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Aim: To investigate the association between physical activity and immunogenicity among SARS-CoV-2 seropositive patients with autoimmune rheumatic diseases prior to and following a 2-dose schedule of CoronaVac (Sinovac inactivated vaccine). *Methods*: This was a prospective cohort study within an open-label, single-arm, phase 4 vaccination trial conducted in Sao Paulo, Brazil. In this substudy, only SARS-CoV-2 seropositive patients were included. Immunogenicity was assessed by seroconversion rates of total anti-SARS-CoV-2 S1/S2 immunoglobulin G (IgG), geometric mean titers of anti-S1/S2 IgG, frequency of positive neutralizing antibodies, and neutralizing activity before and after vaccination. Physical activity was assessed through a questionnaire. Model-based analyses were performed controlling for age (<60 or ≥60 y), sex, body mass index (<25, 25–30, and >30 kg/m^2), and use of prednisone, immunosuppressants, and biologics. *Results:* A total of 180 seropositive autoimmune rheumatic disease patients were included. There was no association between physical activity and immunogenicity before and after vaccination. *Conclusions:* This study suggests that the positive association between physical activity and greater antibody responses seen in immunocompromised individuals following vaccination is overridden by previous SARS-CoV-2 infection and does not extend to natural immunity.

Keywords: physical inactivity, vaccine, COVID-19, immunosuppression

Patients with autoimmune rheumatic diseases (ARD) have a reduced vaccine-induced immunogenicity against SARS-CoV-2 compared with non-ARD individuals, irrespective of the vaccine platform.[1–3] However, the immune response to natural infection seems to be similar among ARD and non-ARD individuals.[4]

Physical activity has been shown to improve cell-mediated and humoral immunity, promote enhanced immunosurveillance, and modulate chronic inflammation.[5,6] Possibly owing to these mechanisms, a physically active lifestyle was recently associated with better and longer SARS-CoV-2 vaccine immunogenicity in ARD patients without previous SARS-CoV-2 infection.[7,8] Whether physical activity may also superimpose to a better immune response to natural SARS-CoV-2 infection in ARD patients remains unknown.

The aim of this study is to investigate possible associations between physical activity and immunogenicity among SARS- CoV-2 seropositive patients before and after a 2-dose schedule of CoronaVac SARS-CoV-2 vaccine.

Methods

This is a prospective cohort study within an open-label, single-arm, phase 4 vaccination trial (clinicaltrials.gov #NCT04754698), conducted at a tertiary referral hospital in Sao Paulo, Brazil.[1] The protocol was approved by the institutional ethics committee. Written informed consent was obtained before participants' enrollment.

ARD patients aged ≥18 years, diagnosed with rheumatoid arthritis, systemic lupus erythematosus, axial spondyloarthritis, psoriatic arthritis, primary vasculitis, primary Sjögren syndrome, systemic Smaira et al sclerosis, idiopathic inflammatory myopathies, and primary antiphospholipid syndrome, who were seropositive for SARS-CoV-2-specific antibodies (i.e., anti-S1 or S2 immunoglobulin G [IgG] or neutralizing antibodies) at baseline (before vaccination scheme) were included. Detailed inclusion and exclusion criteria for the main cohort and subgroup analysis for seropositive patients are described elsewhere.[1,9]

Participants underwent a 2-dose schedule of CoronaVac (Sinovac Life Sciences, batch #20200412).[1] Immunogenicity was assessed before and after vaccination (first and second doses) by measuring seroconversion rates of total anti-SARS-CoV-2 S1/ S2 IgG (considering values > 15.0 UA/mL; seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG), geometric mean titers of anti-S1/S2 IgG, and frequency of neutralizing antibodies (inhibition ≥ 30%). Geometric mean titers of anti-S1/S2 IgG and frequency of neutralizing antibody assays are thoroughly described elsewhere.[1,7]

Typical levels of physical activity prior to vaccination were assessed using a telephone-based survey. This survey consisted of 8 questions that pertained to 4 distinct domains of physical activity, namely, leisure time, household activities, work, and commuting. The participants were inquired about the number of days per week and the minutes per day they spent engaging in moderate- to vigorous-intensity activities in each domain. Participants were classified as either physically active or inactive according to World Health Organization guidelines (ie, physical inactivity defined as <150 min/wk of moderate- to vigorous-intensity aerobic activity).[10]

Comparison between groups (active vs inactive) was performed using chi-square test for categorical variables and Kruskal–Wallis test for continuous variables. Adjusted analyses were performed controlling for age (<60 or ≥60 y), sex, body mass index <25, 25–30, and >30 kg/m^2), and use of prednisone, immunosuppressants, and biologics. We conducted linear regressions for log-transformed IgG. Linear regression coefficients and 95% confidence intervals for log-transformed dependent variables were back transformed and presented as percent changes. Detailed statistical analyses were described elsewhere.[7] Analyses were conducted using R statistical environment (R, version 4.1.0 for Windows).

Results

A total of 180 seropositive ARD patients were included. Physically active (n = 107) and inactive (n = 73) ARD patients were similar for all clinical characteristics. All patients had 100% seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG and frequency of neutralizing antibodies at baseline (Table 1).

Adjusted models showed that physical activity was not associated with immunogenicity either before (Figure 1A) or after (Figure 1B) vaccination.

Discussion

This study showed that physical activity does not associate with immunogenicity in SARS-CoV-2 seropositive ARD patients either before or after CoronaVac vaccination.

