International Journal of
Active & Healthy Aging
e-ISSN :3023-6045
https://ndpapublishing.com/index.php/ijaha

Intervention with A Multi-Component Exercise Program in Managing Fatigue Perception in Individuals Who Experienced COVID-19: A Quasi-Experimental Study

Francisco FİGUEROA-CAVERO*[1], Sandra Elvia HERNÁNDEZ-VALENCİA[1] and Andrea PEGUEROS-PÉREZ[1]

[1]*Centro Nacional de Investigación y Atención en Medicina del Deporte. Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra (INRLGII). Mexico City, Mexico.*

Article Info
Received: 06.12.2024
Accepted: 23.12.2024
Published:30.12.2024

Keywords
Multi-Component Exercise
Post COVID-19 Sequelae
Fatigue

ABSTRACT

Introduction: Following the acute phase of respiratory illness caused by the SARS-CoV-2 virus, a significant number of patients report persistent fatigue. Fatigue is considered debilitating and disabling, affecting quality of life, work performance, and social/familial relationships. Multicomponent exercise prescription and dosage in its various forms has proven to be a preventive and therapeutic strategy in numerous medical conditions. However, to date, evidence regarding its effect on fatigue secondary to SARS-CoV-2 infection remains scarce. **Objective**: To evaluate the effect of a multicomponent exercise program on self-perceived fatigue, aerobic capacity, lower-limb muscle strength, body fat percentage, and muscle mass in individuals aged 30 to 60 years with history of COVID-19. **Methodology**: A quasi-experimental study (pretest-posttest trial) included 15 individuals reporting fatigue via the Fatigue Severity Scale (FSS) and with a history of more than 12 weeks post-SARS-CoV-2 infection. All participants completed a 12-week multicomponent exercise program. The primary outcome was a reduction in fatigue perception. Secondary outcomes included aerobic capacity, lower-limb muscle strength, body fat percentage, and muscle mass. **Results**: Self-perceived fatigue decreased by 2.5 points (95% CI: 1.7–3.2; p = 0.001). Aerobic capacity increased by 10.8 mL/kg/min (95% CI: 5.7–19.9; p = 0.006). No statistically significant changes were observed in muscle strength, body fat percentage, or muscle mass at the end of the follow-up period. **Conclusions**: The multicomponent exercise program for reducing post-COVID-19 self-perceived fatigue can be considered an effective tool for managing post-COVID-19 sequelae in populations with persistent symptoms who have not received prior treatment.

1. INTRODUCTION

The infectious disease COVID-19, caused by the SARS-CoV-2 coronavirus, first emerged in 2019 in China. It is a highly contagious disease with a wide range of clinical symptoms, most commonly cough, fever, and dyspnea [1] . As of November 2023, more than 770 million confirmed cases and approximately 6.9 million deaths have been reported globally. The Americas are the most affected region, with over 100 million confirmed cases [2].

In Mexico, approximately 7.6 million positive cases and around 330,000 deaths have been reported by November 2023. The age group with the highest incidence of cases is 25 to 50 years, with a nearly equal distribution between men (50.1%) and women (49.9%). Of the total cases, 82.15% were managed on an outpatient basis [3].

It has been widely documented that following SARS-CoV-2 respiratory infection, a variety of new symptoms can appear, some recurrent and others continuous. Approximately 10% of the population experiences prolonged illness. Cases extending beyond three weeks from symptom onset are classified as long COVID, while those persisting for more than 12 weeks are referred to as post-COVID-19 condition [4].

Following infection with the SARS-CoV-2 virus, a wide range of symptoms has been reported as sequelae of the disease, collectively referred to as post-COVID-19 condition. Many of these sequelae remain insufficiently described to date [5]. Post-COVID-19 condition is defined as a set of signs and

*Corresponding author

e-mail: docfiguec@hotmail.com
ORCID ID: 0000-0002-3499-6403

Research Artıcle/ DOI: 10.5281/zenodo.14553367

How to cite this article

Figueroa-Cavero, F., Hernández-Valencia, S.E., And Pegueros-Pérez, A. (2024). Intervention with A Multi-Component Exercise Program in Managing Fatigue Perception in Individuals Who Experienced COVID-19: A Quasi-Experimental Study. *Int. J. Act. Health Aging, 1(1), 76-85.*

symptoms that develop during or after the acute phase of COVID-19 and persist for more than 12 weeks without being attributable to any other diagnosis [6].

The most common post-COVID-19 symptoms include fatigue, dyspnea, anxiety, headache, and chest pain, which have been reported to persist for more than 60 days following diagnosis or the onset of symptoms [7, 8]. For instance, in a systematic review by Goërtz et al., 97% of COVID-19 patients reported more than five persistent symptoms three months after infection. Among these, fatigue (94.9%) and dyspnea (89.5%) were the most frequently noted. Similarly, a systematic review by Mexican researchers identified fatigue (58%) and headache (44%) as the most prevalent symptoms [9].

