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Effects of Combined Exercise Training on Symptoms and Physical Fitness in Young Adults with Mild Long COVID

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Purpose: The aim of this study was to examine whether a combined exercise (EX), including aerobic, resistance, and inspiratory muscle training, reduces fatigue and dyspnea, improves physical fitness, and if increased physical fitness after exercise is associated with attenuating symptoms in young adults with mild long coronavirus disease (COVID) symptoms. **Methods:** Twenty-eight young adults (aged 23±4 years) with long COVID were randomly assigned to either the EX group (n=14), which underwent aerobic, resistance, and inspiratory muscle training three times per week for 8 weeks, or the control (CON) group (n=14). Symptoms of dyspnea and fatigue were assessed using self-report questionnaires. Cardiorespiratory fitness was directly measured during cardiopulmonary exercise testing, while muscle strength was measured by isokinetic muscle testing. These variables were measured before and after the exercise intervention. **Results:** Compared to the CON group, the EX group showed improvements in symptoms of fatigue and dyspnea, maximal oxygen consumption (VO_{2peak}), and peak torque, with significant interaction effects observed ($p<0.05$). The EX group exhibited a mean difference of 2.9 mL/kg/min in VO_{2peak} (95% confidence interval [CI], 1.8－4.0) and 13.0 Nm (95% CI, 6.1－19.8) in peak torque compared to the CON group ($p<0.05$). Improvements in VO_{2peak} were negatively associated with attenuations in both fatigue and dyspnea after the exercise intervention ($p<0.05$). **Conclusion:** These findings indicate that EX training can effectively alleviate symptoms and improve physical fitness in young adults with mild long COVID. Structured exercise training may serve as an effective intervention to improve the health of those with long COVID.

Keywords: Post-acute COVID-19 syndrome, Exercise, Cardiorespiratory fitness, Muscle strength

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Introduction

It is generally understood that individuals recover to their pre-infection health state within 2–3 weeks following a coronavirus disease 2019 (COVID-19) infection, but the condition termed “long COVID” is characterized by symptoms persisting beyond these periods[1]. The global prevalence of long COVID is estimated at approximately 43%[2], indicating a significant and ongoing public health problem that has continued to affect people globally even after the World Health Organization (WHO) declared that COVID-19 was no longer defined as a Public Health Emergency of International Concern[3].

Long COVID is characterized by a broad spectrum of symptoms, including fatigue and dyspnea, often accompanied by reduced physical fitness level and physical function, which can limit daily activities and reduce the quality of life[4,5]. The substantial health burden posed by these symptoms underscores the critical need for effective management strategies for long COVID[6]. However, the pathogenesis underlying long COVID remains largely unclarified, complicating efforts to develop effective treatments[7]. Trials of pharmacological agents for managing long COVID to date are few and are characterized by a lack of internal and external validity, which limits their generalizability[8]. There is a need for urgent identification of effective strategies to manage this condition. In this context, various non-pharmacological strategies, including exercise, have been proposed as potentially effective for managing long COVID symptoms[9].

Regular physical activity and exercise are well-documented for their benefits in enhancing physical function and fitness, as well as for modulating inflammation and immune function[10]. Given the hypothesis that chronic systemic inflammation and immune dysregulation may underlie the development of long COVID[7], engaging in exercise may serve as a viable intervention strategy. Indeed, emerging evidence suggests that exercise interventions may be beneficial for improving symptoms associated with long COVID, including enhancements in cardiorespiratory fitness (CRF) and muscle strength[11].

However, the majority of these studies often lack control groups, making it difficult to distinguish between the effects of exercise and natural recovery over time[11]. Furthermore, despite that long COVID can potentially affect individuals regardless of age or severity of the initial COVID-19 infection[12], most previous studies have focused on those with a history of hospitalization or in middle-to-older age groups[13,14]. Evidence indicates that long COVID symptoms can persist up to a year after infection, with a notably high prevalence reported among young adults with mild symptoms[15]. In addition, a recent cross-sectional study revealed that higher levels of physical fitness, including CRF and muscle function, were associated with lower severity of long COVID symptoms, suggesting the potential role of improving fitness for managing long COVID[16]. However, there is a lack of studies examining the association between improvements in physical fitness following exercise interventions and the magnitude of symptom alleviation in long COVID.

