HOSTED BY
ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Journal of Sport and Health Science 13 (2024) 277–279

Guest editorial

Exercise immunology: Novel insights

The coronavirus disease 2019 (COVID-19) pandemic heightened worldwide attention on the influence of exercise on the immune system. Questions were raised about whether regular moderate-to-vigorous physical activity (MVPA) could help prevent COVID-19 or mitigate symptoms when ill. Could MVPA bolster immunity among those most prone to COVID-19 including the elderly, obese, and immunocompromised patients? Does regular MVPA dampen systemic inflammation, thereby lessening the COVID-19 cytokine storm? Clinicians inquired whether MVPA enhanced the antibody response to COVID-19 vaccinations. Athletes and coaches sought guidance on whether it was safe to train when sick. What nutritional strategies can help the athlete counter immune dysfunction during periods of intensive training? What role does MVPA play in the rehabilitation of individuals with post-acute sequelae of COVID-19 (PASC), also called long COVID? Other questions were focused on basic science issues. Does MVPA augment immune function and surveillance against pathogens including the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other viruses? What specific types of immune cells are mobilized during acute exercise bouts? In response to these questions, the *Journal of Sport and Health Science* (*JSHS*) and other journals published several impactful papers and reviews on exercise-immunology.[1–10] This special topic was organized by *JSHS* to highlight emerging and novel insights in exercise immunology and to strengthen scientific understanding in this rapidly growing area of scientific endeavor.

In the paper by Synders et al., a cohort of 84 athletes with confirmed SARS-CoV-2 infection were followed to identify factors associated with a prolonged time to return to full performance (RTFP). Symptomatic compared to asymptomatic athletes took more than twice the days (64 days *vs.* 30 days on average) to RTFP, and predictive factors including being a female or endurance athlete and having whole body/systemic symptoms. The issue of RTFP following COVID-19 and other similar respiratory illnesses is of high importance to athletes and the medical staff and has been addressed previously by the American College of Sports Medicine and the International Olympic Committee.[11,12] In this study, 1 in 7 athletes reported COVID-19-related symptoms after a period of 3 months. The authors cautioned that athletes with persistent symptoms or PASC should receive appropriate support and surveillance. Emerging data indicate that a distinctive symptom of PASC is post-exertional malaise that is associated with extensive muscle abnormalities including compromised mitochondrial function, muscle damage, immune dysfunction, and microclots.[4] RTFP can be extended for athletes experiencing PASC.

The narrative review by Burtscher et al. examined the combined stressors of intensive training and hypoxia on immune responses. This is an important consideration for athletes that engage in high volumes of altitude training. One systematic review identified high altitude training as a risk factor for acute respiratory illness in athletes.[13] Living at a very high altitude has been linked through transcriptomics to a downregulation of innate immune system-related genes including those involved in myeloblast differentiation and neutrophil activation.[14] Depending on the total stress workload, exercise and hypoxia can either stimulate or impair immune system functions. The authors recommended appropriate acclimatization, training volumes, and nutritional strategies to mitigate the potential negative immune consequences of high-altitude training or exercising in a hypoxic state.

The cross-sectional study of 79 older healthy adults conducted by Böttrich et al. investigated immune, lifestyle, and metabolic factors related to subclinical atherosclerotic plaque (SAP). Innate and adaptive immune responses play a role in the development of atherosclerosis, and this study focused on regulatory T cells (Tregs) and 2 subsets including resting Tregs and memory Tregs (mTregs). Tregs comprise 2%–4% of all peripheral $CD4^+$ T-cells (T-helper) and limited evidence suggests that Tregs exert anti-inflammatory effects and promote heart muscle regeneration and vascular repair.[15] In this study, 37% of adults were classified as having mild SAP. Older age, higher blood pressure, and a proportional shift from resting Tregs to mTregs were associated with SAP. Additionally, serum low-density lipoprotein cholesterol and cardiopulmonary fitness were linked with this shift in Tregs subsets. The authors suggested that mTregs could be considered as a biomarker for SAP.