Since the early stages of the pandemic, epidemiological studies worldwide have highlighted fatigue as one of the most common post-COVID-19 symptoms. For example, in an Egyptian population sample, fatigue was present in 72.8% of cases, while anxiety was reported in 38% [7]. In an Italian study, fatigue (53%) and dyspnea (43%) were the predominant symptoms [10].

It is noteworthy that approximately 65% of individuals returned to their pre-infection health status within 14 to 21 days after a positive test result [11]. However, a portion of the population experienced prolonged recovery, particularly when attempting to resume physical exercise [12] . This prolonged recovery may be attributed to an inadequate antibody response following viremia, resulting in inflammatory and autoimmune reactions. Additional contributing factors include physical deconditioning and mental health challenges, such as post-traumatic stress, arising from the acute phase of the illness [13].

Fatigue is a complex concept that is challenging to define with precision, as it is often linked to various clinical aspects. It is generally described as pathological and persistent levels of physical, mental, and/or cognitive exhaustion that do not improve with rest or sleep [14]. Fatigue is disabling and significantly impacts quality of life, work performance, and social or familial relationships [15].

The biological mechanisms underlying chronic fatigue associated with COVID-19 are not yet fully understood. However, studies have focused on inflammatory regulation imbalances, increased cerebrospinal fluid resistance, and dysfunction in the cerebellum and frontal lobe [16]. Another theory posits a cerebral vascular origin, attributing fatigue to intracerebral hypoperfusion potentially caused by micro-emboli formed during the acute phase of the disease [17].

Given its multifactorial nature, models of fatigue composition attribute both mental and physical characteristics to the condition. Physical aspects include drowsiness, low energy states, and muscle weakness [18]. Overweight and obesity are closely associated with fatigue [19], as they predispose individuals to reduced muscle mass, weakness, and long-term functional limitations [20].

Fatigue has been widely documented in association with other infectious diseases, such as influenza. In cases of severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV), fatigue has been reported to persist for up to 40 months post-infection [21].

Regarding COVID-19, fatigue is defined as a decline in physical and/or mental performance resulting from central, psychological, and peripheral changes caused by the disease.

The exact mechanism by which SARS-CoV-2 causes fatigue remains unknown. Notably, its presence is not correlated with disease severity or positive inflammatory biomarkers [21]. Some researchers hypothesize that SARS-CoV-2 infection may involve peripheral mechanisms, such as the virus's ability to invade tissues, including skeletal muscle, via angiotensin-converting enzyme 2 (ACE2) receptors and excessive secretion of interleukin-6 (IL-6). These disruptions impair muscle homeostasis and promote muscle mass loss, resulting in general weakness and the establishment of fatigue [22]. Several predisposing factors for post-COVID-19 fatigue include advanced age, female sex, severe acute-phase disease, preexisting comorbidities, and pre-infection diagnoses of anxiety or depression [23].

Additionally, after the acute phase of SARS-CoV-2 infection, respiratory patterns may change due to reduced diaphragmatic motion. The diaphragm performs 80% of respiratory work, and its diminished function increases reliance on accessory muscles of the neck and shoulders. This results in shallow breathing, which exacerbates fatigue, respiratory difficulty, and energy expenditure [4]. Such changes negatively impact an individual's aerobic capacity, which is a known predisposing factor for fatigue [24] and a powerful predictor of cardiovascular morbidity and mortality [25]. Psychological stress during the acute and subacute phases of infection has also been implicated as a risk factor for long-term fatigue[26].

Currently, no objective method exists for evaluating fatigue. However, several subjective scales have been developed to quantify the self-perception of fatigue. The three most widely used are the Fatigue Severity Scale (FSS), the Chalder Fatigue Scale (CFS), and the Fatigue Impact Scale

(FIS) [27]. Among these, the FSS has been applied in post-COVID-19 patients [28].

The FSS consists of nine items designed to assess whether fatigue impacts motivation, exercise, physical functioning, daily activities, and social life [29]. It uses a 7-point Likert scale, where respondents rate their level of agreement or disagreement. An average score of ≥ 4.0 indicates a significant self-perception of fatigue. This tool has been validated in Spanish, including for general populations in Mexico and among medical residents [30, 31].

The management of post-COVID-19 fatigue remains undefined, with limited evidence from controlled clinical trials. However, since post-viral fatigue is considered a subacute form of chronic fatigue syndrome (CFS), it is assumed that management strategies for CFS can be applied to post-COVID-19 fatigue [26, 32].

Several studies have demonstrated that multicomponent exercise is effective in reducing fatigue associated with chronic conditions such as osteoarthritis, rheumatoid arthritis, Parkinson's disease, and multiple sclerosis [33]. Its outcomes are comparable to other therapies, such as adaptive pacing and cognitive behavioral therapy, while offering the added benefits of being more cost-effective and accessible [34].

Chronic fatigue syndrome is one condition in which the effects of exercise on fatigue have been evaluated, showing positive results. Therefore, it can be reasonably assumed that this therapeutic approach may also benefit fatigue related to SARS-CoV-2 infection [35].

