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RAPID COMMUNICATIONS
Clinical trials

Exercise training in long COVID: the EXER-COVID trial

Robinson Ramírez-Vélez [1,2,*†], Julio Oteiza [3], Gaizka Legarra-Gorgoñon [1], Sergio Oscoz-Ochandorena [1], Nora García-Alonso [1], Yesenia García-Alonso [1], María Correa-Rodríguez [4,5], Adrian Soto-Mota [6,7], and Mikel Izquierdo [1,2,*†]

[1]Navarrabiomed, Hospital Universitario de Navarra (HUN), Universidad Pública de Navarra (UPNA), Instituto de Investigación Sanitaria de Navarra (IdiSNA), 31001 Pamplona, Spain; [2]CIBER of Frailty and Healthy Aging (CIBERFES), Instituto de Salud Carlos III, 28029 Madrid, Spain; [3]Servicio de Medicina Interna, Hospital Universitario de Navarra (HUN), Universidad Pública de Navarra (UPNA), Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain; [4]Department of Nursing, Faculty of Health Sciences, University of Granada, 18016 Granada, Spain; [5]Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain; [6]Metabolic Diseases Research Unit, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City, Mexico; and [7]Tecnologico de Monterrey, School of Medicine, Mexico City, Mexico

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Post-COVID-19 syndrome, also referred to as long COVID is a multisystemic condition characterized by fatigue, headaches, attention deficits, low energy, functional impairment, sleep disturbance, and dyspnea.[1] While the underlying mechanisms of long COVID remain unclear, several hypotheses have been proposed, including persisting viral reservoirs, immune dysregulation, alterations in the host microbiome, autoimmunity, and endothelial dysfunction.[2] Treatments such as vaccinations, pharmacotherapy, nutritional support, rehabilitation, and physical exercise have been shown to improve symptoms.[3–5]

A 2023 review[1] highlighted that existing research is insufficient to definitively improve outcomes for patients with long COVID. 'The authors emphasized an urgent need for evidence-based rehabilitation interventions to support individuals affected by long COVID, noting that current guidelines are largely based on expert opinion and observational data'.[5] Recent evidence suggests that exercise-based rehabilitation can enhance physical fitness, reduced symptoms of depression and anxiety, and improved long COVID outcomes.[3,4] A systematic review further indicated that exercise-based rehabilitation is associated with improvements in functional exercise capacity, dyspnea, and quality of life (QoL), with a higher likelihood of better outcomes than standard care.[3] Progressive resistance training (PRT), in particular, has been shown to alleviate dyspnea and discomfort in respiratory conditions and to reverse age-related declines in skeletal muscle.[4,6,7] However, despite the general tolerance of exercise, guidelines cautioning against exercise in similar populations may require reconsideration.[5,8] These recommendations are supported despite the well-established detrimental effects of physical inactivity, which is closely linked to secondary health conditions and declining QoL.[9]

It appears reasonable to cautiously incorporate exercise into rehabilitation protocols, with careful adjustments to intensity based on each patient's symptoms and abilities.[7,9,10] We hypothesized that non-hospitalized patients with long COVID would benefit from structured exercise. In a randomized cross-over trial, we assessed the effects of a 6-week personalized PRT intervention, with a 5-day washout period between arms on cardiopulmonary fitness, muscular strength, long COVID symptoms, QoL, and emotional distress.

Inclusion and exclusion criteria required a confirmed diagnosis of long COVID (per the WHO definition) with mild or moderate symptoms, no history of hospitalization, and no previous heart or lung disease.[7,8] The intervention comprised of 12 supervised PRT sessions conducted twice weekly, as previously described.[7] During the usual care phase, participants adhered strictly to standard care protocols and were instructed to avoid other structured exercise programs.

