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Viewpoint

Physical activity: A coadjuvant treatment to COVID-19 vaccination?

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The recently developed vaccines against infection with the SARS-Cov-2 virus hold great promise for reducing the burden of COVID-19 and achieving herd immunity, which will hopefully restore normal life in the near future. Yet, there are several unresolved issues regarding actual vaccination efficacy in real life scenarios, especially in the mid to long term. Potential inter-individual variability of induced immune responses is another issue, with numerous factors — whether modifiable or not — potentially influencing vaccination efficacy (Zimmermann and Curtis, 2019). One lifestyle-related (and thus modifiable) factor is physical exercise.

Although specific studies with COVID-19 vaccines have not been conducted, experience from previous vaccination programs (notably influenza) suggests that *regular exercise practice* might be an effective strategy for boosting antibody responses. For instance, young elite athletes have a more pronounced increase in T-cells and neutralizing antibodies after influenza vaccination than age-matched controls (Ledo et al., 2020). There is also cross-sectional evidence for a beneficial effect of sustaining high physical activity levels in older adults, with very active older Chinese women (>65 years) who walked more (over 18,509 steps/day on average) in the weeks following vaccination showing a better immunological response (*i.e.*, greater expansion of monocytes and plasmablasts in peripheral blood, and higher induction of antibodies at 18-month follow-up) than their less active peers (less than 10,927 steps/day) (Wong et al., 2019). Similarly, older adults who had trained in sports for 17 or more years on average had a higher antibody response to influenza vaccination than age-matched untrained individuals (de Araújo et al., 2015). There is also evidence from intervention studies supporting a beneficial role of regular exercise. Notably, a study with participants aged ~70 years who were previously sedentary and had poor influenza vaccine responses found that those randomized to a moderate-intensity cardiovascular exercise (3 sessions per week of up to 60 min per day) showed marked improvements in influenza seroprotection throughout the entire influenza season compared with the control group (Woods et al., 2009).

A more controversial issue is the effects of *acute exercise* interventions (*i.e.*, a single exercise bout) on vaccine responses. The rationale for studying acute exercise effects comes from data in animal studies showing that an acute stressor in close temporal proximity to immune challenge can enhance the response to delayed-type hypersensitivity and antibody response to vaccination (Millán et al., 1996; Silberman et al., 2003). In young adults, acute stress through either a mental task or an exercise bout (four 4-minute cycling steps at increasing workloads up to ~80% of peak power output) before vaccination induced a stronger antibody response — albeit only statistically significant in women — as compared with a control condition, with this effect seemingly mediated by exercise-induced increases in the release of the myokine interleukin-6 (Edwards et al., 2006). A later study by the same group showed that performing eccentric contractions of the deltoid and biceps *brachii* muscles of the non-dominant arm 6 h before influenza vaccination (also in the non-dominant arm) improved cell-mediated response (as reflected by enhanced interferon-γ responses) in men and increased antibody responses in women (Edwards et al., 2007). Other studies have, however, failed to find a beneficial effect of acute exercise on the antibody response to vaccination. A recent study in older adults (mean age 73 years) reported no effects of a resistance exercise bout performed before influenza vaccination on antibody titers or influenza-like symptoms during a 6-month follow-up, although exercise did reduce vaccination reactions (Bohn-Goldbaum et al., 2020). Some authors have reported no consistent immunostimulatory effects of acute bouts of low-to-moderate-intensity endurance exercise (40–45 min at ~55–65% of maximum heart rate) before influenza or pneumococcal vaccination in either young or old adults, although greater exercise benefits on immune responses were observed in women (Long et al., 2012; Ranadive et al., 2014).

