Exercise Immunology
The Current State of Man and Mouse

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Abstract

The mechanisms governing the body’s response to physical exercise have been investigated from various perspectives including metabolism, nutrition, age and sex. Increased attention to the immune system during recent decades is reflected by a rapidly growing number of publications in the field. This article highlights the most recent findings and only briefly summarises more basic concepts already reviewed by others. Topics include Th1/Th2 cytokine balance, inoculation time, age and immune compensation. Some less investigated areas are discussed including studies in children, the environment and dendritic cells.

Because physical exercise enhances some aspects and suppresses other aspects of immunity, the biological significance of alterations in the immune system are unknown. So far, no link between immunological alterations and infection rate has been established and infection after strenuous physical exercise is equally likely to be the result of exercising with an already established rather than a new infection. If there is an increased risk for infections with increased exercise duration and intensity, why do overtrained athletes not display the greatest risk for upper respiratory tract infections? Increased knowledge on immune system modulations with physical exercise is relevant both from a public health and elite athlete’s point of view.

1. Background

Physical exercise will affect the immune system in a highly specific manner influenced by mode and duration of exercise, time of tissue sampling, subject characteristics, the environment and numerous other factors. Researchers have, however, been able to agree on some generalisations regarding immunological changes in response to physical exercise. More than 250 scientific articles have been published specifically in the field of exercise immunology in the last 3 years (figure 1). This is nearly one-third of all publications in the field and some recent reviews deal with focused topics in exercise immunology such as: resistance exercise, cytokines, muscle adaptation, circulating leucocyte functions, sport psychology, diet and cancer.

Consequently, the question to be answered is not if the immune system is influenced by physical exercise, but how. What are the molecular mechanisms governing altered infection rates, cancer genesis and interaction between the immune system and other organs such as skeletal muscle and the nervous system? This article discusses some recent findings in the area of exercise immunology, focusing on research aimed beyond descriptive information.

Exercise-induced leucocytosis can be attributed mainly to neutrophilia, and to a lesser extent to lymphocytosis and monocytes. After prolonged exercise, leucocyte numbers may decrease below...
the numbers at rest.\textsuperscript{14} Changed leucocyte numbers have been attributed to catecholamines and cortisol\textsuperscript{15,16} but it is evident that the scheme is complex, involving a multitude of simultaneous signals such as cytokines, adhesion molecules, growth factors and cell-cell interaction.\textsuperscript{17,18} The source of leucocytes appearing in circulation after physical exercise can be blood vessel walls, lung, gastrointestinal tract and spleen.\textsuperscript{15} Additionally, the cells entering circulation have short telomere length and are probably not mobilised from the bone marrow or the thymus.\textsuperscript{16} In contrast, Suzuki et al.\textsuperscript{19} suggest that neutrophils are released from the bone marrow after physical exercise, influenced by interleukin (IL)-6 and macrophage colony-stimulating factor (M-CSF). A question still puzzling researchers is where all leucocytes migrate to when their numbers in blood decrease. Several options remain open including adhesion to endothelial vessels, skin, spleen and lungs. It appears that cells do not migrate to human skeletal muscle after exercise because multiple biopsies (used in most published studies) and eccentric exercise will result in an equal amount of infiltration.\textsuperscript{5,20}

Circulating monocyte numbers have been found to increase or not change during and after acute exercise and may be decreased during prolonged periods of intense endurance training.\textsuperscript{14,21} The in vitro function and in vivo cell surface receptor expression can also be altered by exercise.\textsuperscript{17,22} In a study by Suzuki et al.,\textsuperscript{19} it was demonstrated that although neutrophil and monocyte cell function were enhanced after a marathon race, their biological actions were inhibited by an increased antioxidative defence in plasma. During periods of decreased training in endurance athletes, monocyte function can be enhanced.\textsuperscript{23}