Exercise has demonstrated short-, medium-, and long-term health benefits by preventing, delaying, mitigating, and even reversing metabolic, pulmonary, cardiovascular, neurocognitive, inflammatory, rheumatic, and musculoskeletal diseases. Consequently, it is considered to have a positive impact on persistent post-COVID-19 symptoms [36]. Exercise, regardless of the individual's characteristics, must adhere to general planning principles, summarized by the acronym FITTVP, which refers to the following components [37]:

Frequency

Refers to the number of exercise sessions performed over a period, such as sessions per day, week, or month.

Intensity

Defines the dose or workload needed to elicit a response that follows the principle of overload, such as the weight of a dumbbell, running speed, or perceived effort during an activity.

Time

Measures the duration of exercise within a session, for example, 30 minutes of walking, 5 minutes of light cycling, or 15 seconds of push-ups.

Type

Describes the specific characteristics of the exercise, ensuring adherence to the principle of specificity, such as continuous walking, interval walking, or pyramid strength training.

Volume

Represents the total amount of activity performed, calculated as the product of frequency, intensity, and time, for example, total sets, steps, or distance covered.

Progression

Involves incremental increases in any of the above components, adhering to the principle of gradual overload, such as adding 4 repetitions every 2 weeks or extending a walking session by 5 minutes weekly [38].

The term multicomponent exercise is increasingly common, referring to routines combining various exercise types, such as aerobic, strength, balance, flexibility, coordination, and power training. These exercises work synergistically to provide combined benefits for participants [39].

Aerobic exercise: Lowers blood pressure, enhances mitochondrial biogenesis, improves pulmonary function and aerobic capacity, boosts immune function, and supports weight management. Strength training: Increases muscle mass and strength, enhances exercise tolerance, and reduces insulin resistance. Flexibility training: Improves joint mobility, prevents muscle injuries, and reduces stress.

Enhances coordination, prevents falls, and improves reaction speed [36]. A systematic review by Larun et al. on chronic fatigue syndrome (CFS) patients concluded that exercise significantly reduces fatigue, improves sleep quality, enhances physical function perception, and boosts overall well-being compared to conventional treatments such as relaxation activities or adaptive stimulation therapies [40].

Due to the essential role of exercise prescription in managing fatigue, the European Federation of Sports Medicine has recommended that individuals recovering from SARS-CoV-2 infection undergo an initial evaluation and tailored exercise prescription by a sports and exercise medicine physician [41].

While exercise has proven effective in managing fatigue in various diseases, robust evidence on its application to post-COVID-19 fatigue is still lacking. Given that fatigue is a multifactorial condition, it is proposed to design a multicomponent exercise program tailored for individuals in post-COVID-19 condition. This program would aim to produce therapeutic effects on factors that indirectly alleviate fatigue, such as body weight, muscle strength, and aerobic capacity.

2. MATERIALS AND METHODS

This study was conducted as a Master's Thesis [42] with a quasi-experimental pre-test/ post-test trial involving men and women aged 30 to 60 years with a history of SARS-CoV-2 infection and subsequent COVID-19 disease, who reported fatigue and were treated at the Sports Medicine Department of the Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra (INRLGII). Participants were selected based on predefined inclusion criteria: confirmed SARS-CoV-2 infection via positive PCR or rapid antigen test, at least 12 weeks post-COVID-19 recovery, a Fatigue Severity Scale (FSS) score ≥ 4, autonomous ambulation, and no physical limitations preventing participation in a multicomponent exercise program. Patients with active COVID-19 symptoms, body mass index (BMI) > 35 kg/m^2, history of restrictive cardiovascular disease (e.g., myocarditis), major psychological disorders, or uncontrolled comorbidities were excluded. Those who missed evaluation appointments, experienced injuries or illnesses that precluded exercise, reinfection with SARS-CoV-2, or voluntarily withdrew from the protocol were withdrawn from the study. The intervention group followed an exercise program comprising aerobic, strength, flexibility, and balance components, with no additional co-interventions for fatigue or secondary outcomes. Sample size calculations, based on Pouchot et al.'s findings on fatigue in rheumatoid arthritis populations, required at least 23 participants to detect a 20% reduction in mean FSS scores with 80% power ($\alpha = 0.05$). Accounting for a 25% attrition rate, 30 participants were intended to be enrolled.

Patients were recruited from the Sports Medicine Department of the INRLGII based on inclusion criteria and after signing informed consent. Candidates underwent an initial assessment to verify health status and general fitness for physical exercise. This included medical history and physical examination, administration of the FSS, and laboratory tests (complete blood count, blood chemistry, and lipid profile). Resting electrocardiogram (ECG) were performed using a BTL-08 LX ECG device (BTL, UK) in a supine position after five minutes of rest. Body composition was analyzed using bioelectrical impedance analysis (BIA) with an InBody 370S device (InBody, South Korea). Isokinetic dynamometry of knee flexors and extensors was conducted using a Biodex 4 Pro dynamometer (Biodex, USA) at an angular velocity of 60°/s. Aerobic capacity was determined via treadmill exercise testing with cardiac monitoring using a Schiller CS-200 device (Schiller, USA) and the Bruce protocol to measure relative maximal oxygen consumption (VO_2max).

