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Physical Activity: A Strategy to Improve Antibody Response to a SARS-CoV-2 Vaccine Booster Dose in Patients With Autoimmune Rheumatic Diseases

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Abstract

Background: Physical activity associates with improved immunogenicity following a 2-dose schedule of CoronaVac (Sinovac's inactivated SARS-CoV-2 vaccine) in patients with autoimmune rheumatic diseases (ARD). This study evaluates whether physical activity impacts vaccine-induced antibody responses to a booster dose in this population. *Methods:* This was a phase-4 trial conducted in São Paulo, Brazil. Patients with ARD underwent a 3-dose schedule of CoronaVac. One month after the booster, we assessed seroconversion rates of anti-SARS-CoV-2 S1/S2 IgG, geometric mean titers of anti-S1/S2 IgG, frequency of positive neutralizing antibodies, and neutralizing activity. Physical activity was assessed through questionnaire. *Results:* Physically active (n = 362) and inactive (n = 278) patients were comparable for most characteristics; however, physically active patients were younger ($P < .01$) and had a lower frequency of chronic inflammatory arthritis ($P < .01$). Adjusted models showed that physically active patients had ~2 times odds of seroconversion rates (OR: 2.09; 95% confidence interval, 1.22 to 3.61), ~22% greater geometric mean titers of anti-S1/S2 IgG (22.09%; 95% confidence interval, 3.91 to 65.60), and ~7% greater neutralizing activity (6.76%; 95% confidence interval, 2.80 to 10.72) than inactive patients. *Conclusions:* Patients with ARD who are physically active have greater odds of experiencing better immunogenicity to a booster dose of CoronaVac. These results support the recommendation of physical activity to improve vaccination responses, particularly for immunocompromised individuals.

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

Introduction

Robust evidence now shows that immunocompromised patients, such as those with autoimmune rheumatic diseases (ARD) have reduced immunogenicity to SARS-CoV-2 vaccines compared to controls, irrespective of the vaccine platform.[1–3] The underlying altered immune system in these patients in the context of a lower antibody response to vaccine may increase the risk of developing severe COVID-19 and might be associated with prolonged infection and viral shedding.[4–8] As new SARS-CoV-2 variants can arise during the course of such persistent cases of COVID-19, strategies are needed to improve vaccine responses among patients with dysfunctional immune systems.[9]

In interim analyses from a phase-4 vaccination trial, we showed that patients with ARD who were physically active (ie, achieving ≥150 min/wk of moderate to vigorous physical activity) had higher antibody titers and seroconversion rates than their physically inactive peers after 2 doses of CoronaVac (Sinovac's inactivated SARS-CoV-2 vaccine).[10] Moreover, being physically active was also associated with an increment in antibody persistence through 6 months after the 2-dose schedule.[11] Herein we report the association between physical activity and antibody responses in patients with ARD who received a booster dose (ie, third one) of CoronaVac.

Methods

This was a prospective cohort study within an open-label, single- arm, phase-4 vaccination trial (clinicaltrials.gov #NCT04754698), conducted at a tertiary referral hospital in São Paulo, Brazil. The protocol was approved by the institutional ethics committee. Written informed consent was obtained before participants' enrollment. Details on the study protocol (eg, setting, eligibility criteria, vaccination protocol, antibody assays) were described elsewhere.[2]

In brief, patients with ARD were eligible if they were ≥18 years old and diagnosed with rheumatoid arthritis, systemic lupus erythematosus, axial spondyloarthritis, psoriatic arthritis, primary vasculitis, primary Sjögren's syndrome, systemic sclerosis, systemic autoimmune myopathies, or primary antiphospholipid syndrome according to established disease criteria for each disease.[2] Exclusion criteria at baseline were: history of anaphylactic response to vaccine components, acute febrile illness or symptoms compatible with COVID-19 at vaccination, Guillain–Barré syndrome, decompensated heart failure (class III or IV), demyelinating disease, previous vaccination with any SARS-CoV-2 vaccine, history of live virus vaccine up to 4 weeks before, inactivated virus vaccine up to 2 weeks before, and receipt of blood products up to 6 months before the study, hospitalized patients, and pre-vaccination COVID-19 assessed by anti-SARS-CoV-2 S1/S2 IgG and/or neutralizing antibodies (NAb). Participants who had reverse transcription-polymerase chain reaction-confirmed COVID-19 after receiving first vaccine dose were excluded.[2]