Due to the actions of catecholamines, lymphocytes usually increase in circulation during exercise and return to baseline levels or below within a few hours after exercise. The number and function of natural killer (NK) cells display the most homogenous response to exercise (increase during and decrease after),\textsuperscript{16,24-26} but subpopulation variations have been observed.\textsuperscript{17} In general, T cells are more prone to change with exercise than B cells and altered T cell numbers can affect B cell immunoglobulin production. However, some types of exercise, even if strenuous, do not result in changes in circulating lymphocyte numbers, i.e. eccentric cycling (figure 2). If the exercise is of extreme duration, lymphocyte number may decrease below resting value also during exercise.\textsuperscript{27} There appears to be no effect of training on resting number of blood lymphocytes\textsuperscript{28,29} and even overtrained athletes can have normal cell counts.\textsuperscript{30}
Another important aspect is that although resting numbers of leucocyte populations may have returned to baseline after one exercise bout, the response to a second identical exercise session may be different.\cite{33} The practical application for athletes awaits evaluation but stresses the importance of sufficient recovery and order of exercise mode and duration for optimal performance development. It could also explain differences in results between studies using similar exercise protocols when the subjects may not have been in an identical state of recovery.

Researchers have suggested possible links between changes in the immune system, infection rate, muscle adaptation and physical performance. Few direct correlations between these variables have been published to support these hypotheses. For example, no direct explanation for the observed increased risk for upper respiratory tract infections (URTI) in some athletes has been described. In one early study by Lee et al.\cite{34} it was concluded that decreased in vitro immune function was not linked to increased incidence of URTI. This statement still awaits validation or disapproval.

This article will highlight some recent observations (with a focus on publications between 2000 and 2003) regarding immune function and physical exercise, including some alternative interpretations of published data as well as novel findings. Limitations are set to studies of healthy subjects and excludes: exercise and cancer reviewed by Hayes et al.,\cite{35} Friedenreich and Orenstein\cite{12} and Fairey et al.,\cite{13} HIV reviewed by Nixon et al.;\cite{37} myositis reviewed by Lundberg\cite{38} and Lawson Mahowald;\cite{39} fibromyalgia reviewed by Sim and Adams;\cite{40} rheumatoid arthritis reviewed by Pool and Axford;\cite{41} and Vlieland and Breedveld;\cite{42} (also, van den Ende et al.\cite{43} recently published a comprehensive study on rheumatoid arthritis and exercise); intracellular signalling reviewed by Mooren et al.;\cite{44} oxidative stress reviewed by König et al.;\cite{45} and nutrition most recently summarised by Venkatraman and Pendergast.\cite{10}

<table>
<thead>
<tr>
<th>Exercise Protocol</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eccentric walking (5 x 30 steps)</td>
<td>2.9</td>
</tr>
<tr>
<td>Down-hill running (4˚ for 45 min)</td>
<td>2.7</td>
</tr>
<tr>
<td>Down-hill running (8˚ for 45 min)</td>
<td>2.5</td>
</tr>
<tr>
<td>Eccentric cycling (30 min)</td>
<td>2.3</td>
</tr>
<tr>
<td>Two soccer games</td>
<td>2.1</td>
</tr>
<tr>
<td>Up-hill running (4˚ for 45 min)</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**Fig. 2.** Changes in blood lymphocyte numbers in response to different exercise protocols demonstrating the heterogeneous changes depending on exercise mode and duration. Each line is the mean cell number from one mode of exercise, as indicated by the key. Resting numbers inserted (cells/mL x 10⁶).\cite{17,30,32}

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2. Exercise, Infection and Vaccination

Among coaches, athletes and researchers, it is commonly accepted that strenuous physical exercise can increase susceptibility to infections. However, the well known J-shaped curve describing infection sensitivity and exercise intensity still awaits its immunological explanation. There is evidence supporting decreased risk for infection in exercising compared with sedentary older women, middle-aged men and women as well as increased incidence rates of URTI with increased amounts of training and faster finish times in a marathon. In contrast, infectious episodes were decreased in overtrained compared with well trained athletes in one study. Due to the large number of uncontrolled variables in human epidemiological studies (e.g. previous infections, pathogen exposure, other stressors than exercise) conclusive evidence and a mechanistic explanation for altered infection sensitivity in humans is difficult to obtain.