Candidates were deemed fit for exercise if no abnormalities were observed in the resting ECG or during the exercise test, such as conduction disturbances, cardiac ischemia, or myocarditis. Cardiovascular risk was stratified according to the American College of Sports Medicine guidelines [39]. Eligible patients meeting all inclusion criteria were invited to participate in the study. Investigators provided detailed explanations of the study's objectives, benefits, and risks, and candidates were given sufficient time to consider participation. Participation was formalized by signing informed consent.

The enrolled patients followed a 12-week multicomponent exercise program comprising aerobic, strength, flexibility, and balance exercises. They attended an initial teaching session at the INRLGII before continuing the program at home. Weekly contact was maintained via phone or text to address questions and monitor for adverse effects.

At the end of week six, patients were reevaluated for progress, and the exercise program was progressed for phase 2 of the protocol for which a new teaching session was conducted to implement it. At the end of week 12, a final evaluation was performed, including laboratory parameters, ECG, body composition, isokinetic dynamometry, and aerobic capacity. Patients received a comprehensive report summarizing their progress and changes observed throughout the study.

The study protocol was approved by the Ethics and Research Committees from the Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra with registry INRLGII 78/21. Participant provided informed consent, with the volunteer form covering research details, risks, benefits, confidentiality, and participant rights. The research strictly adhered to the ethical principles of the Declaration of Helsinki, prioritizing participant's rights and well-being in design, procedures, and confidentiality measures.

2.1. Multicomponent exercise program

A multicomponent exercise program was prescribed, consisting of a 12-week macrocycle, divided into two mesocycles of 6 weeks each, and six microcycles of 2 weeks each. The components of the program included aerobic exercise, strength, flexibility, and balance (Fig. 1).

		MACRO					
		MESO 1			MESO 2		
		MICRO 1	MICRO 2	MICRO 3	MICRO 4	MICRO 5	MICRO 6
CONTINUOUS AEROBIC	Frequency (d/w)	2	2	2	2	3	3
	Volume (min)	20	25	30	30	30	40
	Intensity (Borg)	6 to 8	9 to 11	9 to 11	12 to 13	12 to 13	12 to 13
DECREMENTAL INTERVALIC AEROBIC	Frequency (d/w)	-	-	-	2	2	2
RESISTANCE	Frequency (d/w)	2	2	3	3	3	3
	# exercises (sup-inf-core)	4 (0-0-4)	6 (1-1-4)	6 (1-1-4)	8 (3-3-2)	8 (3-3-2)	8 (3-3-2)
	Sets	3	3	3	4	4	4
	Reps	8	8	10	10	12	15
BALANCE	Frequency (d/w)	2	2	3	3	3	3
	Sets	4	4	4	4	4	4
	Time (sec)	20	10	30	15	20	10

Figure 1. Exercise program planification

Each component of the exercise program was structured as follows:

Aerobic Exercise

Continuous walking was performed, with a progressive increase in duration during each microcycle. The program started with 20 minutes and increased by 5 minutes each microcycle, reaching a maximum of 30 minutes by the third microcycle. The intensity began at the "very light" range (Borg scale 6-8) and progressed to "light" (Borg scale 9-11) in the second microcycle, maintaining this intensity throughout the third microcycle. During the second mesocycle, continued progressive increases in work volume were made, and the intensity was increased to a "somewhat hard" range (Borg scale 12-13).

Decremental Interval Aerobic Exercise

At the second mesocycle, a decremental interval training method was introduced, performed twice a week. This method included five intervals at 75% of the heart rate reserve (HRR) or a Borg scale of 14-17, alternated with recovery intervals.

Strength Training

Two strength training plans were followed, one for each mesocycle, focusing on exercises for the upper body, lower body, and core mixed in two circuits of 3 exercises in mescycle 1 (circuit 1:half plank, alternating supermans and high push-up. Circuit 2: knees up laying upward, glute bridge and chair squat). During mesocycle 2 we implemented two circuits of 4 exercises (circuit 1: Half push-up, standing dumbell miitary press, chair dips, dead bug. Circuit 2: half squat, resistance band deadlift, step up, inverted dead bug). Progressive increases in work volume were implemented in each microcycle.

Balance Exercise

Balance training was incorporated into the program, with progressions in both the duration of the exercise and the level of difficulty with each microcycle. This balance work was conducted on the same days assigned for strength training. The training consisted of a single balance exercise performed on the assigned strength training day.

2.2. Statistical analysis

Descriptive statistics were performed for the sociodemographic variables, expressed in frequencies, median, and interquartile range (IQR). Since the distribution of the variables was not considered normal, the Wilcoxon signed-rank test was used. For both the primary and secondary outcomes, a 95% Confidence Interval (CI) was established, and a p-value of less than 0.05 was considered statistically significant. The statistical analysis was conducted using SPSS version 22 for Windows.

3. RESULTS

A total of 67 individuals were screened, of whom 34 met the inclusion criteria and agreed to participate in the study. However, only 15 participants were included in the final analysis due to various factors that hindered their continued participation in the intervention (Figure 2).

