Evidence-based physical activity for COVID-19: what do we know and what do we need to know?

Bruno Gualano

Since the WHO declared COVID-19 a pandemic in March 2020, scientists have put great effort into increasing our understanding of the linkages between this new disease and the multiple factors that potentially affect its prognosis. Evidence began to accumulate that COVID-19 can be more lethal in individuals with clinical conditions that weaken immune function. As regular physical activity (PA) knowingly improves immunity,[1] a growing number of studies have investigated whether PA could change the natural course of COVID-19.

PA AND COVID-19 OUTCOMES IN THE GENERAL POPULATION

The first indication that PA could be a predictor of severity of COVID-19 outcomes derived from a community-based cohort study of 387 109 adults in the UK, showing that physical inactivity increased the relative risk (RR) of COVID-19 hospital admission by 32%.[2] Supporting these data, another population-based study of 48 440 individuals in the USA showed participants who were consistently inactive had a greater risk of hospitalisation (adjusted OR (aOR): 2.26), admission to the intensive care unit (ICU) (aOR: 1.73) and death (aOR: 2.49) than those who were consistently meeting PA guidelines.[3] Similar findings were obtained by a nationwide cohort study of 12 768 adults in South Korea, in which participants who adhered to recommendations for both aerobic and strengthening activities had a lower risk of SARS-CoV-2 infection (adjusted RR (aRR): 0.85), severe COVID-19 outcomes (aRR: 0.42) and COVID-19-related death (aRR: 0.24) than those who did not.[4] These self-reported data were reinforced by an accelerometer-based study of 82 253 UK participants, in which odds of severe COVID-19 outcomes decreased by 37% in women and 16% in men per 30 min of daily moderate-to-vigorous PA.[5] Collectively, these studies suggest that meeting PA guidelines is associated with reduced risks of developing severe COVID-19.[1–5] As athletes often exhibit mild disease, one may conjecture that higher levels of PA may further improve protection, although this needs confirmation.[6]

PA AND COVID-19 PROGNOSIS IN HOSPITALISED PATIENTS

It remains controversial whether PA levels are associated with a better prognosis among already hospitalised patients. A retrospective study of 552 patients hospitalised with COVID-19 in Spain estimated that sedentary lifestyle was associated with a ~6-fold increase in the risk of mortality.[7] However, recall bias cannot be ruled out, since questionnaires were completed up to 120 days after discharge, and for those who died, patients' relatives provided the data. In fact, in a small-scale cohort study of 200 patients hospitalised with moderate-to-severe COVID-19 in Brazil, PA over the past 12 months was not associated with length of stay or any other clinical outcome.[8] This does not mean that PA is futile in preventing severe cases of COVID-19, but that its benefits may vary across stages of the disease.

PA ENHANCES VACCINE-INDUCED IMMUNOGENICITY

Vaccines have been key to mitigating severe COVID-19 cases, but vaccine-induced immunogenicity may be lower in immunosuppressed patients or older individuals. For those populations, it has been speculated that PA could act as a behavioural adjuvant to vaccines.[1] A phase IV trial of 898 immunocompromised patients receiving a two-dose schedule of CoronaVac showed that being active (achieving ≥150 min/week of moderate-to-vigorous PA) was associated with greater seroconversion rates (aOR: 1.4) and geometric mean titres (32%) versus being inactive.[9] Greater benefits were observed in patients performing ≥350 min/week of PA versus the least active group (≤30 min/week), whereas excessive sedentary behaviour (>8 hours/day) partially blunted the PA-mediated improvements on vaccine immunogenicity.[9] Importantly, secondary analysis showed that PA was also related to better humoral vaccine responses in a cohort of 197 non-immunocompromised participants, suggesting generalisability of the findings. A subsequent study derived

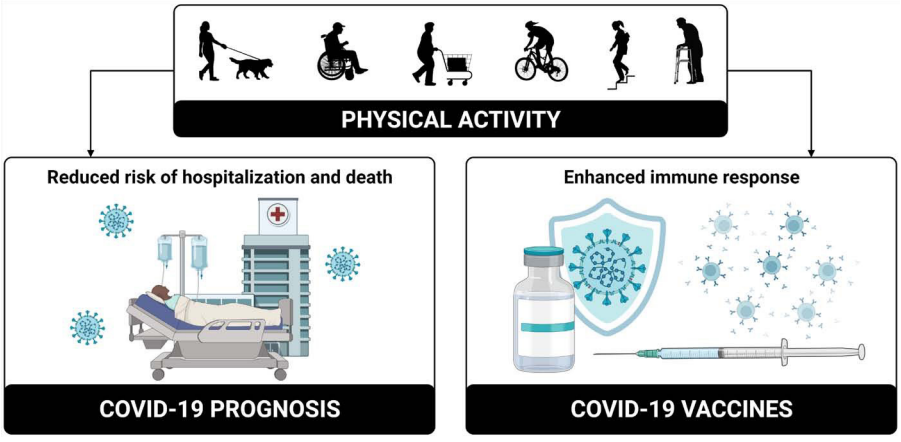

Figure 1 Observational studies have supported the potential benefits of regular physical activity in preventing severe cases of COVID-19 (eg, hospital admissions and deaths) and enhancing SARS-CoV-2 vaccine responses. Effectiveness assessments of population-based public health interventions, randomised controlled trials, and molecular and cellular physiological studies are necessary to unravel the roles and mechanisms of physical activity in this disease.

Applied Physiology & Nutrition Research Group; Laboratory of Assessment and Conditioning in Rheumatology; Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil

Correspondence to Professor Bruno Gualano, University of Sao Paulo, Sao Paulo 01246-903, Brazil; gualano@usp.br

from the same trial showed that PA was associated with greater antibody persistence 6 months after the second dose of CoronaVac among immunocompromised patients.[10] These studies suggest that PA enhances immunogenicity to SARS-CoV-2 vaccination and sustains its effects over time, which is crucial for those exhibiting suboptimal responses to vaccines. It remains to be determined whether this enhanced humoral response translates into increased vaccine effectiveness to prevent disease in the real world, and whether the immune response to other vaccine platforms associates with PA in the same way as inactivated vaccines do.

FUTURE DIRECTIONS

Lessons learnt from almost 2 years of intensive research on COVID-19 along with our already robust knowledge of exercise immunology and clinical exercise physiology form the basis for a global call for action: promote PA during this pandemic and others (figure 1). There should be a particular emphasis on groups with compromised immune systems and chronic diseases. As with other areas of investigation into COVID-19, several gaps remain. Cross-sectional designs are prone to potential reverse causality and selection bias (collider), therefore precluding causative inferences. Large-scale, randomised controlled trials and effectiveness evaluations of public health programmes should validate and extend data obtained from observational studies and gather knowledge on the optimal PA recommendation to prevent severe COVID-19. Moreover, the use of experimental models may be useful to gather information on molecular and cellular physiological mechanisms underlying the effects of PA in this disease. It is also important to evaluate whether PA can mitigate SARS-CoV-2 transmission and reinfection and prevent and/or treat persistent symptoms (ie, long COVID-19).

Perhaps more than any other tool, PA fulfils four critical areas of an effective healthcare intervention: affordability, accessibility, acceptability and availability. Governments, non-governmental organisations and private companies supporting research on COVID-19 across the world should be made aware that PA science is a field that should be prioritised.

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ORCID iD

Bruno Gualano http://orcid.org/0000-0001-7100-8681

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