Therefore, these aspects suggest a need for targeted study to examine the efficacy of exercise interventions in young adults with mild long COVID, in comparison to maintaining a usual lifestyle. This study aimed to fill this gap by investigating whether a structured exercise training intervention can mitigate symptoms of long COVID and improve physical fitness in young adults with mild long COVID, while also assessing the potential correlation between improvements in fitness and symptom alleviation.

Methods

1. Participants and study design

This study included young adults aged 19 to 39 years experiencing symptoms of long COVID. The criteria for long COVID symptoms were based on the commonly reported symptoms in the literature[17], including persistent fatigue and dyspnea, with symptoms relieving at 6 months post-infection[18]. Inclusion criteria were (1) 4 weeks to 6 months since diagnosis of COVID-19; (2) experiencing persistent fatigue and/or dyspnea; (3) no history of hospitalization due to COVID-19; (4) no history of COVID-19-specific treatment or medication. Participants underwent a screening process, including health and medical history questionnaires, and were excluded if they had cardiovascular, musculoskeletal, metabolic, inflammatory diseases, or any medical/physical limitations.

Initially, 39 participants were recruited through community online boards and flyers posted at local community. After a thorough explanation of the study's purpose and procedures, those who voluntarily agreed to participate signed an informed consent. Nine participants were excluded based on the inclusion criteria and lack of interest or scheduling conflicts, resulting in a total of 30 participants. These participants were randomly assigned to either a combined exercise (EX) group (n=15) or a control (CON) group (n=15). The EX group engaged in a structured exercise program 3 times/wk for 8 weeks, while the CON group maintained their usual lifestyles. The overall study design is presented in Fig. 1. All procedures were approved by the Institutional Review Board (IRB) of University of Seoul (No. IRB-2022-11-004).

2. Measurements

All dependent variables were measured by the same researcher before and after the intervention using consistent standard operating procedures. All measurements were taken under the following conditions; participants refrained from vigorous physical activity, smoking, alcohol consumption, and food intake prior to the measurements. Post-intervention measurements for the EX group were taken 48 hours after the last exercise session to ensure enough recovery.

Anthropometrics were measured using extensometer and weight scales. Body composition measures, including body mass index, body fat percentage (%), and skeletal muscle mass (kg), were assessed using a bioelectrical impedance analysis device (BWA 2.0, Inbody). Blood pressure (BP) was measured after 10-minute rest in a supine position using an automated oscillometric device (Mobile-O-Graph NG, IEM) on the left upper arm. BP measurements were taken in duplicate, with a 3-minute interval, and the mean value was used for analysis. Additional measurements were taken when the difference between the measurements was greater than 10 mm Hg, and the mean of the two closest readings was used.

3. Long COVID symptoms

Long COVID symptoms and severity were assessed using self-reported questionnaires. The types of symptoms were surveyed based on the major symptom list provided by WHO, while the severity of fatigue and dyspnea was evaluated using specific questionnaires. Fatigue was measured using the validated Korean version of the Fatigue Severity Scale (FSS), which evaluates the severity of fatigue over nine items on a scale from 1 to 7[19]. The FSS scores are presented as mean values, with a score of 4 or above considered clinically significant fatigue[20]. Dyspnea was assessed using the Korean version of the modified Medical Research Council (mMRC) scale recommended by the American Thoracic Society for measuring dyspnea. The mMRC scale ranges from 0 to 4, classified as "no symptoms" to "severe dyspnea"[21].

4. Physical fitness testing

CRF was evaluated using a maximal cardiopulmonary exercise test (CPET) on a treadmill (TM 55 Treadmill, Quinton Cardiology Systems) following the Bruce protocol. Criteria for maximal exercise included achieving two of the following: a rate of perceived exertion of 18 or above, a respiratory exchange ratio (RER) of 1.15 or above, or an exercise heart rate reaching 90% of the predicted maximum. Continuous 12-lead electrocardiogram monitoring and BP measurements at 2-minute intervals during the test stages were used to monitor exercise responses. Gas exchange