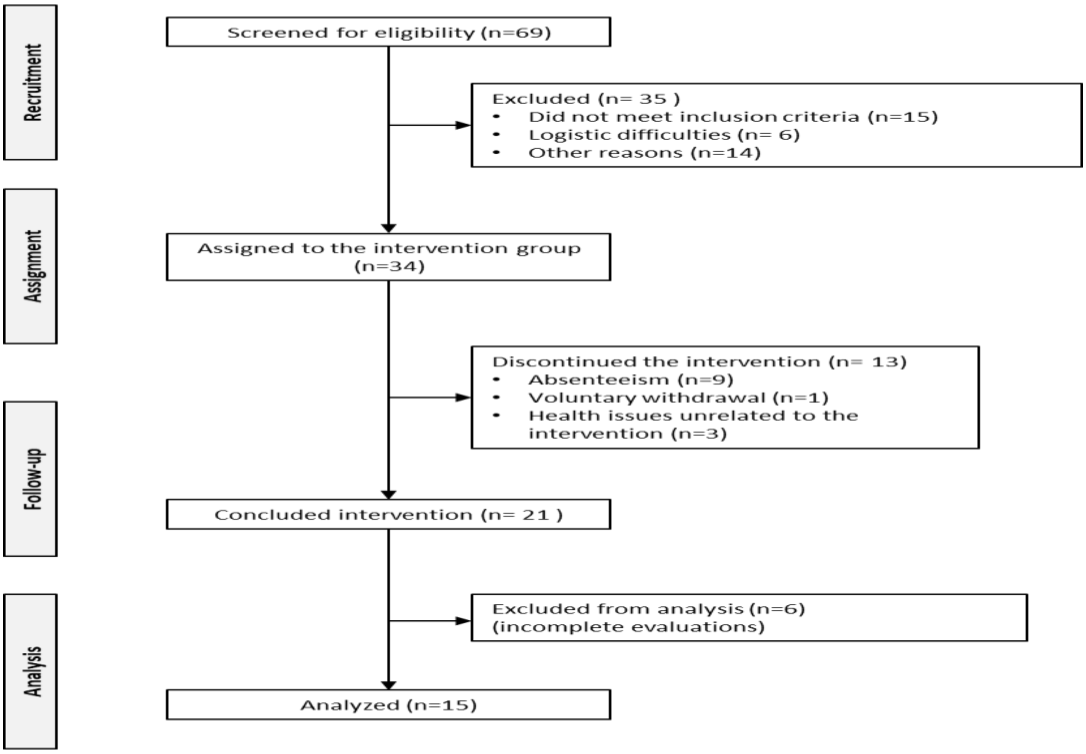

Figure 2. Diagram of participant flow through the different protocol stages

The median age of the sample was 50 ± 19 years, with 20% being male and 80% female. The median time since the acute phase of the disease was 38 ± 102 weeks. The median self-perceived fatigue level at baseline was 5.3 ± 0.8, exceeding the cutoff point of 4, which is considered positive for diagnosing fatigue; this symptom was present in 100% of the sample. The complete sample basal characteristics are shown in Table 1.

Table 1. Sample basal characteristics

VARIABLES	Total n=15 median (IQR)
Age (years)	50 (37 - 56)
Weight (kg)	70 (62.6 - 80)
Height (m)	1.61 (1.52 - 1.66)
BMI (kg/m2)	28 (23.5 - 31.6)
Weeks since infection	38 (12 - 114)
Fatigue (FSS)	5.3 (4.8 - 5.9)
Fat %	39.5 (29 - 42.8)
Muscle %	33.3 (31.3 - 40)
VO2 max rel (ml/kg/min)	35.3 (24.5 - 35.3)
Right knee extensor peak torque (N/m)	104 (104 - 110.4)
Left knee extensor peak torque (N/m)	107 (107 - 111.8)

Following the 12-week intervention with the multicomponent exercise program, there was a statistically significant reduction in fatigue self-perception (Median difference: 2.5; 95% CI: 1.7–3.2; $p < 0.001$), representing a 36% decrease (Fig. 3).