Patients were previously immunized with a 2-dose schedule of CoronaVac (Sinovac Life Sciences) as described elsewhere.[2] The third dose was given 6 months after the second dose (September 2021).[12] The immunogenicity was assessed 1 month after the booster dose using seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (considering positive values >15.0 UA/mL), geometric mean titers of anti-S1/S2 IgG (GMT), frequency of positive NAb (inhibition ≥30%), and neutralizing activity (including only patients with positivity for NAb).[1,2]

A telephone-based survey assessed physical activity in 4 domains: leisure time, household activities, work, and commuting. Participants were classified as either physically active or inactive according to WHO Guidelines (ie, physical inactivity defined as <150 min/wk of moderate- to vigorous-intensity aerobic activity).[13]

Unadjusted models comparing active versus inactive patients were performed using χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Data are presented as percentages and median [interquartile range]. Model-based anal- yses using R statistical environment (R-4.1.0 for Windows) were performed controlling for age (<60 or ≥60 y), sex, and body mass index (<25 kg/m^2; 25–30 kg/m^2; >30 kg/m^2), use of prednisone, immunosuppressants, and biologics. Immunogenicity data and physical activity status were added as fixed effects. Logistic regressions were conducted to estimate odds ratio (OR) and 95% confidence interval (CI) for rates of IgG seroconversion and NAb positivity. Linear regressions were conducted to estimate coefficients and 95% CIs for natural log-transformed GMT (which was back transformed) and neutralizing activity and presented as percent changes.

Table 1 Baseline Characteristics of Patients With ARD According to Physical Activity Status

	Active ARD (n = 362)	Inactive ARD (n = 278)	*P*
Age, y	48.0 [39.2–59.0]	56.0 [45.2–65.0]	<.001
Sex, female	276 (76.24)	211 (75.89)	.993
Weight, kg	72.0 [62.0–82.4]	72.0 [61.0–83.7]	.778
Height, cm	160.0 [155.0–166.0]	160.0 [154.0–166.0]	.379
BMI, kg/m^2	27.8 [24.5–31.2]	27.5 [24.2–31.6]	.952
Overweight/obese	262 (72.37)	192 (69.06)	.686
Smoking	31 (8.56)	26 (9.35)	.835
Comorbidities			
Systemic arterial hypertension	155 (42.81)	131 (47.12)	.314
Diabetes mellitus	36 (9.94)	40 (14.38)	.109
Dyslipidemia	95 (26.24)	81 (29.13)	.469
Cardiomyopathy	24 (6.62)	14 (5.03)	.498
Chronic renal disease	12 (3.31)	18 (6.47)	.091
Chronic obstructive pulmonary disease	3 (0.82)	11 (3.95)	.01
Asthma	16 (4.41)	9 (3.23)	.575
Interstitial lung disease	18 (4.97)	31 (11.15)	<.01
Pulmonary hypertension	2 (0.55)	4 (1.43)	.414
Hematologic disease	1 (0.27)	1 (0.35)	1.00
Hepatic disease	11 (3.03)	15 (5.39)	.195
Cancer	4 (1.10)	4 (1.43)	.739
Stroke	9 (2.48)	8 (2.87)	.860
Tuberculosis	0 (0.0)	2 (0.71)	.188
ARD			
Chronic inflammatory arthritis (RA, axSpA, and PsA)	158 (43.9)	190 (69.1)	<.01
Other ARD (SLE, primary vasculitis, SSc, pSSj, IIMM, and PAPS)	204 (56.1)	88 (31.2)	<.01
Current therapy			
Prednisone	136 (37.56)	113 (40.64)	.373
Biologic	120 (33.14)	112 (40.28)	.075
Immunosuppressants	228 (62.98)	182 (65.46)	.571
Total physical activity, min/wk	401.0 [240.0–720.0]	0.0 [0.0–60.0]	<.001

Abbreviations: ARD, autoimmune rheumatic disease; axSpA, axial spondyloarthritis; BMI, body mass index; IIMM, idiopathic inflammatory myopathies; PAPS, primary antiphospholipid syndrome; PsA, psoriatic arthritis; pSSj, primary Sjögren syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. Note: Biologics include TNF inhibitor, abatacept, tocilizumab, belimumab, secukinumab, rituximab, and ustekinumab. Immunosuppressants include methotrexate, leflunomide, mycophenolate mofetil, azathioprine, tofacitinib, cyclophosphamide, tacrolimus, and cyclosporine. Missing data for weight and BMI (n = 1). Data are presented as median [interquartile range] and *n* (%).