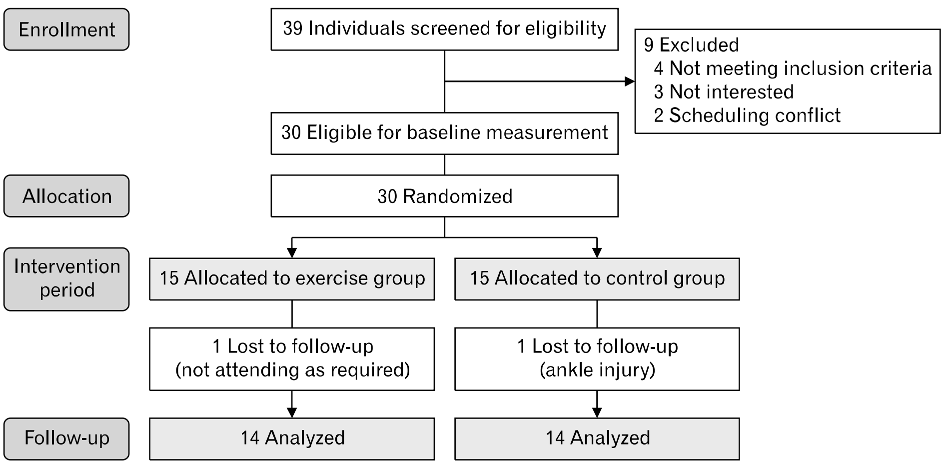

Fig. 1. Experimental design.

measurements were taken every 15 seconds with a gas analyzer (TrueOne 2400, Parvomedics) using a breath-by-breath method. Maximal oxygen consumption (VO_{2peak}) was determined by the highest 30-second average of oxygen consumption obtained during the test. The percentage of predicted VO_{2peak} was calculated based on age, sex, height, weight, and exercise protocol. The anaerobic threshold (AT) was identified as the point where the carbon dioxide production exceeds oxygen consumption, presented as a percentage of VO_{2peak} at that point.

Muscle strength was assessed using an isokinetic muscle strength test with a Biodex System 4 Pro (Biodex Medical Systems), evaluating knee extension and flexion movements of the dominant leg. Participants were fastened to the equipment with straps around the chest and thigh to minimize movement outside the knee joint. The axis of the knee joint was aligned with the dynamometer's axis, and the range of motion and leg weight were calibrated. Participants performed five repetitions at a velocity of 60°/sec to measure muscle strength and power, and 10 repetitions at 180°/sec to assess muscle endurance with a 2-minute rest between each test. To familiarize participants with the testing procedure and equipment, two practice attempts at 70% effort were allowed before the actual test. Muscle strength was presented as peak torque and relative peak torque (peak torque/body weight [BW]), muscle power as average power, and muscle endurance as total work performed.

5. Interventions

The exercise intervention consisted of supervised sessions 3 times/wk for 8 weeks, with each session lasting approximately 60 minutes. The exercise protocol included aerobic, resistance, and respiratory muscle training which started and ended with a 5-minute warm-up and cool-down, respectively. This exercise protocol was designed based on effective exercise prescription for long COVID from previous research[11].

Aerobic training was performed on a treadmill at an intensity of 50%–70% of heart rate reserve (HHR) for 30 minutes. The intensity was set using the Karvonen equation based on the maximal heart rate measured during the CPET, and progressively increased from 50%–60% HRR in weeks 1–4 to 60%–70% HHR in weeks 5–8. Heart rate was monitored using a wireless heart rate monitor (Fitbit Charge 2, Fitbit). Resistance training targeted major muscle groups through four exercises (upper extremity, chest press, and seated row; lower extremity, leg extension, and leg curl) using weight machines. Each exercise was performed for two sets of 12 repetitions at 40%–50% of one repetition maximum (1RM), with a 2-minute rest interval between sets. The 1RM for each exercise was assessed at the first exercise session and re-evaluated at week 5 to adjust the exercise intensity. Respiratory muscle training involved inspiratory muscle training using a hand-held inspiratory resistance device (IM1910, GH INNOTEK). Participants inhaled against given resistance to strengthen the inspiratory muscles, primarily the diaphragm. Participants performed three sets of 10 repetitions at 40%–50% of their maximal inspiratory pressure (MIP), with each repetition consisting of 5 seconds of resistance breathing followed by 5 seconds of relaxed exhalation. The intensity was set at 40% of MIP for weeks 1–4 and increased to 50% for weeks 5–8. MIP was estimated using a predictive equation based on the participant's age and sex[22]. Data of participants in the EX group who attended at least 80% of the total exercise sessions (20 out of 24 sessions) were analyzed. The CON group was instructed not to engage in additional physical activities and to maintain their usual lifestyle throughout the 8-week period.