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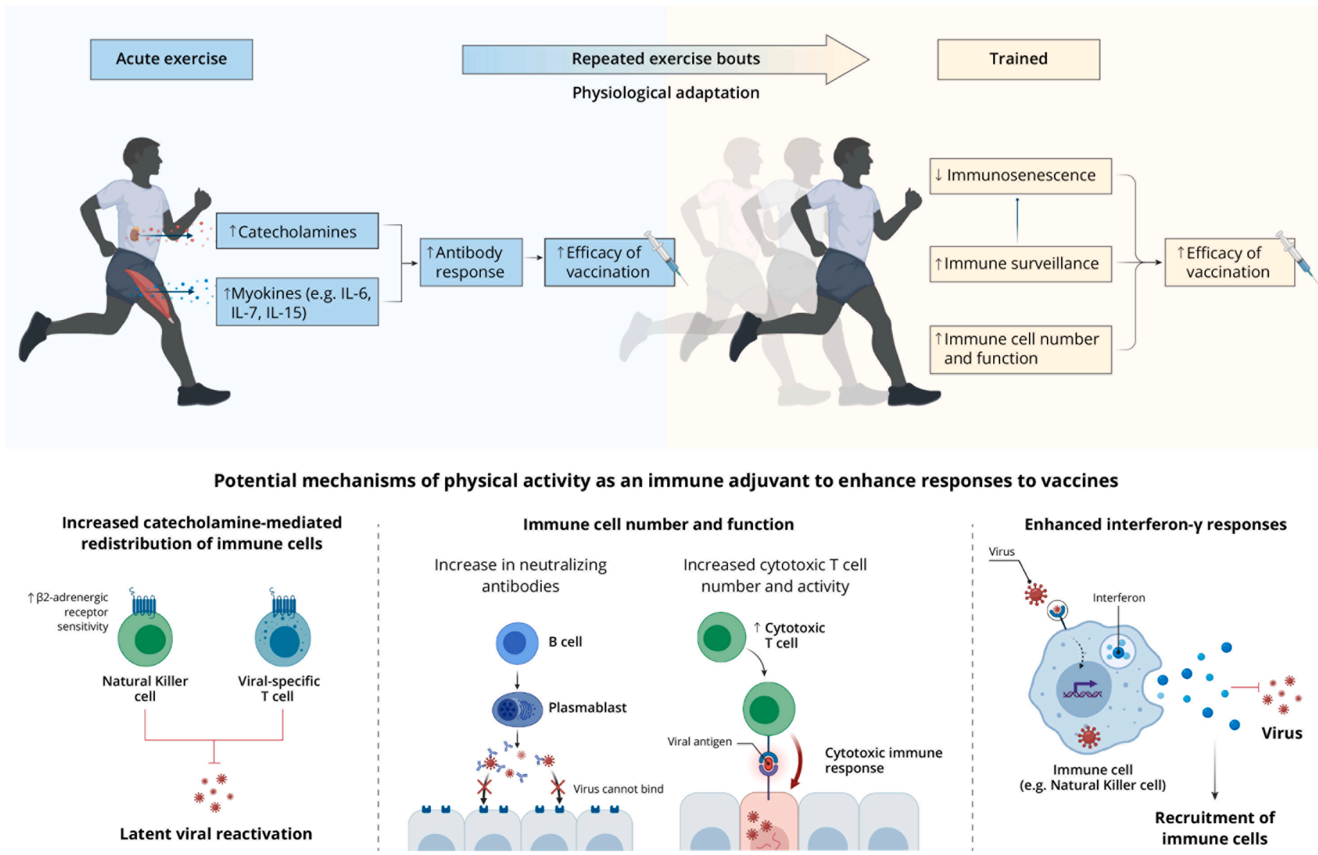

Fig. 1. Potential mechanisms explaining the benefits of regular — and potentially acute — exercise performed before vaccination to enhance immune response. Abbreviation: IL, interleukin.

Ensuring vaccination efficacy and safety is critical, particularly for the most vulnerable population segments such as frail older adults. Even though these individuals will likely be among the first to be vaccinated and evidence to date suggests a high efficacy of most COVID-19 vaccines in both old and young individuals (Soiza et al., 2021), scarcer evidence is available for very old frail adults with multiple comorbidities, a population segment sparingly included in clinical trials (Soiza et al., 2021; van Marum, 2020). Although at this point there is not enough evidence to discern whether older adults might present a lower antibody response to COVID-19 vaccination (Soiza et al., 2021), previous data suggests a negative influence of age on the effectiveness of influenza vaccination (*i. e.*, 11% among individuals aged ≥65 years *vs* 52% in those aged 50–54) (McLean et al., 2015). In this regard, gradual impairment of the immune system with age ('immunosenescence') is a substantial contributor to increased risk or morbidity and mortality (including from viral infections) in older individuals, with this phenomenon potentially attenuated by the boosting effect that regular exercise has on immune function (Duggal et al., 2019).