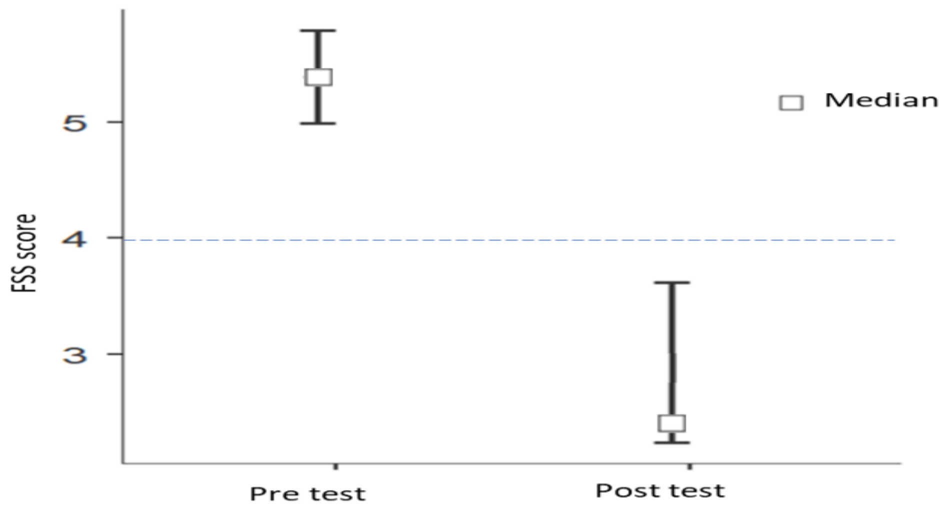

Figure 3. Fatigue Self-Perception pre and post differences

Among the secondary outcomes, we observed that aerobic capacity (VO2 max rel) at the end of the follow-up had statistically significant improvement, being the only secondary variable with such positive change (Table 2).

Table 2. Post-intervention intragroup changes

	Median difference	CI 95%	p *
Fatigue	2.5	[1.7 – 3.2]	<0.001
VO2 max rel (ml/kg/min)	10.8	[5.7 – 19.9]	0.006
PT right knee extensor (N/m)	2.1	[4 – 8.9]	0.426
PT left knee extensor (N/m)	3.5	[2.6 – 9]	0.5
Fat %	0.9	[-0.4 – 2.2]	0.09
Muscle %	0.3	[-0.95 – 0.5]	0.3

* Wilcoxon W test.

4. DISCUSSION

The observed effect on fatigue self-perception in individuals recovering from COVID-19 after undergoing a 12-week multicomponent exercise program was positive. Our findings showed a significant decrease in the primary outcome following exposure to the intervention. These results align with those reported in other epidemiological studies, which have demonstrated the effectiveness of physical exercise interventions in reducing fatigue associated with chronic conditions such as osteoarthritis, rheumatoid arthritis, Parkinson's disease, and multiple sclerosis [33, 43].

Scientific evidence has highlighted fatigue self-perception reductions in up to 71% of participants, with some studies even reporting its remission after exercise interventions. These findings, however, differ from our results, possibly due to variations in the scales used to assess fatigue [44–49]. It is worth noting that the current tools for fatigue evaluation rely on subjective data and are unable to quantify its intensity accurately.

In addition to improvements in fatigue perception, our study revealed a significant increase in relative maximal oxygen consumption (VO2MaxRel) at the end of the intervention. This finding suggests that aerobic capacity may be directly associated with fatigue. Most participants had, on average, nine months since the acute phase of COVID-19, with some exceeding two years. Despite this prolonged recovery, residual fatigue was still present, but it responded well to the intervention. Importantly, our study included individuals who underwent outpatient management without severe complications requiring hospitalization during the acute phase. This population represents the majority of those affected by the disease globally [3, 50], making multicomponent exercise a potentially accessible first-line treatment for the largest segment of the post-COVID-19 population experiencing fatigue.

The improvement in fatigue perception may partly be attributed to the angiogenic effects of aerobic exercise, which increases oxygen consumption and mitigates hypoperfusion and endothelial dysfunction described in post-COVID-19 fatigue [51]. It is important to emphasize that the current scientific literature evaluating the efficacy of multicomponent exercise on fatigue self-perception is limited. Methodological differences among studies, including their observational designs, preclude direct comparisons. Our quasi-experimental design offers clarity on the intervention's effect but lacks the rigor of a randomized control trial. Additionally, prior studies typically evaluated interventions lasting a maximum of six weeks, often with tele-rehabilitation components [46] , contrasting with our progressive, incremental 12-week program that demonstrated favorable outcomes. Furthermore, the small sample sizes in prior studies, ranging from 1 to 30 participants, limit the power of their findings. This limitation was also evident in our study, as we were unable to achieve the planned sample size.

While our intervention exceeded the initial hypothesis of a 20% reduction in fatigue perception, it is important to note that the design does not allow conclusions regarding its superiority over other therapeutic tools. Future research should focus on experimental studies that compare the proposed exercise program with standard reference treatments for managing post-COVID-19 fatigue.

Defining and categorizing the pathophysiological mechanisms of post-COVID-19 fatigue remains essential, as its underlying mechanisms are not yet fully understood. Fatigue is recognized as a multifactorial condition [18], and our study highlights the direct effect of improved aerobic capacity on reducing fatigue perception. Combining this improvement with additional therapeutic approaches, such as psychotherapy or psycho-emotional management strategies, could further reduce fatigue perception.

Study limitations included challenges during recruitment and participant follow-up. Despite dissemination efforts through institutional print media and digital platforms, engagement was low. Adherence to the intervention was also a critical factor, with high initial absenteeism leading to dropout or delays in intervention and evaluation. A strategy of weekly text message follow-ups was implemented to address this issue, providing reminders, addressing exercise-related concerns, and encouraging attendance at evaluation appointments. This approach significantly improved adherence and reduced absenteeism.

