substrate that is lowered with prolonged exercise	Not recommended; body stores exceed exercise-lowering effects
Branched chain amino acids (BCAAs)	BCAAs (valine, isoleucine, and leucine) are the major nitrogen source for glutamine synthesis in muscle	Not recommended; data inconclusive, and rationale based on glutamine
Carbohydrates	Maintain blood glucose during exercise, lowers stress hormones, and thus counters immune dysfunction	Recommended; up to 60 g/h of heavy exertion helps dampen immune inflammatory responses, but not immune dysfunction
Bovine colostrums	Mixture of immune, growth and hormonal factors improve immune functions and the neuroendocrine system; lower illness risk	Jury still out, with mixed results
Probiotics	Improve intestinal microbial flora, and thereby enhance gut and systemic immune function	Jury still out, with mixed results
N-3 PUFA (fish oil)	Exert anti-inflammatory effects postexercise	Not recommended; not different from placebo
β-Glucan	Receptors found on immune cells, shows supplementation improve innate immunity and reduces infection rate	Not recommended; human studies with athletes do not show any benefits
Herbal supplements (e.g., Ginseng, Echinacea)	Contain bioactive molecules that augment immunity and counter infection rates	Not recommended; human studies do not show consistent support within an athletic context
Quercetin	In vitro studies show strong evidence for anti-inflammatory antioxidative and anti-pathogenic effects. Animal data indicate increase in mitochondrial biogenesis and endurance performance; reduction in illness	Recommended when mixed with other flavonoids and nutrients; human studies show strong reduction in illness rates during heavy training and mild stimulation of mitochondrial biogenesis and endurance performance in untrained subjects; anti-inflammatory and antioxidative effects when mixed with green tea extract and fish oil

Reproduced from Walsh NP, Gleeson M, Pyne DB, Nieman DC, Dhabhar FS, Shephard RJ, Oliver SJ, Bermon S, Kajeniene A: Position statement. Part two: Maintaining immune health. Exerc Immunol Rev 2011, 17:64–103, with kind permission of Dr. Hinnak Northoff

can increase the severity and duration of the infection. Although rare, myocarditis could develop with life-threatening consequences [11]. For that reason the tables below show practical guideline for athletes and coaches once infections have been acquired (Tables 24.3 and 24.4).

24.5 Future Directions

The role of moderate exercise as a preventive and therapeutic tool to treat common cold has to be explored in detail. There is increasing evidence that moderate exercise might have the capability to

Table 24.3 Guidelines for exercise during episodes of URTI in athletes

Day of illness	Recommendations
1st	No strenuous exercise or competitions when experiencing URTI symptoms like sore throat, coughing, runny or congested nose
	No exercise when experiencing symptoms like muscle/joint pain and headache, fever, generalized feeling of malaise, diarrhea or vomiting
	Drink plenty of fluids, keep from getting wet and cold, and minimize life-stress
	Consider use of topical therapy with nasal drainage, decongestants and analgesics if feverish
	Report illness to team physician or health care personnel and keep away from other athletes if you are part of a team training or travelling together
2nd	If fever is >37.5–38 °C, or coughing increases as well as diarrhea or vomiting: *no training*
	If no fever or malaise and no worsening of "above the neck" symptoms: *light exercise (pulse <120 bpm)* for 30–45 min, indoor during winter and by yourself
3rd	If fever and URTI or gastrointestinal infections (GI) symptoms are still present: consult your physician. Quinolones should be avoided whenever possible because of an increased risk of tendinopathy
	If no fever or malaise and no worsening of initial symptoms: *moderate exercise (<150 bpm)* for 45–60 min, preferably indoor and by yourself
4th	If no symptom relief: do not to exercise but make an office visit to your doctor
	If first day of improved condition, follow the guideline below

Adapted from Walsh NP, Gleeson M, Pyne DB, Nieman DC, Dhabhar FS, Shephard RJ, Oliver SJ, Bermon S, Kajeniene A: Position statement. Part two: Maintaining immune health. Exerc Immunol Rev 2011, 17:64–103, with kind permission of Dr. Hinnak Northoff

Table 24.4 Guidelines for return to exercise after infections

Recommendations

- Wait 1 day without fever and with improvement of URTI symptoms before returning to exercise
- Stop physical exercise and consult your physician if a new episode with fever or worsening the initial symptoms or persistent coughing and exercise-induced breathing problems occur
- Use the same numbers of days to step up to normal training as spent off regular training because of illness
- Observe closely your tolerance to increased exercise intensity and take extra day off if recovery is incomplete
- Use proper outdoor clothing and specific cold air protection for airways when exercising in temperatures below −10 °C the first week after URTI

Adapted from Walsh NP, Gleeson M, Pyne DB, Nieman DC, Dhabhar FS, Shephard RJ, Oliver SJ, Bermon S, Kajeniene A: Position statement. Part two: Maintaining immune health. Exerc Immunol Rev 2011, 17:64–103, with kind permission of Dr. Hinnak Northoff

improve immunosurveillance against URTI. More interventional research is needed to determine how this effect can be maximized [3, 14]. Future studies should make an effort to improve methodological issues such as randomization, selection of subjects, and report adverse events. Additionally, future investigations need to improve the description physical activity and/or exercise intensity and to identify the source of cells producing the high amounts of cytokine in response to a muscle contraction, which will aid in identifying their role in the repair and growth of muscle [15]. Also, it is time to examine the role of exercise on clinical outcomes in various groups including patients with immune disorder or malignant disease [15].

24.6 Concluding Remarks

The concluding remarks that the authors feel are most noteworthy have been bulleted.
- Although the "J-shaped curve" hypothesis is generally accepted by consensus, the available experimental evidence is not enough to support it.
- Not only does exercise intensity or duration seem to be responsible for increasing the risk

of URTI, other individual factors such as age, fitness condition, nutritional status, psychological wellbeing, and previous health status increase the exposure to pathogens.

- Strenuous exercise produces quick leukocytosis that mainly is mediated by neutrophils and lymphocytes demargination from others pools. Also, delayed neutrophilia mainly provoked by neutrophils, which was released from the bone marrow was observed.
- Exercise has a biphasic response regarding numbers of circulating lymphocytes and lymphocyte subsets with an increase in the number of cells occurring during exercise as well as a decrease in cell quantity after exercise. The degree of this change is intensity and duration dependent.
- Evidence regarding immunonutritional supplements remains controversial. There is not enough evidence to recommend most of them.
- Estrogens alone are not responsible for immune sex differences in exercise-induced immune system changes. More research is needed to clarify cytokine release differences between the sexes that control variables such as menstrual cycle, OC use, fitness level, and exercise intensity.
- Cessation of exercise or reduction in the amount and intensity of exercise may improve the time of recovery from a URTI infection. However, athletic competition or training maintained at high intensity levels may increase the severity of the disease or even compromise the life of the athlete.

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