6. Randomization procedures, sample size calculation, and statistical analysis

Participants were randomly assigned in a 1:1 ratio to either a combined EX group or a CON group, using a simple randomization allocation method based on a random number table. The sample size for this study was determined based on previous research investigating the effects of an 8-week exercise intervention on long COVID symptoms, CRF, and muscle strength in adults with long COVID[13]. The results showed an approximate 2.1 mL/kg/min increase in VO_{2peak}, with an effect size ($p\eta^2$) of 0.14. Using G*Power software with an effect size (f) of 0.403, a significance level of 0.05, and a power of 95%, the calculated required sample size was 24 participants. Considering potential dropouts, the final sample size was set at 30 participants (15 participants in each group).

Data were presented as frequencies, percentages, or means± standard deviations. The normality of data was tested using independent t-tests and Shapiro-Wilk tests, respectively. For normally distributed data, a two-way analysis of variance with repeated measures was used to examine changes and mean difference with a 95% confidence interval (CI) in dependent variables by intervention (EX vs. CON) and time (baseline vs. follow-up). Bonferroni post-hoc tests were conducted to examine changes within groups over time and differences between groups at each time point. For non-normally distributed variables, changes (⊿) were analyzed using the Kruskal-Wallis test (for number of long COVID symptoms and mMRC scores). Correlation analysis was performed to explore the relationship between improvements in CRF, muscle strength, and the alleviation of long COVID symptoms. All statistical analyses were conducted using SPSS-PC version 27.0 (IBM Corp.), with significance set at $p<0.05$.

Results

Of the 30 participants in the study, one from the EX group dropped out for not attending as required exercise sessions and one from the CON group withdrew for reasons unrelated to the study, resulting in a final sample of 28 participants (EX, n=14; CON, n=14). No injuries, adverse effects, or worsening of symptoms were reported due to the exercise intervention, and the average attendance rate for the exercise sessions was 91%. Baseline characteristics and COVID-19-related status are shown in Table 1. The mean age of participants was 23.1±3.8 years, and the average duration since COVID-19 infection was 96±56 days. All participants experienced fatigue symptoms, with 13 (46.4%) reporting symptoms of dyspnea.

Changes and mean differences in change of characteristics and long COVID symptoms before and after the intervention are presented in Table 2, with no significant group differences at baseline. Body fat percentage significantly decreased in the EX group compared to baseline (p=0.008), and skeletal muscle mass significantly increased (p=0.021), although no interaction effects were found. The number of long COVID symptoms significantly decreased in the EX group compared to the CON group (p=0.001). A significant decrease in fatigue, as measured by the FSS, was found in the EX group compared to the CON group (mean difference, −1.12; 95% CI, −1.56 to −0.68) with significant interaction effects ($p<0.001$). At follow-up, the EX group reported FSS scores below the clinically significant value (mean score >4),

Table 1. Baseline characteristics of exercise and control groups

Variable	Exercise group (n=14)	Control group (n=14)
Sex, male:female	5:9	4:10
Age (yr)	22.8±3.6	23.4±4.2
Body mass index (kg/m^2)	22.1±3.3	20.9±1.9
Percent body fat (%)	27.4±7.7	23.8±6.6
Skeletal muscle mass (kg)	24.8±6.4	24.8±6.8
Systolic blood pressure (mm Hg)	121.0±9.1	116.1±9.6
Diastolic blood pressure (mm Hg)	75.6±6.9	75.1±5.5
Resting heart rate (beats/min)	61.9±7.7	65.6±8.2
COVID-19-related status		
Time from infection (day)	101±57	93±59
Number of infections	1.4±0.5	1.3±0.5
Number of vaccinations	2.4±0.8	2.5±0.7
Number of long COVID symptoms	2.6±0.8	2.6±1.2
Severity of long COVID symptoms		
Fatigue Severity Scale	5.11±1.04	4.72±1.03
Modified Medical Research Council	1.1±0.3	1.2±0.6
Prevalence of long COVID symptoms		
Fatigue	14 (100)	14 (100)
Dyspnea	6 (42.9)	7 (50.0)
Persistent cough	6 (42.9)	7 (50.0)
Memory, cognitive, or sleep problems	6 (42.9)	4 (28.6)

Values are presented as number only, mean±standard deviation, or number (%).
COVID-19: coronavirus disease 2019.