Results

A total of 640 patients were analyzed (Table 1). Physically active (n = 362) and inactive (n = 278) patients with ARD were comparable for most characteristics; however, active patients were significantly younger ($P < .001$) and had a lower frequency of chronic inflammatory arthritis ($P < .01$) than inactive ones.

Figure 1 presents the unadjusted comparisons between physically active versus inactive patients. One month after the booster dose, seroconversion rates of total anti-SARS-CoV-2 S1/S2 IgG (52.0% vs 37.0%; $P < .01$), GMT (224.5 [66.0 to 399.2] vs 145.5 [37.1 to 385.5], $P = .01$), and neutralizing activity (84.4% [63.8% to 95.4%] vs 76.0% [49.2% to 93.6%], $P < .01$) were significantly greater in ARD active versus inactive patients. No difference was observed in frequency of positive NAb between the 2 groups ($P > .05$).

The adjusted models are shown in Figure 2. One month after the booster dose, being obese ($P < .01$) and using prednisone ($P < .01$), biologics ($P < .01$), and immunosuppressants ($P = .01$) were associated with poor immunogenicity. Conversely, being physically active was associated with improved immunogenicity ($P < .01$).

Point estimates from logistic regression models indicated that physically active patients had ~2 times greater odds of seroconversion rates (OR: 2.09; 95% CI, 1.22 to 3.61), ~22% greater GMT (22.09%; 95% CI, 3.91 to 65.60), and ~7% greater neutralizing activity (6.76%; 95% CI, 2.80 to 10.72) than inactive ones. Being physically active was not associated with NAb positivity (OR: 1.15; 95% CI, 0.78 to 1.68).