The systematic review by Kotewitsch et al. identified non-coding RNAs (ncRNAs) and microRNAs (miRNAs) that were linked to exercise-induced immune responses. ncRNAs exert

https://doi.org/10.1016/j.jshs.2024.01.007
Cite this article: Nieman DC. Exercise immunology: Novel insights. *J Sport Health Sci* 2024;13:277–9.

regulatory effects on gene expression and some are involved in hormonal and metabolic regulatory effects on the immune system during exercise. ncRNAs are classified as miRNAs, long ncRNAs, and circular RNAs. miRNAs are short ncRNA molecules that regulate gene expression at multiple levels and some are involved in post-transcriptional regulation and immune cell development, inflammation, and immune responses.[16] Circulating extracellular vesicles carry miRNAs and facilitate intercellular crosstalk and the regulation of inflammation and other immune responses. This review described 15 endurance exercise miRNAs with immune system targets, and two related to resistance exercise. Pathway analysis of these miRNAs showed a linkage to Toll-like receptor cascades. Key miRNAs included miR-15, miR-29c, miR-30a, miR-142/3, miR-181a, and miR-338. In general, this novel review showed that miRNAs are involved in exercise-induced effects on the immune system including immune cell distribution and function, and the production of anti-inflammatory cytokines.

About 1 in 3 blood leukocytes are lymphocytes, and of these, one in ten are B cells. Despite this low frequency, B cells ($CD19^{+}$) play a critical role in the humoral component of the adaptive immune system.[17,18] This systematic review of 67 studies by Walzik et al. evaluated the effects of acute (22 studies) and chronic exercise (45 studies) on B cells, immunoglobulins, and markers of secretory immunity. In general, these authors determined that acute exercise has a significant impact on B cell counts and secretory and plasma immunoglobulins. Blood B cell concentrations decrease after prolonged and intensive exercise and complement the egress of most lymphocyte subsets from the blood compartment due to increases in stress hormones.[19] Most B cell-related outcomes do not change in response to chronic exercise training. The process of establishing evidence-based conclusions was limited due to the large heterogeneity in study populations and designs, exercise workloads, and the lack of proper control conditions.

The 20-year systematic review by Luo et al. focused on the role of exercise training in alleviating inflammation in adolescents and adults with autoimmune diseases. About 4% of the world's population is affected by autoimmune diseases, and this proportion rises to 10% in some countries such as the United Kingdom.[20] Most autoimmune disorders are more common in women than in men and can develop at any age depending on the individual autoimmune disease. Common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, psoriasis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, inflammatory bowel disease, Graves' disease, Sjögren's syndrome, and Hashimoto's thyroiditis. Inflammation undergirds most autoimmune diseases as the immune system attacks the healthy cells of tissues and organs by mistake.[21] This systematic review of 87 papers showed that moderate training protocols using both aerobic and resistance exercises tended to exert anti-inflammatory effects in individuals with autoimmune disorders. More clinically meaningful improvements in inflammation biomarkers may require greater exercise workloads and weight loss, but this may exceed the capabilities of most patients. Acute exercise, generally of moderate intensity due to patient limitations, had a modest and transient effect in increasing some inflammation biomarkers. The authors concluded that most patients with autoimmune disorders can safely adopt moderate exercise training protocols but changes in inflammation biomarkers will be modest at best.

The papers included in this special topic support the profound effects that exercise has on the immune system.[22,23] Appropriate exercise training workloads support the immune system in its varied roles and mediate multiple health benefits.[23]

Competing interests

The author declares that he has no competing interests.