The primary endpoint was a change in peak Oxygen uptake ($\dot{V}O_2$). Both intent-to-treat and per-protocol (PP) analyses were performed. Multiple imputation chain equations were applied to handle missing data for the primary outcome using predictive mean matching. Secondary endpoints included 22 patient-reported outcome measures regarding long-COVID symptoms, derived from standardized questionnaires on QoL, depression, and psychological distress. Maximal muscle strength assessments (handgrip, pectoral press, bilateral leg-press, knee

* Corresponding authors. Email: robin640@hotmail.com, robinson.ramirez@unavarra.es; Email: Mikel.izquierdo@gmail.com
† Both authors contributed equally to the study.

Table 1 Efficacy end points

End points	Median (1st and 3rd quartile) [sample size]						Mean differences (95% IC) [*P* value]		
	Group 1 (AB)			Group 2 (BA)					
	Baseline	Period 1	Period 2	Baseline	Period 1	Period 2	Treatment effect	Carry-over effect	Period effect
	Week 0	Week 6 (A1)	Week 12 (B2)	Week 0	Week 6 (B1)	Week 12 (A2)	(A1 + A2) vs. (B1 + B2)	(A1 + B2) vs. (B1 + A2)	(A1 + B1) vs. (B2 + A2)
Primary outcome									
Peak $\dot{V}O_2$ (ITT)**, mL/kg/min[a]	20.85 (16.87 to 24.67)	24.84 (19.90 to 29.58)	22.75 (18.60 to 29.15)	21.30 (17.85 to 24.40)	22.46 (18.60 to 24.95)	25.15 (21.50 to 29.54)	2.10 (1.25 to 2.94)	−1.33 (−6.36 to 3.69)	−0.86 (−1.78 to 0.07)
	[50]	[50]	[50]	[50]	[50]	[50]	[<0.0001]	[0.600]	[0.069]
Peak $\dot{V}O_2$ (PP)**, mL/kg/min	20.85 (16.87 to 24.67)	24.70 (19.22 to 30.07)	22.10 (18.00 to 26.50)	21.30 (17.85 to 24.40)	21.70 (19.30 to 24.30)	25.00 (21.60 to 28.60)	2.40 (1.56 to 3.25)	−0.79 (−5.97 to 4.39)	−0.57 (−1.55 to 0.42)
	[50]	[46]	[43]	[50]	[47]	[44]	[<0.0001]	[0.762]	[0.254]
Secondary outcomes (PP)									
VT1 $\dot{V}O_2$, mL/kg/min[b]	9.30 (7.34 to 11.57)	11.18 (8.37 to 11.18)	10.16 (7.70 to 10.16)	10.29 (7.88 to 11.01)	9.96 (8.67 to 11.31)	10.39 (9.03 to 12.03)	0.46 (−0.13 to 1.04)	−0.86 (−2.93 to 1.20)	0.04 (−0.55 to 0.64)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.122]	[0.407]	[0.886]
$\dot{V}E/\dot{V}CO_2$ slope[c]	33.10 (31.25 to 39–65)	34.40 (31.20 to 37.50)	35.40 (32.10 to 39.10)	33.10 (31.25 to 39.65)	34.40 (31.20 to 37.50)	35.40 (32.10 to 39.10)	0.82 (−0.09 to 1.72)	1.71 (−2.37 to 5.79)	−0.15 (−1.07 to 0.77)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.076]	[0.406]	[0.749]
Watt at Peak $\dot{V}O_2$, W	125 (100 to 125)	125 (100 to 125)	125 (125 to 150)	125 (100 to 125)	125 (100 to 125)	125 (125 to 150)	14.88 (9.89 to 19.87)	−21.52 (−58.24 to 15.08)	−1.79 (−7.73 to 4.16)
	[50]	[46]	[43]	[50]	[47]	[44]	[<0.0001]	[0.245]	[0.552]
Grip strength, kg	24.43 (19.66 to 34.71)	23.16 (17.20 to 31.47)	22.51 (16.89 to 28.66)	24.40 (21.11 to 31.65)	25.03 (20.45 to 33.34)	28.04 (22.61 to 33.63)	0.49 (−0.16 to 1.14)	−1.10 (−8.94 to 6.63)	−0.73 (−1.37 to −0.09)
	[49]	[47]	[44]	[49]	[47]	[42]	[0.138]	[0.780]	[0.025]
Pectoral press, 1 RM kg[d]	42.50 (32.00 to 58.00)	59.00 (43.50 to 69.00)	58.00 (43.00 to 68.00)	41.00 (36.00 to 60.00)	45.00 (33.75 to 62.75)	54.50 (45.75 to 78.75)	6.82 (4.80 to 8.84)	−5.45 (−23.73 to 12.72)	−13.73 (−16.65 to −10.81)
	[50]	[45]	[43]	[50]	[46]	[42]	[<0.0001]	[0.552]	[<0.0001]
Bilateral leg-press, 1 RM kg[d]	150 (83.75 to 195.00)	210.00 (183.00 to 279.50)	202.50 (162.75 to 262.50)	148.00 (113.75 to 203.50)	176.00 (132.00 to 250.00)	233.00 (196.00 to 287.00)	36.13 (26.61 to 45.65)	−8.02 (−62.93 to 46.88)	−22.97 (−34.23 to −11.70)
	[50]	[46]	[43]	[50]	[47]	[44]	[<0.0001]	[0.772]	[<0.0001]