Table 2. Comparison of characteristics and long COVID symptoms between exercise and control groups after intervention

Variable	Exercise group (n=14)		Control group (n=14)		Mean difference in change (95% CI)	p-value		
	Baseline	Follow-up	Baseline	Follow-up		Time	Group	Time ×group
Characteristic								
Body mass index (kg/m^2)	22.1±3.3	21.9±3.1	20.9±1.9	21.0±1.7	−0.8 (−0.3 to 0.1)	0.415	0.293	0.194
Percent body fat (%)	27.4±7.7	24.6±8.5*	23.8±6.6	22.8±5.9	−1.9 (−3.3 to −0.5)	0.011	0.325	0.190
Skeletal muscle mass (kg)	24.8±6.4	25.6±6.5*	24.5±6.8	25.0±6.9	0.7 (0.2 to 1.2)	0.009	0.881	0.513
Systolic blood pressure (mm Hg)	121.0±9.1	117.6±10.1	117.6±10.1	114.0±8.3	−2.8 (−5.4 to −0.2)	0.038	0.210	0.617
Diastolic blood pressure (mm Hg)	75.6±6.9	75.4±7.8	75.1±5.5	73.7±4.9	−0.8 (−3.0 to 1.5)	0.506	0.610	0.590
Resting hear rate (beats/min)	61.9±7.7	58.8±6.8	65.6±8.2	64.6±9.8	−2.0 (−4.7 to 0.6)	0.125	0.103	0.428
Number of long COVID symptoms	2.6±0.8	0.4±0.6	2.6±1.2	2.1±0.6	NA		<0.001‡	
Severity of long COVID symptoms								
Fatigue Severity Scale	5.11±1.04	2.94±1.28*†	4.72±1.03	4.66±1.10	−1.12 (−1.56 to −0.68)	<0.001	0.078	<0.001
Modified Medical Research Council	1.1±0.3	0.1±0.3	1.2±0.6	1.1±0.5	NA		<0.001‡	

Values are presented as mean±standard deviation unless otherwise specified.
COVID: coronavirus disease, CI: confidence interval, NA: not applicable.
*$p<0.05$ vs. baseline; †$p<0.05$ vs. control group; ‡$p<0.05$ for Kruskal-Wallis test.

Table 3. Comparison of cardiorespiratory fitness and musculoskeletal fitness between exercise and control groups after intervention

Variable	Exercise group (n=14)		Control group (n=14)		Mean difference in change (95% CI)	p-value		
	Baseline	Follow-up	Baseline	Follow-up		Time	Group	Time ×group
Cardiorespiratory fitness								
VO_{2peak} (mL/kg/min)	38.3±6.4	42.8±7.3*	38.2±7.4	39.5±7.4	2.9 (1.8 to 4.0)	<0.001	0.518	0.007
Predicted VO_{2peak} (%)	94.5±9.9	105.6±13.1*	93.8±12.0	97.5±15.0	7.4 (4.4 to 10.4)	<0.001	0.344	0.019
Anaerobic threshold (%VO_{2peak})	56.2±4.9	62.3±4.1*,†	54.5±3.5	55.5±4.9	3.5 (2.4 to 4.6)	<0.001	0.012	<0.001
RER at max	1.25±0.08	1.23±0.08	1.25±0.08	1.23±0.08	−0.02 (−0.06 to 0.02)	0.229	0.928	0.999
Maximal HR (beats/min)	193.3±8.3	193.4±6.1	191.8±7.2	189.1±8.2	−1.3 (−3.1 to 0.5)	0.154	0.286	0.115
Exercise time (sec)	625±87	670±85*	620±105	621±107	23 (13 to 33)	<0.001	0.463	<0.001
Musculoskeletal fitness								
Muscle strength (60°/sec)								
Peak torque-extension (Nm)	107.8±38.3	129.6±32.1*	115.2±51.5	119.3±45.5	13.0 (6.1 to 19.8)	0.001	0.925	0.012
Peak torque/BW-extension (%)	173.8±41.8	213.0±32.7*	192.9±62.6	202.2±50.1	24.2 (12.3 to 36.2)	<0.001	0.813	0.016
Peak torque-flexion (Nm)	51.3±23.3	64.8±20.7*	50.7±21.0	55.2±20.2	9.0 (5.7 to 12.3)	<0.001	0.525	0.009
Peak torque/BW-flexion (%)	80.8±23.0	105.2±21.6*	86.4±30.1	94.4±24.6	16.2 (10.3 to 22.0)	<0.001	0.774	0.008
Muscle power (60°/sec)								
Average power-extension (W)	67.1±25.2	85.9±25.2*	73.2±34.1	79.4±30.1*	13.2 (7.2 to 19.3)	<0.001	0.983	0.006
Average power-flexion (W)	32.0±15.8	45.3±14.8*	32.3±15.7	37.1±12.6*	10.8 (7.8 to 13.7)	<0.001	0.477	<0.001
Muscle endurance (180°/sec)								
Total work-extension (J)	840.8±253.8	1,018.9±292.2*	881.2±359.3	1,015.3±383.0*	156.1 (97.4 to 214.8)	<0.001	0.879	0.448
Total work-flexion (J)	403.1±162.8	577.6±182.8*	433.9±212.1	514.5±245.5*	127.5 (86.6 to 168.5)	<0.001	0.830	0.026