5. Conclusion

The multicomponent exercise program aimed at reducing the self-perception of post-COVID-19 fatigue demonstrates a favorable trend as a treatment tool. Thus, it can be considered an effective approach for managing post-COVID-19 sequelae in the population segment that continues to experience symptoms—specifically fatigue—and has not yet received appropriate treatment. It is essential to continue raising awareness and generating scientific evidence about the need to recognize and address post-COVID-19 sequelae.

Conflict of Interest

No conflict of interest is declared by the authors. In addition, no financial support was received.

Ethics Committee

The study protocol was approved by the Ethics and Research Committees from the Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra with registry INRLGII 78/21.

Author Contributions

Study Design, FFC, APP, SHHV; Data Collection, FFC; Statistical Analysis, FFC, SHHV; Data Interpretation, FFC, SHHV; Manuscript Preparation, FFC, APP, SHHV; Literature Search, FFC, APP. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Liu, X., Liu, C., Liu, G., Luo, W., & Xia, N. (**2020**). COVID-19: Progress in diagnostics, therapy and vaccination. *Theranostics*, *10*(17), 7821–7835. [PubMed]
2. WHO. (**2023**). WHO Coronavirus (COVID-19) Dashboard. [CrossRef]
3. CONAHCYT. (**2021**). COVID-19 México. [CrossRef]
4. Greenhalgh, T., Knight, M., A'Court, C., Buxton, M., & Husain, L. (**2020**). Management of post-acute covid-19 in primary care. *The BMJ*, *370*. [PubMed]
5. Johns Hopkins. (**2020**). Coronavirus Resource Center. *University and Medicine*. [CrossRef]
6. Venkatesan, P. (**2021**). NICE guideline on long COVID. *The Lancet Respiratory Medicine*, *9*(2), 129. [PubMed]

7. Kamal, M., Abo, M., Amal, O., & Haitham, H. (**2021**). Assessment and characterisation of post-COVID-19 manifestations, (September 2020), 1–5. [PubMed]
8. Nasserie, T., Hittle, M., & Goodman, S. N. (**2021**). Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19. *JAMA Network Open*, *4*(5), e2111417. [PubMed]
9. Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (**2021**). More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv*. [PubMed]
10. Carfi A, Bernabei R, Landi F, et al. (**2020**). Persistent symptoms in patients after acute COVID-19. *JAMA*, *324*, 603–605. [PubMed]
11. Tenforde MW, Kim SS, Lindsell CJ, E. (**2020**). CDC COVID-19 Response Team. IVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network — United States, March-June 2020. [PubMed]
12. Salman, D., Vishnubala, D., Le Feuvre, P., Beaney, T., Korgaonkar, J., Majeed, A., & McGregor, A. H. (**2021**). Returning to physical activity after covid-19. *The BMJ*, *372*, 1–6. [PubMed]
13. Wu, F. (n.d.). Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *The Lancet*. [CrossRef]
14. Glaus, A., Crow, R., & Hammond, S. (**1996**). A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. *Supportive Care in Cancer*, *4*(2), 82–96. [PubMed]
15. Duarte Ayala, R. E., Velasco Rojano, Á. E., Sánchez Sosa, J. J., & Reyes Lagunes, L. I. (**2017**). Adaptación y validación de la escala de impacto de fatiga. *Acta de Investigación Psicológica*, *7*(1), 2585–2592. [CrossRef]
16. VanElzakker, M. B., Brumfield, S. A., & Lara Mejia, P. S. (**2019**). Neuroinflammation and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Critical Review of Research Methods. *Frontiers in Neurology*, *9*. [PubMed]
17. Batra, A., Clark, J. R., LaHaye, K., Shlobin, N. A., Hoffman, S. C., Orban, Z. S., Liotta, E. M. (**2021**). Transcranial Doppler Ultrasound Evidence of Active Cerebral Embolization in COVID-19. *Journal of Stroke and Cerebrovascular Diseases*, *30*(3), 105542. [PubMed]
18. Susan E. Hardy, and S. A. S. (**2010**). Qualities of Fatigue and Associated Chronic Conditions Among Older Adults. *J Pain Symptom Manage*, *39*(6), 1033–1042. [PubMed]
19. VGONTZAS, A. N., BIXLER, E. O., & CHROUSOS, G. P. (2006). Obesity-Related Sleepiness and Fatigue. *Annals of the New York Academy of Sciences*, *1083*(1), 329–344. [PubMed]
20. Cooper, R., Hardy, R., Bann, D., Sayer, A. A., Ward, K. A., Adams, J. E., & Kuh, D. (**2014**). Body mass index from age 15 years onwards and muscle mass,strength, and quality in early old age: Findings from the MRC national survey of health and development. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *69*(10), 1253–1259. [PubMed]
21. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. (**2020**). Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS ONE*, *15*(11). [PubMed]
22. Ferrandi, P.J.; Always, S.E.; Mohamed, J. S. (**2020**). The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies. *Journal of Applied Physiology*, *129*, 864–867. [PubMed]
23. Cabrera Martimbianco, A. L., Pacheco, R. L., Bagattini, Â. M., & Riera, R. (**2021**). Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. *International Journal of Clinical Practice*, *75*(10). [PubMed]
24. Rooney, S., Wood, L., Moffat, F., & Paul, L. (**2019**). Is Fatigue Associated With Aerobic Capacity and Muscle Strength in People With Multiple Sclerosis: A Systematic Review and Meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *100*(11), 2193–2204. [PubMed]
25. Acevedo, M., Valentino, G., Bustamante, M. J., Orellana, L., Adasme, M., Baraona, F., Navarrete, C. (**2020**). Cardiorespiratory fitness improves prediction of mortality of standard cardiovascular risk scores in a Latino population. *Clinical Cardiology*, *43*(10), 1167–1174. [PubMed]
26. Gaber, T. (**2021**). Assessment and management of post-COVID19 fatigue. *Progress in Neurology and Psychiatry*, *25*(1), 36–39. [CrossRef]
27. Rupp, T. L., Garbarino, S., Guglielmi, O., & Lanteri, P. (**2017**). Concepts of Fatigue, Sleepiness, and Alertness☆. In *Reference Module in Neuroscience and Biobehavioral Psychology*. Elsevier. [CrossRef]
28. Raman, B., Cassar, M. P., Tunnicliffe, E. M., Filippini, N., Griffanti, L., Alfaro-Almagro, F., Neubauer, S. (**2021**). Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*, *31*, 100683. [PubMed]
29. Krupp, L. B. (**1989**). The Fatigue Severity Scale. *Archives of Neurology*, *46*(10), 1121. [PubMed]
30. Duarte, R. E., Velasco, E., Sánchez-Sosa, J. J., & Reyes-Lagunes, L. I. (2019). Validación psicométrica de la Escala de gravedad de fatiga en médicos residentes mexicanos. *Educación Médica*, *20*(1), 28–36. [CrossRef]
31. Velasco-Rojano, E. (**2017**). Validación de la Escala de Gravedad de Fatiga en Población General de la Ciudad de México. *Revista Evaluar*, *17*(2). [CrossRef]
32. Lapp, C. W., & John, J. F. (**2021**). Managing COVID-19 post viral Fatigue Syndrome. *Fatigue: Biomedicine, Health & Behavior*, *9*(1), 1–8. [CrossRef]
33. van Erp, L. W., Roosenboom, B., Komdeur, P., Dijkstra-Heida, W., Wisse, J., Horjus Talabur Horje, C. S., … Groenen, M. J. M. (**2021**). Improvement of Fatigue and Quality of Life in Patients with Quiescent Inflammatory Bowel Disease Following a