Continued

Table 1 *Continued*

End points	Median (1st and 3rd quartile) [sample size]						Mean differences (95% IC) [*P* value]		
	Group 1 (AB)			Group 2 (BA)					
	Baseline	Period 1	Period 2	Baseline	Period 1	Period 2	Treatment effect	Carry-over effect	Period effect
	Week 0	Week 6 (A1)	Week 12 (B2)	Week 0	Week 6 (B1)	Week 12 (A2)	(A1 + A2) vs. (B1 + B2)	(A1 + B2) vs. (B1 + A2)	(A1 + B1) vs. (B2 + A2)
Knee extension, 1 RM kg[d]	66.00 (45.50 to 86.00)	97.50 (69.00 to 130.75)	91.00 (64.00 to 122.00)	71.00 (51.75 to 98.00)	76.00 (59.00 to 101.00)	93.50 (78.25 to 132.00)	12.24 (8.69 to 15.79)	−3.95 (−24.80 to 16.9)	−7.85 (−11.93 to −3.77)
	[50]	[46]	[43]	[50]	[47]	[44]	[<0.0001]	[0.707]	[<0.0001]
Back press, 1 RM kg[d]	48.00 (40.00 to 63.50)	60.00 (48.00 to 84.25)	58.00 (47.00 to 76.00)	47.00 (38.75 to 70.25)	49.00 (40.00 to 73.00)	59.00 (48.25 to 90.75)	7.39 (5.27 to 9.51)	−10.7 (−40.57 to 19.18)	−3.97 (−6.47 to −1.46)
	[50]	[46]	[43]	[50]	[47]	[44]	[<0.0001]	[0.478]	[0.002]
Total body lean mass, %	59.25 (54.15 to 65.82)	59.90 (53.90 to 66.10)	57.45 (53.67 to 65.82)	60.45 (54.36to 64.35)	57.95 (54.08 to 62.93)	59.20 (55.95 to 63.45)	0.50 (−0.20 to 1.21)	−0.33 (−6.56 to 5.89)	−0.59 (−1.29 to 0.11)
	[46]	[47]	[44]	[48]	[46]	[45]	[0.159]	[0.915]	[0.097]
Total body fat mass, %	38.55 (31.77 to 44.10)	37.70 (31.40 to 44.50)	40.45 (31.65 to 44.62)	37.70 (32.93 to 43.65)	39.70 (34.38 to 43.05)	39.00 (33.90 to 42.15)	−0.16 (−0.41 to 0.08)	−0.34 (−6.92 to 6.24)	0.26 (0.02 to 0.50)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.190]	[0.919]	[0.035]
ALM/height^2, Kg/m^2[e]	6.97 (6.02 to 8.21)	7.19 (6.39 to 8.68)	7.09 (6.25 to 8.49)	6.73 (5.85 to 8.26)	6.76 (5.95 to 8.09)	6.84 (6.06 to 8.32)	0.06 (0.00 to 0.12)	0.52 (−1.77 to −0.74)	−0.06 (−0.12 to 0.00)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.041]	[0.414]	[0.041]
Quality of life (EQ-5D), points[f]	0.73 (0.61 to 0.83)	0.76 (0.67 to 0.85)	0.75 (0.61 to 0.84)	0.71 (0.66 to 0.84)	0.78 (0.63 to 0.85)	0.78 (0.67 to 0.86)	0.02 (−0.03 to 0.07)	0.02 (−0.1 to 0.14)	0.01 (−0.04 to 0.06)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.421]	[0.716]	[0.631]
Quality of life (VAS), Points[g]	40.00 (30.00 to 60.00)	60.00 (40.00 to 70.00)	50.00 (40.00 to 60.00)	40.00 (30.00 to 50.00)	50.00 (37.50 to 60.00)	50.00 (40.00 to 70.00)	4.65 (1.45 to 7.85)	−4.31 (−18.58 to 9.97)	−1.40 (−4.74 to 1.95)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.005]	[0.550]	[0.409]
Depression (CES-D 10), points[h]	15.00 (14.00 to 18.00)	10.00 (7.00 to 15.00)	15.00 (13.00 to 18.00)	16.00 (13.00 to 18.00)	16.00 (12.25 to 18.00)	11.00 (9.00 to 16.00)	−4.14 (−5.66 to −2.63)	2.15 (−1.03 to −5.33)	−0.40 (−2.19 to 1.38)
	[50]	[46]	[43]	[50]	[47]	[44]	[<0.0001]	[0.181]	[0.654]
Psychological distress (K10), Points[i]	18.00 (15.00 to 28.00)	19.50 (13.75 to 26.00)	18.00 (15.00 to 28.00)	20.00 (16.00 to 24.50)	21.00 (17.00 to 27.00)	18.50 (14.25 to 24.00)	−2.28 (−4.30 to −0.25)	1.65 (−2.89 to 6.20)	1.48 (−0.58 to 3.54)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.028]	[0.471]	[0.157]