Values are presented as mean±standard deviation unless otherwise specified.
CI: confidence interval, VO_{2peak}: maximal oxygen consumption, RER: respiratory exchange ratio, HR: heart rate, BW: body weight.
*$p<0.05$ vs. baseline; †$p<0.05$ vs. control group.

with a mean of 2.94±1.28, whereas the CON group remained above the value. Dyspnea, measured by the mMRC scale, also significantly decreased in the EX group compared to the CON group ($p<0.001$), whereas the CON group continued to report mild dyspnea.

Changes in measures and mean differences in change of physical fitness are presented in Table 3, with no significant between-group differences at baseline. CRF, indicated by VO_{2peak}, increased in the EX group compared to the CON group (mean difference, 2.9 mL/kg/min; 95% CI, 1.8–4.0), with significant interaction effects (p=0.007), in which 4.5 mL/kg/min increase in the EX group. AT significantly increased in the EX group compared to the CON group with a significant interaction effect observed ($p<0.001$), and was greater in the EX group at follow-up ($p<0.001$). Significant increases in the percentage of predicted VO_{2peak} and exercise time were found in the EX group compared to the CON group, with interaction effects observed ($p<0.05$). There were no significant changes in maximum RER or maximal heart rate.

For muscle strength, peak torque at 60°/sec increased in the EX group compared to the CON group for both extension (mean difference, 13.0 Nm; 95% CI, 6.1–19.8) and flexion (mean difference, 9.0 Nm; 95% CI, 5.7–12.3) with significant interaction effects ($p<0.05$). Relative peak torque (peak torque/BW) and average power significantly increased in the EX group compared to the CON group, with interaction effects observed ($p<0.05$). While total work performed at 180°/sec for flexion significantly increased with interaction effect (p=0.026) in the EX group compared to the CON group, no significant interaction effect was found for extension.

The correlations between changes in CRF, muscle strength, and long COVID symptoms are shown in Fig. 2. Significant negative correlation (r=−0.401) was found between the increases in VO_{2peak} and improvement in fatigue (p=0.035), while no significant correlation was shown for dyspnea (p=0.291). However, no significant correlation was found between improvements in fatigue or dyspnea and peak torque at 60°/sec ($p>0.05$).

Discussion

In this study, the results indicated significant improvements in both symptoms of long COVID and physical fitness in the EX group compared to the CON group. Furthermore, the study found significant correlations between increases in CRF and the alleviation of long COVID-related fatigue after intervention, highlighting the potential effectiveness of the EX regimen as a non-pharmacological intervention for young adults with long COVID.