2.1 Time of Inoculation

In controlled animal studies, it has been demonstrated that the relationship between time of infection (inoculation) and exercise is decisive for the outcome of the infection. Rats subjected to bacterial infection (Francisella tularensis) after swimming until exhaustion displayed protection from infection/complications while exercise performed after infection resulted in more severe symptoms (figure 3). Mice subjected to moderate exercise (45 minutes of swimming/day) did not display decreased survival from Toxoplasma gondii infection and a small increase in survival with voluntary running exercise after Salmonella typhimurium infection has also been documented. It has also been found that compared with untrained mice, trained mice have decreased myocardium damage when inoculated by a bacterial (tularemia) or a viral (influenza) infection, while exercising during an ongoing viral infection can increase lethality. Infected mice with herpes simplex virus (HSV-1) after exercise to voluntary fatigue (no electrical stimulation) on a treadmill also resulted in increased morbidity and mortality. Similar results were found in horses subjected to 5 days of strenuous exercise before infected with an influenza virus. Horses were immunised against the influenza virus, then either exercised or rested for 5 days. Three out of four exercised horses became sick upon post-exercise virus challenge but none of the rested. Blood monocytes IL-2 production was unchanged while interferon (INF)-γ production was decreased. The authors suggest altered CD8+ T cell or NK cell function as one possible cause of increased susceptibility to infection. Interestingly, resting CD8+ T cell percentage and CD4/CD8 ratio before exercise were
predictors of infection in military recruits, suggesting a subclinical infection prior to exercise (Figure 4) [Malm et al., unpublished data]. Contrary to the findings by Folsom et al., Lunn et al. could not detect adverse effects of exercise on infection protection in immunised horses, although lymphocyte proliferation was decreased in a similar fashion in both studies. The exercise intensity in the latter study was lower, possibly explaining the different findings.

2.2 Acute Stress

Some recent studies have concluded that the innate immunity is enhanced by acute physical activity and will protect the host from infection. Acute stress in the form of electric tail shock can increase the rate of recovery from bacterial inflammation. In the study by Flesher et al., chronic physical exercise did not alter recovery after inflammation. In conjunction with the known psychological effects on the immune system, it is possible, as suggested by Davis et al.,[60] that the observed differences between the studies by Ilbäck et al., Davis et al.,[60] and Folsom et al. are due to voluntary versus forced exercise until exhaustion and/or viral versus bacterial infection. Prolonged decrease in alveolar macrophage functions, decreased lymphocyte proliferation and monocyte cytokine production appear to be possible causes of the increased infection rates, morbidity and mortality in animals. In horses, alveolar macrophage oxidative burst activity was decreased with high-intensity training, supporting the findings by Davis et al.[60] Unfortunately no correlation calculations between exercise intensity, infection rate and immune function were performed in any of these studies.

2.3 Airway Hyper-Responsiveness versus Upper Respiratory Tract Infections

Gleeson et al. concluded that URTI in elite swimmers was related to reactivation of latent Epstein-Barr virus. These authors suggested that the virus shedding was either the cause of the URTI or a sign of upset immune balance, resulting in an URTI. In most studies, URTI are self-reported and there is a risk that some cases of increased airway hyper-responsiveness (AHR), an inflammatory event of non-pathogenic origin, is mistakenly reported as URTI. AHR is induced by a variety of factors such as dry, cold air and chemical substances. These are all elements encountered by athletes commonly believed to experience increased rates of URTI (runners, skiers and swimmers). Thus, it is not convincingly demonstrated that increased rates of symptoms of URTI in some athletes are due to a novel infection caused by decreased immune function.