Continued

Table 1 *Continued*

End points	Median (1st and 3rd quartile) [sample size]						Mean differences (95% IC) [*P* value]		
	Group 1 (AB)			Group 2 (BA)					
	Baseline	Period 1	Period 2	Baseline	Period 1	Period 2	Treatment effect	Carry-over effect	Period effect
	Week 0	Week 6 (A1)	Week 12 (B2)	Week 0	Week 6 (B1)	Week 12 (A2)	(A1 + A2) vs. (B1 + B2)	(A1 + B2) vs. (B1 + A2)	(A1 + B1) vs. (B2 + A2)
Resilience (BRCS), Points[j]	19.00 (18.00 to 21.00)	18.00 (16.00 to 19.00)	16.00 (13.00 to 18.00)	19.00 (18.00 to 20.75)	18.00 (16.00 to 20.00)	16.50 (13.00 to 19.00)	−0.15 (−1.00 to 0.70)	0.57 (−1.87 to 3.02)	1.80 (1.04 to 2.56)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.721]	[0.643]	[<0.0001]
Cognitive capabilities (MoCA), points[k]	26.00 (24.00 to 28.00)	28.00 (26.00 to 29.00)	28.00 (26.00 to 29.75)	26.00 (24.00 to 28.00)	27.00 (24.75 to 29.00)	28.00 (26.50 to 29.00)	0.53 (0.11 to 0.96)	−0.93 (−2.85 to 0.99)	−0.51 (−0.94 to −0.09)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.014]	[0.337]	[0.019]
Cognitive performance (TMT-A), s[l]	24.43 (16.66 to 34.71)	23.16 (17.20 to 31.47)	22.51 (16.89 to 28.66)	23.71 (19.90 to 32.98)	24.39 (18.70 to 24.39)	23.92 (19.78 to 30.21)	1.60 (0.11 to 3.09)	−0.16 (−4.72 to 4.4)	0.69 (−0.84 to 2.21)
	[50]	[46]	[43]	[50]	[47]	[44]	[0.036]	[0.944]	[0.371]