Fatigue, one of the most common symptoms reported by individuals with long COVID[17], showed significant improvement

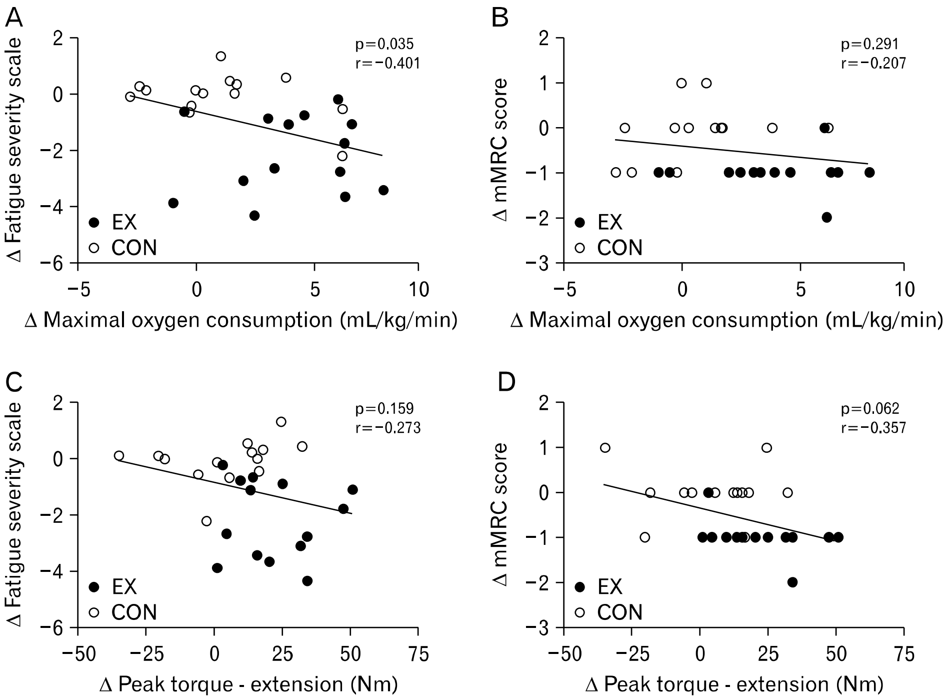

Fig. 2. Correlation between changes in cardiorespiratory fitness, muscle strength, and long COVID symptoms. (A) Maximal oxygen consumption vs. fatigue severity scale. (B) Maximal oxygen consumption vs. mMRC score. (C) Peak torque (extension) vs. fatigue severity scale. (D) Peak torque (extension) vs. mMRC score. EX: exercise group, CON: control group, mMRC: modified Medical Research Council.

following the 8-week EX program, aligning with findings from previous studies that have demonstrated the positive effects of exercise training on the relief of long COVID symptoms[13,14,23]. However, these studies predominantly involved individuals with a history of hospitalization or were conducted in middle-to-older age groups. Our results further extend the understanding of the role of exercise interventions on long COVID treatment among young adults with a notably high prevalence of mild long COVID symptoms[15].

In addition, Jimeno-Almazán et al.[23] found that patients with long COVID without a history of hospitalization, who performed aerobic and resistance training, showed significant improvements in fatigue, assessed by FSS. Interestingly, while the improvement of fatigue in the study was from 5.0±1.4 to 3.4±1.7, our study observed a change from 5.1±1.0 to 2.9±1.3, indicating a notable difference in the magnitude of improvement. Considering that the duration and frequency of the exercise (8 weeks, 3 times/wk) were the same, it is speculated that the inclusion of respiratory muscle training in our EX regimen might have contributed to the additional improvement in fatigue. Additionally, since the mean age of participants in our study was 23 years, it is possible that the younger population experienced a greater improvement in fatigue compared to older participants (mean age of 46 years) in previous research. Thus, these results extend the findings of previous studies by suggesting that a EX strategy may be more effective for improving fatigue of long COVID in young adults.

The mechanisms underlying improvement in long COVID symptoms following exercise training remain uncertain. However, possible mechanisms may include the enhancement of immune function, increase in metabolic rate and energy levels, and improvement in central nervous system fatigue through increased cerebral blood flow[24,25]. These mechanisms are suggested to play a pivotal role in mitigating fatigue in chronic fatigue syndrome[26]. Given that one of the major pathophysiological factors of long COVID involves immune dysfunction, including chronic systemic inflammation, autoimmunity, and immune dysregulation[7], it may be speculated that exercise plays a role in modulating these immune responses, thereby alleviating symptoms.