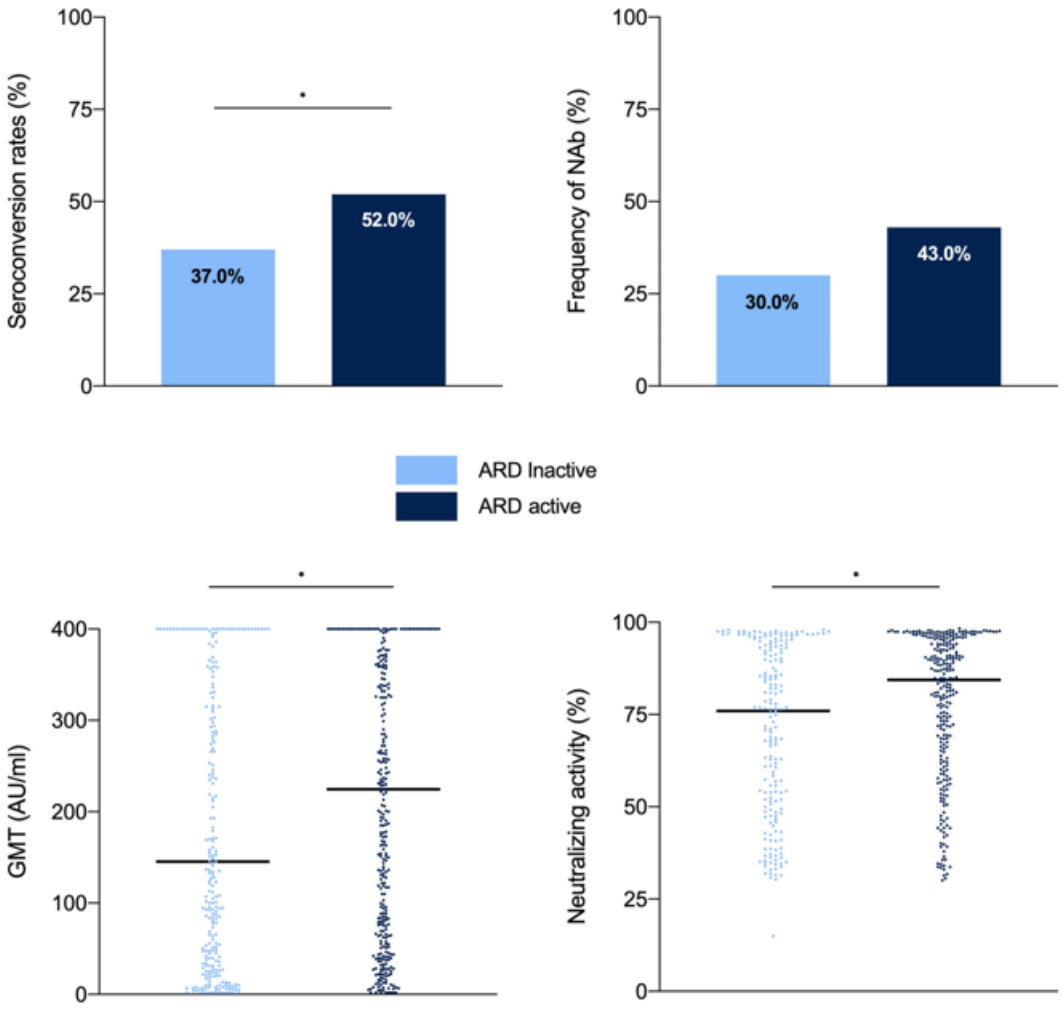

Figure 1 — Unadjusted analysis for immunogenicity data in patients with ARD. Seroconversion was defined as a positive serology (IgG titer ≥15 AU/ mL) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin). Neutralizing activity was calculated for positive cases only (positivity for NAb was defined as a neutralizing activity ≥30%; n = 464) (cPass sVNT Kit, GenScript). Data are expressed as individual data and median for GMT and neutralizing activity and percentages for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and NAb positivity. ARD indicates autoimmune rheumatic diseases; GMT, geometric mean titers of anti-S1/S2 IgG; NAb, neutralizing antibodies.

