Physical ACTIVITY

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Immune Function: Impact of Exercise and Nutritional Interventions

Abstract: *This article provides a brief commentary on the accompanying article, "Nutrition and Physical Activity Interventions to Improve Immunity" by Davison, Kehaya, and Jones. The article reviews the evidence on physical exercise and/or nutrition in modulating immune response, with a specific focus on the prevention of respiratory infection. Given the large scope of the review, an overview of current findings is presented, rather than in-depth discussions, and the nutritional strategies discussed tend to focus on the strategies that have been studied in the context of exercise. Some further insight is provided in the commentary on potential mechanisms that may explain the benefits of exercise, a brief discussion on the impact of obesity and host defense, and future directions for research. In general, the article sufficiently describes the current evidence, and draws appropriate conclusions based on the evidence presented. The article is recommended for audiences that have limited background on these topics, and for those who are familiar with this line of research.*

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The accompanying article, "Nutrition and Physical Activity Interventions to Improve Immunity," provides an overview of the evidence that supports a role for exercise or nutrition in modulating immune function, with particular attention to respiratory infection. The authors correctly point out that the benefits of physical activity on immunity are often overlooked. One potential reason for the lack of attention is that communicable disease may not be deemed as "critical" as noncommunicable diseases such as heart disease or diabetes. However, influenza/pneumonia consistently ranks among the top 10 causes of death in the United States, and the total economic burden of influenza alone is estimated to be $87.1 billion per year.[1] The common cold and other upper respiratory noninfluenza infections are not typically considered to be severe diseases, but due to the high incidence rates, the economic burden is estimated at ~$40 billion annually.[2] Therefore, lifestyle practices that reduce the risk or severity of respiratory infection not only affect health of the individual, but have significant economic consequences and deserve attention.

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The article concludes that regular moderate exercise should be promoted as a strategy to prevent respiratory infection, contradicting the conclusion made in a recent Cochrane Database Systematic Review.[3] The majority of

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studies show some benefit of exercise in terms of reduced severity, duration, or incidence of respiratory infection, but when the studies are reviewed together, the large variability in methods to assess infection limits the likelihood of finding a consistent result. Yet, one reliable finding was a reduction in the number of symptom days per infectious episode. A better understanding of the mechanisms underlying protection could lend greater support for a beneficial role of exercise in respiratory infection. The evidence from experimental animal studies in which exposure to pathogen and amount of physical activity can be controlled demonstrate more consistent results. The authors mention several potential explanations for enhanced protection from infection (eg, postexercise "immunostimulation," shift in type of T helper cell lymphocytes, salivary sIgA), but an in depth analysis of animal experimental studies provides additional insight into mechanisms of action. The findings from several studies using a respiratory infection challenge model illustrate that moderate exercise consistently results in reduced influx of inflammatory cells into the lungs, decreased pathogen load, improved disease outcome, and typically lower chemokine and pro-inflammatory cytokines in the lungs or bronchoalveolar lavage fluid. The anti-inflammatory effect of exercise occurs in both viral infection, and in common respiratory secondary bacterial infections such as *Streptococcus pneumoniae* or in a model of lipopolysaccharide-induced lung injury.[4-8] The impact of exercise appears to be a local respiratory system effect as one study demonstrates that intraperitoneal viral challenge results in no effect of exercise, whereas the immune response to intranasal viral challenge is altered by exercise treatment.[9] It is also significant to note that the anti-inflammatory effect of exercise is beneficial with respect to disease outcome. In contrast, nutritional anti-inflammatory interventions such as fish oil minimize inflammation during influenza infection, but exacerbate disease severity.[10] Integrating the findings from animal and human studies, the available evidence points to the possibility that a reduction in the number of symptom days per infectious episode may result from reduced inflammation. Also, the early reduction in pathogen load observed in animal studies may be due to enhanced immune surveillance, thereby reducing the requirement for a potent inflammatory response, yet further research is needed to define the in vivo mechanisms of immune enhancement.