The impact of exercise intervention on alleviating dyspnea in long COVID appears to vary depending on the form of exercise intervention applied. In the study by Jimeno-Almazán et al.[23], which implemented aerobic and resistance training 3 times/wk for 8 weeks, no significant difference was found in mMRC dyspnea scores when compared to a control group that followed the WHO's self-management guidelines for long COVID. However, a subsequent study by the same research group reported significant improvements in dyspnea when additional respiratory muscle training was included, compared to those who only performed aerobic and resistance training[13]. Some studies have shown that EX training including respiratory muscle training can improve dyspnea in long COVID[14], consistent with the results of our study. Therefore, it is highly plausible that respiratory muscle training contributed to the alleviation of dyspnea, suggesting that including respiratory muscle exercises may be an appropriate intervention strategy for improving dyspnea in long COVID.

In the context of long COVID, dyspnea might result from a range of factors including direct viral damage to pulmonary tissues, persistent inflammation, and impaired oxygen transport[27]. While the mechanism underlying the improvement in dyspnea through exercise remains unclear, it can be suggested that exercise may enhance lung function efficiency of oxygen delivery through enhanced pulmonary blood flow and peripheral circulation[28]. Future research should further investigate the specific mechanisms by which exercise can alleviate long COVID symptoms.

Recent meta-analyses have shown that individuals with long COVID exhibit significantly reduced VO_{2peak}, approximately 4.9 mL/kg/min, compared to asymptomatic individuals[5]. Lower CRF is associated with an increased risk of hospitalization and COVID-19-related mortality, as well as the risk of developing chronic disease after infection[29]. Therefore, improving their CRF is of great importance. Our findings demonstrated significant improvements in VO_{2peak} and other measures of CRF following exercise training. These results are consistent with previous studies, which reported increases in VO_{2peak} of approximately 2.1–2.9 mL/kg/min after conducting EX training 3 times/wk for 8 weeks[13,23]. Thus, the EX program appears to be an effective intervention for improving reduced CRF due to long COVID, and further research is needed to investigate the impact of such improvements on prognosis and future mortality in long COVID population.

A novel finding of this research is the significant negative correlation identified between changes in VO_{2peak} and severity of fatigue, while changes in muscle strength were not. This relationship highlights the potential of exercise-induced improvements in CRF to play a critical role in alleviating long COVID-related fatigue. Recent studies support this association, suggesting that fatigue in long COVID is associated with diminished peripheral oxygen diffusion capacity[27], and that long COVID-related fatigue symptoms exhibit lower CRF compared to those without such symptoms[30]. Thus, the correlations identified in this study extend the cross-sectional study of Jimeno-Almazán et al.[16], which reported that lower CRF is associated with greater severity of long COVID symptoms, suggesting that improvements in CRF through exercise could potentially alleviate long COVID-related fatigue symptoms.

Improvements in muscle strength following EX in individuals with long COVID have been reported in some previous studies. Although the evaluation methods differ from this study, an increase in 1RM and improvements in lower limb muscle function assessed by the sit-to-stand test have commonly been observed[13,14,23]. This study extends those findings, showing effectively enhanced muscle strength parameters by objectively measured using isokinetic muscle function testing.

This study is not without limitations. The small sample size (n=28) limits the generalizability of the findings. The absence of baseline physical fitness data prior to COVID-19 infection limits the ability to directly compare pre- and post-infection fitness levels. Additionally, the individual variation in natural recovery over time was not considered, warranting caution in interpretation. Since the study observed the effect of an 8-week intervention, predicting changes beyond this period is limited. Finally, while this study focused on the primary symptoms of fatigue and dyspnea, long COVID is reported to be associated with a wide array of symptoms (e.g. cognitive function, anxiety, and depression)[7]. Recent meta-analyses indicate that the effects of exercise on cognitive function or mental health issues in individuals with long COVID remain inconclusive[11,31], suggesting that future research should examine the effects of exercise on a broader range of long COVID-related health outcomes. Future research should take these limitations into account, and findings need to be confirmed across different ethnicities, symptoms, severities, and considering various exercise durations and modalities.

In conclusion, the 8-week combined exercise training demonstrated significant effects in alleviating long COVID symptoms and enhancing physical fitness among young adults, with a notable correlation between improvements in CRF and fatigue symptoms. These findings imply that a combined exercise regimen may serve as an effective lifestyle intervention for young adults with mild long COVID.

Conflict of Interest

Sae Young Jae is the Editor-in-Chief, and Kanokwan Bunsawat, Setor K Kunutsor, Kevin S Heffernan are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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