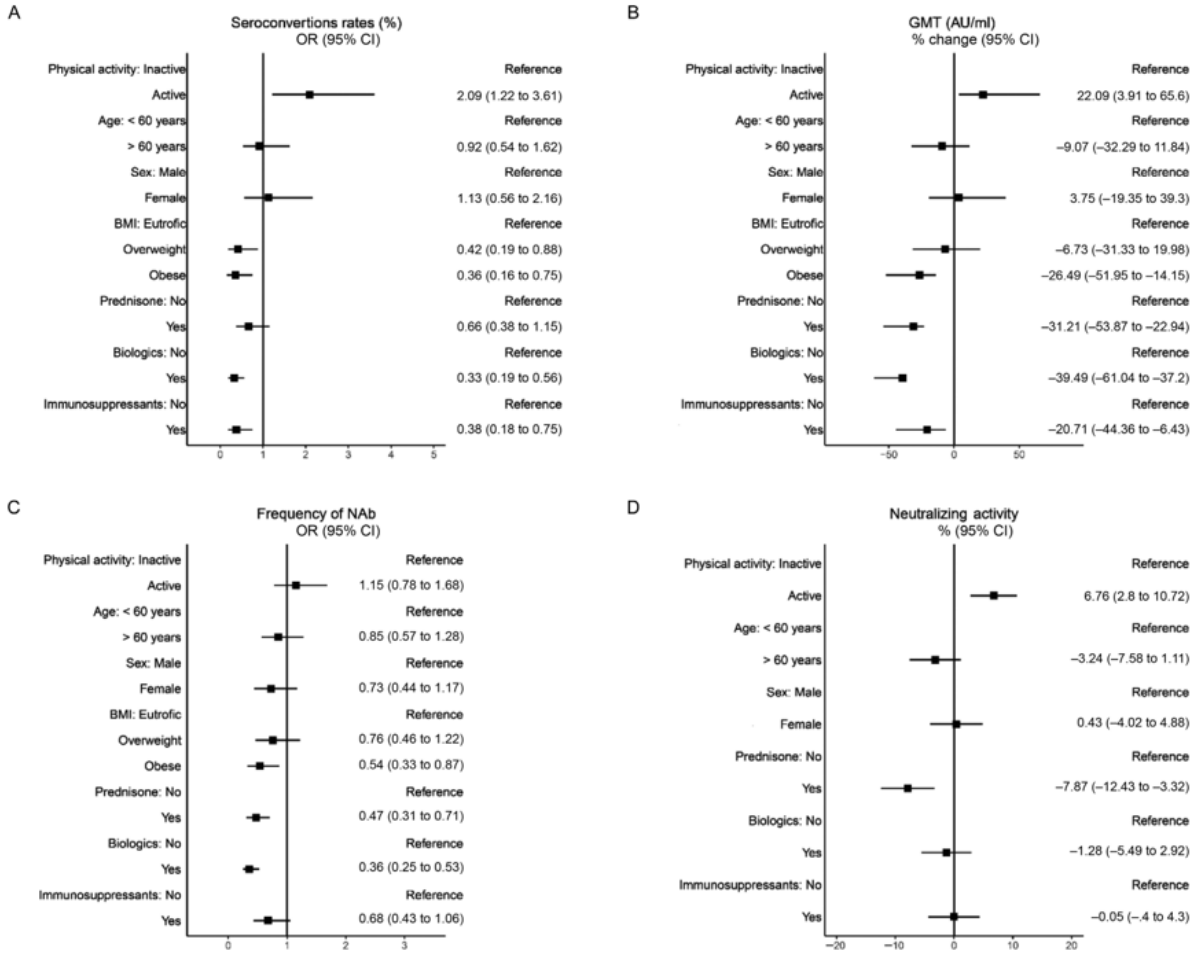

Figure 2 — Adjusted risk factors for immunogenicity data in patients with ARD. Logistic regression to estimate ORs and 95% CIs with binary data obtained for frequency of seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG (SC) and NAb positivity. Linear regression was used for natural log-transformed GMT and neutralizing activity. Adjusted for age, sex, BMI, use of prednisone, immunosuppressants and biologics for seroconversion rates, GMT, and NAb positivity. For neutralizing activity, we only used data of those patients with positivity for NAb (neutralizing activity ≥30%; n=464) (cPass sVNT Kit, GenScript). This analysis was adjusted for age, sex, use of prednisone, immunosuppressants, and biologics. Data expressed as either percent or percent change (95% CI). ARD indicates autoimmune rheumatic diseases; BMI, body mass index; CIs, confidence intervals; GMT, geometric mean titers of anti-S1/S2 IgG; NAb, neutralizing antibodies; ORs, odds ratios.

Discussion

This study showed that a physically active lifestyle is associated with improved humoral responses to a SARS-CoV-2 vaccine booster dose among patients with ARD.

In the present study, the use of prednisone, biologic therapy, and immunosuppressants was associated with poor immunogenicity in response to the booster dose. This aligns with growing evidence showing that these drugs are the most important factors negatively influencing antibody responses to different SARS-CoV- 2 vaccine platforms.[1,2,14–16]

Importantly, we demonstrated herein that physical activity has the opposite effect as it was associated with enhanced booster dose–response in patients with ARD. Notably, physical activity was related to doubling the seroconversion rate and approximately a 20% increase in GMT. This novel finding extends previous observation that being physically active was associated with greater antibody levels after 2 doses of CoronaVac as well as greater antibody persistence through 6 months after immunization.[10,11]

Potential strategies to enhance immunogenicity include the use of heterologous COVID-19 vaccine schedules,[17,18] and the temporary discontinuation of methotrexate, although this was associated with a slight increase in flare rate in patients with rheumatoid arthritis.[19] The series of studies showing a positive association between physical activity and vaccine-induced immunogenicity[10,11,20] suggest that adopting a physically active life- style may be another putative behavioral measure to improve SARS-CoV-2 vaccine responses among immunocompromised individuals.

The mechanisms underlying the potential benefits of physical activity on vaccination responses remain unclear. It is known that a physically active lifestyle improves immune function and induces greater antibody and/or cell-mediated adaptations.[21,22] These effects are thought to be mediated by exercise-induced transient increases in muscle-secreted inflammatory cytokines, leukocytosis response, and muscle damage, leading to leukocyte trafficking and stimulating the activation of immune surveillance in anticipation of antigen entry, which may be of relevance to vaccination.[22–24]

The current findings add to the literature by showing that physical activity not only enhances immunogenicity to a complete schedule of SARS-CoV-2 vaccination[11] but also to a booster dose. These observations point out to the potential utility of a safe, inexpensive, population-wide strategy (ie, physical activity) in enhancing vaccine-induced immunogenicity in patients with auto- immune disorders.[25]

The present study has the advantage of evaluating a large and well-characterized ARD population defined according to specific disease criteria.[2] Limitations include the observational design, lack of measures of cell-mediated immune function and prospective evaluation of disease activity, and the use of questionnaire to assess physical activity. These limitations hamper determining causal and definitive inferences regarding the effects of physical activity on immunogenicity. Efficacy and effectiveness assessments of population-based public health interventions, randomized controlled trials, and molecular and cellular physiological studies are necessary to unravel the potential roles and mechanisms of physical activity on immunogenicity to SARS-CoV-2.[25]

In conclusion, patients with ARD who are physically active have greater odds of experiencing better immunogenicity following a SARS-CoV-2 booster dose. These results strengthen the need for promotion of physical activity to enhance vaccine responses, particularly for individuals with immunosuppressed conditions.

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