A physically active lifestyle prevents immunosenescence through several mechanisms [as reviewed in depth elsewhere (Duggal et al., 2019)] (Fig. 1). These include an increase in lymphocyte β2-adrenergic receptors, allowing for the catecholamine-mediated redistribution of natural killer (NK) cells and viral-specific T-cells between the blood and tissues with each bout of exertion. The frequent redistribution of NK cells and viral-specific T cells with each exercise bout enhances immune surveillance, diminishing the frequency of latent viral reactivation. In turn, this reduces the antigenic load placed on the T-cell compartment and prevents the accumulation of exhausted T cells while maintaining the number and diversity of peripheral naïve T cells. Indeed, physically active older adults are known to have fewer of so called 'senescent' T cells and more naïve T cells compared to their sedentary counterparts. Importantly, preserving a diverse pool of naïve T-cells and functional NK-cells is likely to reduce infection risk, and the regular release of muscle-derived cytokines such as IL-7 and IL-15 has been purported to play important roles in the beneficial effects of exercise on immunity (Duggal et al., 2019). Specifically, IL-7 can help maintain thymic mass (which otherwise atrophies with age) and increase the ability of this lymphoid organ to produce antigen virgin (*i.e.*, 'naïve') T-cells that are essential in mounting immune responses to novel antigens and differentiating into 'memory' T-cells for long-lasting immunity. Moreover, IL-15 plays a critical role in the maintenance of the peripheral T-cell and NK-cell compartments, ensuring that they proliferate and function optimally when encountering virus-infected cells. Thus, exercise-induced attenuation of immunosenescence might help to improve immune responses to vaccination by maintaining the peripheral T-cell pool and their ability to respond to novel vaccine antigens.

Further research is needed to confirm whether apart from *regular exercise* practice in the previous weeks or months, *acute exercise* performed in the hours prior to COVID-19 vaccination might improve immune responses. Particularly, evidence is warranted regarding exercise effects on the immune responses to vaccination of immunocompromised individuals (*e.g.*, cancer patients, frail older adults), as most available evidence in the field comes from data on healthy adults. The specific characteristics (mode, duration and intensity) of chronic or acute exercise that induce the greatest immunostimulatory effects also remain to be identified, as well as the potential confounding effect of important lifestyle factors such as psychosocial stress, nutrition, or sleeping habits. There is also a critical need to understand how exercise training affects the function of antigen-presenting cells (*e.g.*, dendritic cells), which are paramount in the acquisition of antigen 'memory' after vaccination. Notwithstanding, growing evidence supports the role of *regular exercise* for maximizing overall vaccination efficacy and safety, and preliminary evidence with a robust physiological basis suggests that *acute exercise*-induced stress before influenza vaccination (preferably if the exercise stimulus is sufficiently high, *e.g.* whole body exercise at >70% of peak power output or local resistance exercise at >70% of one-repetition maximum) might enhance antibody responses. In the current COVID-19 vaccination program, it would also be interesting to determine whether a single bout of exercise performed immediately prior to administering the first vaccine dose could be advantageous, particularly if found to increase anti-body titers to levels that are comparable with a second dose in non-exercised individuals. This could save a large number of vaccine vials so that they may be given to many more people without delay.

Finally, it must be noted that leading COVID-19 vaccine candidates are using different strategies (*e.g.*, lipid-encapsulated mRNA or adenovirus vectors) from those used in previous influenza vaccines (made of inactivated, attenuated, or recombinant viruses), and therefore the benefits observed for exercise on previous vaccination programs might not be generalizable to the recently developed COVID-19 vaccines. In those countries where vaccination programs are being especially fast and efficacious (*e.g.*, Israel) it might be possible to gather epidemiological data on the possible effect of an active (*vs* an inactive) lifestyle on vaccination efficacy.

Beyond vaccination, the current pandemic has taught us the importance of preventive lifestyle measures. Social distancing, good hygiene and forced lockdowns are indeed necessary, but so too is physical exercise, which is not just safe but has also a potential preventive role, especially for the most vulnerable groups.

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