As the authors suggest, the use of vaccination models to evaluate the immunomodulatory efficacy of physical activity is a clinically relevant approach. The article accurately summarizes the effect of long-term exercise and acute exercise on response to immunization, suggesting that exercise training or higher aerobic fitness are generally associated with improved antibody response, whereas the beneficial effect of acute exercise is less consistent. Other reviews propose the concept that the benefits of exercise are greater when immune response are weak, such as in older adults or reduced vaccine dose.[11] A limitation of the available studies is that sample size tends to be small, making it difficult to clearly establish whether the exercise-induced improvement in antibody response translates to improved protection from infection. In general, the information on physical activity and vaccine response is largely limited in scope to serum antibody, most likely due to the fact that the majority of published studies use antibody response as the sole outcome measure. The review article does not separately address the topic of exercise and cell-mediated immunity (CMI) response to vaccination, yet several recent studies highlight the importance of CMI in protection from infection rather than serum antibody. For example, antigen-specific $CD4^+$ T cells predict protection from influenza infection,[12] and granzyme B producing T cells serve as a better correlate of protection than serum antibody in the aged.[13,14] Tissue resident memory T cells and central memory T cells also play a critical role in protection on infectious challenge,[15-17] but very limited information exists regarding the impact of acute or long-term exercise on CMI. Three of 4 vaccination studies involving human participants which included a measure of CMI observed a positive impact.[18-21] The findings from an experimental study involving vaccination with OVA demonstrate increased $CD4^+$ T cell response in exercise trained mice.[22] Interestingly, the increase in $CD4^+$ T cell cytokine production and proliferation in exercised mice was observed with 2 different routes of vaccine administration (intraperitoneal and subcutaneous delivery), which may have implications for elucidation of underlying mechanisms. Overall, the current evidence suggests that exercise may improve immune response to vaccination, in agreement with the conclusion made by the authors. However, many questions remain to be explored, such as the optimal type of exercise, the timing of exercise in relation to vaccination, the quality of the antibody response, the extent to which immune alterations translate to protection, the impact of exercise on CMI and establishment of memory cell population, and finally, identifying the underlying mechanisms by which exercise improves immunity to vaccination.

The review article also discusses the influence of nutrition on immunity. The potential scope of this topic is enormous, and therefore the authors confine the discussion to "clinically relevant" measures, defined as in vivo measures of immunity and/or infection outcome. An initial discussion of obesity points out that the impact of obesity on host defense has received little attention, but does not bring to light the recent findings that demonstrate a negative impact of obesity on host response to infectious disease. The recent influenza pandemic afforded an opportunity to analyze the risk of infection, and obesity has been implicated as a significant risk factor.[23,24] Obesity also reduces immune response to tetanus, hepatitis, and influenza vaccine.[25-27] Numerous studies demonstrate that that obesity impairs immune response to infection, as recently reviewed by Milner and Beck.[28] One study has found that exercise training minimizes the severity of influenza infection in obese mice,[8] but additional studies are needed to support this finding. Given the prevalence of obesity, a better understanding of the potential protective role of exercise in protection from infectious disease is warranted. In contrast to obesity, malnutrition or deficiency of specific nutrients has been recognized for quite some time as a factor that can contribute to infectious disease incidence and/or severity of infection. Instead of providing an extensive review of nutrient deficiency and immunity, the authors limit the scope of discussion to nutrient strategies that may further enhance immunity assuming a well-nourished state. The authors tend to focus on nutritional strategies that may have some role in affording greater protection from infection under exercise conditions, rather than a wide-ranging discussion of nutrient interventions that may improve host defense against infectious disease. Carbohydrate supplementation, particularly during prolonged activity can minimize alterations of immune response but the majority of current evidence does not yet clearly demonstrate a role for carbohydrate in minimizing risk of infection. The role of other macronutrients, protein and fat, are not reviewed, and there is limited information regarding the role of these nutrients in preventing infection in athletes. Although not discussed in the article, nutrient and immune pathogen-sensing systems share the same cell signaling pathways, and this interaction may affect host defense under conditions of metabolic stress. The rapidly expanding research area of immunometabolism is likely to provide further insight into the alterations of immune response under specific metabolic conditions such as carbohydrate availability, and this topic can be reviewed elsewhere.[29]

The remaining nutrition topics discussed include antioxidants, vitamin D, probiotics, bovine colostrum, and plant-derived dietary supplements, with an emphasis on studies involving athletes and risk of upper respiratory infection. By and large, the authors cite studies with a positive effect on immunity for each of these nutrients or dietary supplements, but the data are inconsistent, again likely due to several reasons such as small sample sizes, variability in outcome measures, timing of nutrient administration in relation to pathogen exposure, lack of pathogen control, and so on. Because of these limitations, the authors conclude that there may be some benefit to each of the nutritional interventions, but current evidence is insufficient, and therefore the recommendation of a well-balanced diet with adequate intake of fruits and vegetables is made. These recommendations are consistent with the US dietary guidelines and provide a common sense approach given the available evidence. There may be special populations for which nutritional supplementation may have specific immune-enhancing benefits, such as the "neophyte" described by the authors as an individual of low fitness level embarking on a new exercise program. However, evidence to support this possibility remains to be established, and therefore the recommendation to follow healthy diet guidelines is prudent.

In conclusion, the 4 major key points in the author's summary are generally supported by the current evidence. These include a benefit of moderate exercise in prevention of respiratory infection, potential "adjuvant-like" properties of exercise during immunization, the use of cautionary approach with respect to dietary supplements, and the consumption of a well-balanced diet with sufficient fruit and vegetable intake. Additional support for these recommendations may be discovered in the future with further research focused on identifying the mechanisms of action. AJLM

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