1-RM, one-repetition maximum; ALM, Appendicular lean mass; BRCS, Brief Resilient Coping Scale; CES-D 10 items, Center for Epidemiological Studies Depression Scale; EQ-5D, EuroQol-5D; K10, 10-item Kessler Psychological Distress scale; MoCA, Montreal Cognitive Assessment; T, time; TMT-A, Trail Making Test A; VAS, visual analogue scale; $\dot{V}E/\dot{V}CO_2$ slope, ventilatory efficiency; $\dot{V}O_2$peak, Peak oxygen consumption; VT_1, first ventilatory threshold.

*Group 1 (AB) underwent a 6-week exercise intervention and switch period, followed by a 6-week usual care period, and group 2 (BA) underwent a 6-week usual care period and switch period, followed by a 6-week exercise intervention. ** intention-to-treat (ITT) analyses (results of the primary analysis using a prespecified multiple imputation for missing values via predictive mean matching model), ** per-protocol (PP) analyses for primary and secondary end point considering all available data (without imputation).

[a]$\dot{V}O_2$peak, in milliliters of oxygen per kilogram of body weight per minute, was defined as the highest 30-s average within the last minute of exercise. Lower values represent worse exercise capacity.

[b]VT_1 was set by the V-slope method, and the minute ventilation to carbon dioxide production slope ($\dot{V}E/\dot{V}CO_2$ slope) was calculated using the entire exercise data. Lower values represent worse exercise efficiency.

[c]$\dot{V}E/\dot{V}CO_2$ slope is a unitless index that is defined by minute ventilation (in L/min) relative to carbon dioxide production (in L/min) throughout exercise. Lower values represent a better exercise ventilatory response.

[d]The 1-RM test measured the maximum weight that could be lifted 1–2 times while maintaining proper form. Higher values represent better muscular strength.

[e]ALM, which represents the appendicular fat-free mass minus the bone mineral content, was assessed using dual-energy X-ray absorptiometry. ALM/(height)^2 in kg/m^2 was calculated as weight divided by height squared. Higher values represent better muscle quality.

[f]Higher scores reflect better health-related QoL, ranging from 0 to 1.

[g]General health visual analog scale from 0 'poorest health' to 100 'perfect health'.

[h]Higher scores reflecting more severe depressive symptoms, score range: 0 to 30.

[i]Higher scores indicate severe distress, score range: 10 to 50.

[j]Higher scores indicate the individual perceives they have a better ability to 'bounce back' and recover from stressful events and/or situations, and life satisfaction, score range: 0 to 10 where 0 means 'the worst possible life overall' and 10 means.

[k]Higher scores indicate better cognitive performance, with scores ranging from 0 to 30 points.

[l]Higher scores reveal greater impairment, maximum score 100 s.

extension, and back press) and cognitive performance (Montreal cognitive assessment and trail making test A) were also evaluated. The study recruitment and data collection spanned from 1 May 2021, to 7 January 2023.

A total of 89 participants completed the full intervention—59 women and 30 men—and were included in the final analysis, having attended at least 80% of exercise sessions. Seven participants were lost to follow-up after six weeks, and an additional four participants at 12 weeks. Statistical analysis revealed no significant carry-over effects for neither the primary endpoint $\dot{V}O_2$, nor the secondary endpoints, *Table 1*.