Regular physical activity is a well-known protective factor against numerous noncommunicable diseases and has been associated with improved immune response to SARS-CoV-2 and other infectious diseases.[6,7,11] In addition, there is now evidence that physical activity may also protect against severe SARS- CoV-2-related outcomes (i.e., admission to intensive care unit and mortality).[12] Although physical activity is associated with enhanced and more durable immunogenicity in ARD patients after vaccination,[7,8] the immune response induced by natural infection may have been strong enough to outweigh any immune stimulatory effects that physical activity could play in this population. In other words, the robust antibody response to natural infection in ARD patients[4] may have created a ceiling effect for physical activity.

The limitations of this study include its observational design, the lack of estimates of vaccine effectiveness and cell-mediated markers, the relatively low number of seropositive patients in the cohort, the assessment of physical activity using a subjective tool, and the cross-sectional assessment of physical activity prior to vaccination, which may not accurately reflect the typical physical activity pattern and health condition before the pandemic.[13]

In conclusion, physical activity is not associated with better immunogenicity in SARS-CoV-2 seropositive ARD patients either before or after vaccination. Combined with previous findings,[7,8] this study suggests that the positive association between physical activity and greater antibody responses seen in immunocompromised individuals following vaccination is overridden by previous SARS-CoV-2 infection, and does not extend to natural immunity.

Table 1 Baseline Characteristics of Patients With ARD

	ARD active (N=107)	ARD inactive (N=73)	*P*
Age, y	47 (37–58)	52 (39–62)	.128
Sex, female	72 (67.3)	58 (79.5)	.105
BMI, kg/m^2	28.6 (24.8–31.3)	28.8 (24.8–31.6)	.456
Smoking	3 (2.8)	3 (4.1)	.955
Comorbidities	61 (57.0)	52 (71.2)	.075
Current therapy			
Prednisone	31 (29.0)	32 (43.8)	.064
Biologics	27 (25.2)	27 (37.0)	.128
Immunosuppressants	59 (55.1)	49 (67.1)	.145
Comorbidities	61 (57.0)	52 (71.2)	.075
Arterial hypertension	45 (42.0)	37 (50.7)	—
Diabetes mellitus	14 (13.1)	11 (15.1)	—
Chronic renal disease	1 (0.9)	3 (17.8)	—
Pulmonary hypertension	1 (0.9)	2 (2.7)	—
Immunogenicity[a]			
Frequency of NAb	107 (100)	73 (100)	—
SC	107 (100)	73 (100)	—
GMT	86.4 (48.8–142)	80.8 (47.7–238)	.548

Abbreviations: ARD, autoimmune rheumatic diseases; BMI, body mass index; GMT, geometric mean titers of anti-S1/S2 IgG; NAb, neutralizing antibodies; SC, seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG. Note: Data expressed as median (interquartile range) or n (%).
[a]After SARS-CoV-2 infection.

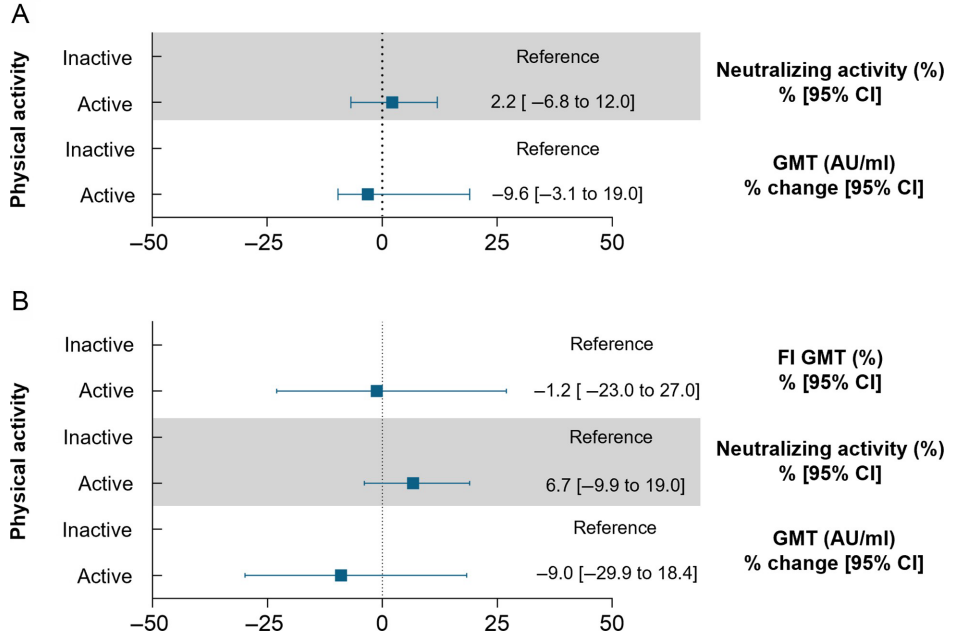

Figure 1 — Adjusted association of physical activity and immunogenicity before and after vaccination (first and second doses) with an inactivated vaccine against SARS-CoV-2 in ARD patients. Antibody responses in SARS-CoV-2 seropositive ARD patients (A) before vaccination and (B) after vaccination (first and second doses). Linear regression to estimate coefficients and 95% CIs. Model-based analyses were performed controlling for age (<60 or ≥60 y), sex, BMI (<25, 25–30, and >30 kg/m^2), and use of prednisone, immunosuppressants and biologics. Data expressed as either percent or percent change and 95% CI. ARD indicates autoimmune rheumatic diseases; BMI, body mass index; CI, confidence interval; FI-GMT, factor-increase in GMT; GMT, geometric mean titers of anti-S1/S2 IgG.

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