2.4 Th1/Th2 Cytokine Balance in Exercise and Age

Moderate exercise appears to gear the immune system towards a more Th1-type cytokine response (IL-2, IL-12) while strenuous exercise enhances the Th2 cytokines (IL-6, IL-10). In theory, moderate exercise should then enhance host protection

![Fig. 4. Prediction of post-exercise infection by CD4+ and CD8+ T lymphocyte number and ratio before a military exercise (n = 10) [Malm et al., unpublished data].](image-url)
exercise can gear it back towards the T\textsubscript{h1}-like function of younger individuals (figure 5). One possible mechanism could be that chronic loss of sympathetic nerve stimulation, one effect of inactivity, down-regulates T\textsubscript{h1} cytokines and delayed-type hypersensitivity.\cite{75}

### 2.5 Long-Term Health Effects

Even though T cell and NK cell recruitment after acute exercise is preserved with age, short-term exercise programmes do not restore decreased immune function at rest in the elderly.\cite{76} Cross-sectional studies indicate that trained elderly have better immune function than untrained,\cite{77} and enhanced immune response to vaccination has been noted in active versus sedentary elderly.\cite{78} However, it remains to be determined if this is due to exercise or other lifestyle factors.\cite{79} Data from a very recent study by Kohut et al.\cite{80} suggest that against viral infection while strenuous exercise should protect from bacterial infection. This view is largely supported by available data from animal studies.

Age also plays a significant role in both human and animal studies of the immune response to exercise. Older people have a T\textsubscript{h2} cytokine dominance (IL-4, IL-5, IL-6, IL-10).\cite{71} Thus, a theoretical link between moderate exercise and improved immune function in the elderly appears possible by boosting their T\textsubscript{h1} response and protection against viral infections.

Younger mice infected with herpes simplex virus 20 minutes after 2.5 hours of running until exhaustion had decreased T\textsubscript{h1} (INF\textsubscript{γ}, IL-2, IL-12) and T\textsubscript{h2} (IL-10) cytokine production 2 days after exercise. Unfortunately, infection rate was not reported in this study.\cite{72} In old but not young mice, moderate exercise was associated with increased antigen-specific IL-2 and INF\textsubscript{γ} production in response to viral challenge.\cite{73} In conjunction with previous findings by Nieman et al.,\cite{74} a possible mechanistic link to the decreased infection rate among older women with exercise can be speculated; when the immune system is altered towards a more T\textsubscript{h2}-like response with age,\cite{71} exercise can gear it back towards the T\textsubscript{h1}-like function of younger individuals (figure 5). One possible mechanism could be that chronic loss of sympathetic nerve stimulation, one effect of inactivity, down-regulates T\textsubscript{h1} cytokines and delayed-type hypersensitivity.\cite{75}

![Fig. 5.](image-url) Suggested cytokine shift with exercise and age, possible linking of moderate physical exercise with improved immune function in the elderly and increased infection sensitivity (viral) with strenuous exercise. DTH = delayed-type hypersensitivity.

![Fig. 6.](image-url) The odds ratio of all-cause of death in men decreased with increased number of men who completed the Vasaloppet cross-country ski races in Sweden (n = 49 219). Mortality decreased with increased number of races, an indicator of prolonged exercise over several years. SMR = standardised mortality ratios (ratio of observed to expected deaths).\cite{81}
In whatever case, the overall mortality rate appears to decrease with long-term physical activity in both men and women, and could be related more to continued exercise for several years than to exercise intensity.\textsuperscript{82} In figure 6, the odds ratio of all-cause of death in men decreased with increased number of completed 90km cross-country ski races (Vasaloppet, Sweden). Exercise intensity, visualised as relative finish time compared with the winner in figure 7, appears not to affect mortality (there are only two deaths in column 100–120% making interpretations intricate and again demonstrating the difficulty in obtaining data on true elite athletes). It is also of importance to note that other lifestyle factors such as diet, work, economy and social situation will influence infection and mortality rates.\textsuperscript{72,82}

3. Elite Athletes

One factor uncontrolled for in published human studies on infections and exercise is the time of infection. As athletes exercise on a daily basis, they will perform exercise both before and after encountering a pathogen. Consequently, it cannot be known from epidemiological studies on humans whether observed symptoms after strenuous exercise are the result of increased susceptibility of a novel pathogen, or more severe symptoms of an already established infection. A recent study suggests that dormant viral infections (Epstein-Barr virus) can be related to URTI in athletes.\textsuperscript{68} In figure 8, a grouping of collected data (URTI or not 3 weeks before the race) demonstrated that only runners with a pre-race history of URTI experienced increased URTI symptoms after a marathon.\textsuperscript{83} In epidemiological studies, this division of data is important when establishing the cause of observed infections. The optimal test would of course be virus titre on all subjects.