We assessed potential differences therapeutic effects between group 1 (AB, exercise first) and group 2 (BA, usual care first) but observed no significant period effect (−0.86 mL/kg/min [95% CI −1.78 to 0.07]). Peak $\dot{V}O_2$ increased by a mean of 2.10 mL/kg/min [95% CI 1.25 to 2.94], with comparable results found in PP analyses. Baseline Ferritin levels were associated with peak $\dot{V}O_2$ change, as demonstrated by both a regression tree analysis and a univariate linear model ($P = 0.01$).

The intervention led to significant improvements in watts at peak $\dot{V}O_2$ and muscle strength (1RM) across pectoral press, bilateral leg-press, knee extension, and back press ($P < 0.001$). Appendicular lean mass (ALM) normalized for height^2 (ALM/height^2) increased by 0.06 kg/m^2 [95% CI 0.00 to 0.12]. However, no significant changes were observed in grip strength or body fat mass post-treatment. Additionally, PRT was associated with reduced depression levels and psychological distress, while visual scores for QoL showed notable improvements, along with enhanced cognitive abilities and performance. The prevalence of COVID-related symptoms decreased between phases, including weakness (RR = 0.75 [95% CI 0.59 to 0.95]), dyspnea (RR = 0.56 [95% CI 0.39 to 0.82]), and memory loss (RR = 0.84 [95% CI 0.72 to 0.97]).

The intervention was prematurely discontinued in two patients due to exercise-related events, including palpitations (two events in period 1) and general pain or discomfort (two events in period 1 and one event in period 2) across three patients. Additionally, two patients were withdrawn during period 1 due to SARS-CoV-2 reinfection, and four more patients opted out of the trial.

Overall, these findings indicate that the PRT program yields both physical and mental benefits. While our results do not offer insights into the optimal duration of exercise programs, the data provide strong support for the use of this nonpharmacological intervention in real-world settings.[9] The absence of functional or exercise tolerance outcomes does limit the interpretability of these results, yet prior evidence has shown that improvements in muscle strength may lead to enhanced functional capacity in individuals recovering from post-COVID-19 syndrome.[10] Furthermore, our exploratory analysis identified a correlation between baseline Ferritin, a well-known inflammation marker, and improvements in peak $\dot{V}O_2$. This suggests that clinical improvements may, at least in part, be mediated by reductions in inflammation. Further mechanistic studies are needed to confirm these findings.

We acknowledge several limitations in our study. First, the inability to blind the intervention may have introduced placebo effects, potentially contributing to some of the observed benefits. Second, enrollment dynamics may have led to exaggerated adherence and responses during the initial period, with enthusiasm waning in the second phase. Third, the order of the intervention was not a significant predictor of differences between phases. Additionally, new treatments and vaccines that emerged during the study period altered the prognosis of COVID-19, though their effect on existing cases of long COVID remains unclear. Furthermore, generalizability to other populations, such as hospitalized patients, is limited due to potentially different responses to the intervention.

Given that exercise was generally well tolerated, current guidelines cautioning against exercise in similar populations may need to be reconsidered.[9,10] It appears reasonable to carefully integrate exercise into rehabilitation protocols, with intensity adjustments tailored to each patients' symptoms and abilities.[8,9] In conclusion, supervised PRT significantly improved cardiorespiratory fitness, strength, mental health, and several manifestations presented in patients with long COVID. This program represents a safe, effective, and low-cost intervention to enhance physical capacity, symptoms, and QoL. Clinicians should consider incorporating such interventions into the management of long COVID.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data sets used and/or analysed during the current study are available from the corresponding authors upon a reasonable request.

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Ethical Approval

This single-center, randomized crossover 'EXER-COVID' trial was approved by the Hospital Universitario de Navarra (HUN) Research Board (ID PI_2020/140).

Pre-Registered Clinical Trial Number

This study was pre-registered with the code NCT04797871 on 15 March 2021.

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