References

1. Chastin SFM, Abaraogu U, Bourgois JG, et al. Effects of regular physical activity on the immune system, vaccination and risk of community-acquired infectious disease in the general population: Systematic review and meta-analysis. *Sports Med* 2021;**51**:1673–86.
2. Nieman DC. Coronavirus disease-2019: A tocsin to our aging, unfit, corpulent, and immunodeficient society. *J Sport Health Sci* 2020;**9**:293–301.
3. Vanhelst J, Srour B, Bourhis L, et al. Association of SARS-CoV-2 infection with physical activity domains and types. *Sci Rep* 2023;**13**:19187. doi:10.1038/s41598-023-46162-4.
4. Appelman B, Charlton BT, Goulding RP, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nat Commun* 2024;**15**:17. doi:10.1038/s41467-023-44432-3.
5. Ahmadi MN, Huang BH, Inan-Eroglu E, Hamer M, Stamatakis E. Lifestyle risk factors and infectious disease mortality, including COVID-19, among middle aged and older adults: Evidence from a community-based cohort study in the United Kingdom. *Brain Behav Immun* 2021;**96**:18–27.
6. Nieman DC. Exercise is medicine for immune function: Implication for COVID-19. *Curr Sports Med Rep* 2021;**20**:395–401.
7. Hamer M, Kivimäki M, Gale CR, Batty GD. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: A community-based cohort study of 387,109 adults in UK. *Brain Behav Immun* 2020;**87**:184–7.
8. Nieman DC, Sakaguchi CA. Physical activity lowers the risk for acute respiratory infections: Time for recognition. *J Sport Health Sci* 2022;**11**:648–55.
9. Sallis R, Young DR, Tartof SY, et al. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: A study in 48 440 adult patients. *Br J Sports Med* 2021;**55**:1099–105.
10. Rahmati M, Shamsi MM, Khoramipour K, et al. Baseline physical activity is associated with reduced mortality and disease outcomes in COVID-19: A systematic review and meta-analysis. *Rev Med Virol* 2022;**32**:e2349. doi:10.1002/rmv.2349.
11. Denay KL, Breslow RG, Turner MN, Nieman DC, Roberts WO, Best TM. ACSM call to action statement: COVID-19 considerations for sports and physical activity. *Curr Sports Med Rep* 2020;**19**:326–8.
12. Snyders C, Pyne DB, Sewry N, Hull JH, Kaulback K, Schwellnus M. Acute respiratory illness and return to sport: A systematic review and meta-analysis by a subgroup of the IOC consensus on "acute respiratory illness in the athlete". *Br J Sports Med* 2022;**56**:223–31.
13. Derman W, Badenhorst M, Eken M, et al. Risk factors associated with acute respiratory illnesses in athletes: A systematic review by a subgroup of the IOC consensus on "acute respiratory illness in the athlete". *Br J Sports Med* 2022;**56**:639–50.
14. Manella G, Ezagouri S, Champigneulle B, et al. The human blood transcriptome exhibits time-of-day-dependent response to hypoxia: Lessons

from the highest city in the world. *Cell Rep* 2022;**40**:111213. doi:10.1016/j.celrep.2022.111213.
15. Albany CJ, Trevelin SC, Giganti G, Lombardi G, Scottà C. Getting to the heart of the matter: The role of regulatory T-cells (Tregs) in cardiovascular disease (CVD) and atherosclerosis. *Front Immunol* 2019;**10**:2795. doi:10.3389/fimmu.2019.02795.
16. Catitti G, De Bellis D, Vespa S, Simeone P, Canonico B, Lanuti P. Extracellular vesicles as players in the anti-inflammatory inter-cellular crosstalk induced by exercise training. *Int J Mol Sci* 2022;**23**:14098. doi:10.3390/ijms232214098.
17. Morbach H, Eichhorn EM, Liese JG, Girschick HJ. Reference values for B cell subpopulations from infancy to adulthood. *Clin Exp Immunol* 2010;**162**:271–9.
18. Martinez F, Novarino J, Mejía JE, Fazilleau N, Aloulou M. Ageing of T-dependent B cell responses. *Immunol Lett* 2021;**233**:97–103.
19. Simpson RJ, Bolau TK, Weyh C, et al. Exercise and adrenergic regulation of immunity. *Brain Behav Immun* 2021;**97**:303–18.
20. Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: A population-based cohort study of 22 million individuals in the UK. *The Lancet* 2023;**401**:1878–90.
21. Li SJ, Wu YL, Chen JH, Shen SY, Duan J, Xu HE. Autoimmune diseases: Targets, biology, and drug discovery. *Acta Pharmacol Sin* 2024;**45**:674–85.
22. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019;**8**:201–17.
23. Nieman DC, Pence BD. Exercise immunology: Future directions. *J Sport Health Sci* 2020;**9**:432–45.

David C. Nieman , Guest editor
Human Performance Laboratory, Appalachian State University, North Carolina Research Campus, Kannapolis, NC 28081, USA
E-mail address: niemandc@appstate.edu

Received 10 January 2024; Accepted 18 January 2024

Available online 25 January 2024