Athletes in general do not display altered immune functions compared with non-athletes; even in overtrained athletes, a general immunosuppression and increased infection rate is not always observed.\textsuperscript{30,54} Taken together with the results on salivary immunoglobulins where correlations between saliva immunoglobulins have been both found\textsuperscript{84} and not observed,\textsuperscript{85} the mechanism influencing suggested altered infection rate in athletes is yet to be described.

Infection rate 3 weeks before the race

<table>
<thead>
<tr>
<th>Infection</th>
<th>No infection</th>
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<tbody>
<tr>
<td>33%</td>
<td>19%</td>
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Infection rate 3 weeks after the race

<table>
<thead>
<tr>
<th>Infection</th>
<th>No infection</th>
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<tbody>
<tr>
<td>17%</td>
<td>16%</td>
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Fig. 8. Infection rate after a marathon. Pre-race history of upper respiratory tract infections determines post-race infection risk.\textsuperscript{83} The results are comparable to findings by Peters and Bateman.\textsuperscript{50}
4. Alternative Immune Functions

4.1 Muscle Adaptation

Other effects than altered infection sensitivity with exercise, but yet linked to the immune system have been recognised. It has been widely accepted that muscle adaptation to physical exercise occurs via an inflammatory mechanism. This view has recently been challenged.[86] Instead, the immune system appears to influence skeletal muscle adaptation via interactions between leucocyte and endothelial cell adhesion molecules,[17,87] release of cytokines and growth factors,[88] all in a non-inflammatory manner. For example, exercise decreases tumour necrosis factor-α (TNFα) levels and increases protein synthesis in elderly compared with young skeletal muscle.[89] In young subjects, no change in muscle TNFα expression was detected after eccentric exercise, but a multitude of skeletal muscle/immune system interactions were demonstrated.[13] As suggested previously, besides being important for fighting infections and repairing tissue damage, the immune system is most likely inevitable for skeletal muscle adaptation to physical exercise.[90,91] However, as with the Th1/Th2 cytokine balance, there might be a conflict of interest between immune system configuration for infection protection and optimal physical performance.

4.2 Metabolism

Traditionally, immune system components such as interleukins have been shown to be also involved in non-immune events. Energy stores and intake influence the cytokine response during and after exercise.[92,93] There is substantial evidence suggesting that cytokines such as IL-6 transmit signals that will influence the body’s substrate utilisation and consequently also physical performance. Based on studies by Bente Pedersen’s group in Copenhagen[94,96] and others,[92,97] Gleeson suggests that muscle-derived IL-6 is linked to energy metabolism and glycogen utilisation.[98] It was also recently suggested that IL-6, released to the blood during endurance exercise[96] can inhibit TNFα-induced insulin resistance in the elderly.[99] Interactions between localised lipid deposits surrounding lymph nodes, cytokines and the immune system has also been discussed.[100]

Local cell signals and energy turnover will influence activation and proliferation of leucocytes participating in current immunological events. These processes are not necessarily reflected in altered circulating cell number and function.

5. Future Areas of Interest

Apart from the topics discussed in the sections above, new research areas have emerged with potential interest for future investigations.

5.1 Children

Most publications on exercise and the immune system have used young male subjects and a few have investigated the elderly. The influence of physical exercise on children should be of interest in order to establish the mechanisms responsible for positive long-term health effects of exercise and development of physical performance. Surprisingly little research is dedicated to this cause.[101,102]

5.2 Environment

Regardless of study design, the environment will affect the outcome, particularly in exercise immunology. It has also been demonstrated that both heat[103,104] and cold[105,106] will alter the immune response to physical exercise. Some of these results demonstrate that the environment in which exercise is performed causes larger immunological disturbances than the exercise itself.

5.3 Nervous System

A link between the immune system and the nervous system, and possible relationships with immunono-modulation during and after exercise is under investigation. A bidirectional link between the nervous system and the immune system has been established where circulating neuropeptides[107] and growth factors[108] produced by leucocytes can affect the nervous system. Further investigations can eluci-
Exercise Immunology

5.4 Immune Compensation

Exercise will enhance some and inhibit some immune functions, and compensatory mechanisms for observed decreases have been discussed. Recently, Ho et al.\(^{109}\) and Upham et al.\(^{110}\) reported that the number of dendritic cells increases in blood with exercise. Dendritic cells induce T cell activation, are activated by INF\(\gamma\) and are the primary producers of IL-12. With the observed T\(\text{h}1\) cytokine shift during moderate exercise (INF-\(\gamma\), IL-2, IL-12) an important function of dendritic cells in the body’s response to exercise is possible. Increased antigen-presenting capacity of dendritic cells could compensate for the decreased B cell function observed after exercise in some studies. The findings that there is a cross-talk between dendritic cells and NK cells strengthen the arguments for investigations on this cell population in studies of physical exercise.\(^{111}\) To the author’s knowledge, dendritic cells have not been considered in exercise physiology studies other than the above mentioned.

6. Conclusions

- As summarised in figure 9, exercise will increase and decrease some immune variables. So far, the biological significance of these changes have not been established. Physical exercise enhances some and suppresses other aspects of immunity. In vitro alterations of immune system components do not necessitate clinical relevance.
- Observed increases in infection rates in humans after strenuous physical exercise is equally likely to be the result of exercising with an already established, subclinical infection as increased susceptibility to new infections.
- When investigating infection rate, especially among elite athletes, infection rates before as well as after exercise should be observed. Virus titre should be determined in order to separate URTI from AHR.
- There is an apparent difficulty in linking immunological alterations to infection rate. For example, IgA correlation to URTI has not been reproducible.
- The clinical outcome of an infection largely depends on the pathogen, even though symptoms and outcome of some infections is highly influenced by physical exercise.
- Compute correlations (i.e. multiple regression) to reveal synergistic/antagonistic effects. Temporal associations between variables do not necessarily indicate cause and effect.
- Caution should be taken when interpreting functional results from blood samples as these cells may not participate in ongoing immune reaction. Translation of animal studies to humans should, as always, be viewed with caution.
- If there is an increased risk for infections with increased exercise duration and intensity, why do overtrained athletes not display the greatest risk for URTI?
- If highly conditioned athletes may not be protected from virus even if vaccinated, should they then be vaccinated?

In summary, it can be stated that numerous descriptive studies have been performed, and changes in the immune system during and after various forms of physical exercise have been mapped out. In most cases, no correlation between these observations and clinical relevance have been made. The

\[
\begin{align*}
\text{After acute exercise} & \quad \text{After training period} \\
\text{Neutrophil concentration} & \uparrow \quad \text{NK cell function} \\
\text{Monocytes (chemotaxis, adhesion)} & \quad \text{Monocyte function} \\
\text{Dendritic cell concentration} & \quad \text{Vaccination response} \\
\text{DTH (T\(\text{h}1\) cell function)} & \downarrow \quad \text{DTH (T\(\text{h}1\) cell function)} \\
\text{NK cell function} & \downarrow \quad \text{Lymphocyte function} \\
\text{Lymphocyte function} & \quad \text{Mucisak IgA production} \\
\text{Monocytes (chemotaxis, adhesion)} & \quad \text{Monocytes (MHC, enzymes)} \\
\text{DTH (T\(\text{h}1\) cell function)} & \quad \text{DTH (T\(\text{h}1\) cell function)} \\
\end{align*}
\]

Fig. 9. Summary of observed immunological alterations with physical exercise demonstrating both increased and decreased immune functions. DTH = delayed-type hypersensitivity; IgA = immunoglobulin A; MHC = major histocompatibility complex; NK = natural killer.

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evolutionary purpose and mechanistic explanation for altered immune function with physical exercise remains undetermined.

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