Personalized Exercise Program. *Digestive Diseases and Sciences*, *66*(2), 597–604. [PubMed]

34. Moss-Morris, R., Harrison, A. M., Safari, R., Norton, S., van der Linden, M. L., Picariello, F., Mercer, T. (**2021**). Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. *Behaviour Research and Therapy*, *137*, 103464. [PubMed]
35. Gradidge, P. J. L., Torres, G., Constantinou, D., Zanwar, P. P., Pinto, S. M., Negm, A., & Heyn, P. C. (**2023**). Exercise Reporting Template for Long COVID Patients: A Rehabilitation Practitioner Guide. *Archives of Physical Medicine and Rehabilitation.* [PubMed]
36. Jimeno-Almazán, A., Pallarés, J. G., Buendía-Romero, Á., Martínez-Cava, A., Franco-López, F., Sánchez-Alcaraz Martínez, B. J., Courel-Ibáñez, J. (**2021**). Post-COVID-19 Syndrome and the Potential Benefits of Exercise. *International Journal of Environmental Research and Public Health*, *18*(10), 5329. [PubMed]
37. Hayward, V. Ph. D. (**2001**). *Evaluación y prescripción del ejercicio* (2da Edición.). New Mexico. : Paidotribo.
38. American College of Sports Medicine. (n.d.). Principios generales de la prescripción del ejercicio. In *Guidelines for Exercise Testing and Prescription* (10a Edición.). Wolters Kluwer.
39. ACSM. (**2023**). *ACSM´S Guidelines for Exercise Testing and Prescription*. (Lippincott, Williams, & Wilkins, Eds.) (11th ed.).
40. Larun, L., Brurberg, K. G., Odgaard-Jensen, J., & Price, J. R. (**2019**). Exercise therapy for chronic fatigue syndrome. *Cochrane Database of Systematic Reviews*, *2021*(3). [PubMed]
41. Löllgen, H., Bachl, N., Papadopoulou, T., Shafik, A., Holloway, G., Vonbank, K., Zupet, P. (**2020**). Recommendations for return to sport during the SARS-CoV-2 pandemic. 10–12. [PubMed]
42. Figueroa-Cavero, F. (**2024**). *Intervention with a multi-component exercise program in managing fatigue perception in individuals who experienced COVID-19: a quasi-experimental study.* (Master's Thesis). Universidad Nacional Autonoma de Mexico, Mexico City.
43. Arienti, C., Cordani, C., Lazzarini, S. G., Del Furia, M. J., Negrini, S., & Kiekens, C. (**2022**). Fatigue, post-exertional malaise and orthostatic intolerance: a map of Cochrane evidence relevant to rehabilitation for people with post COVID-19 condition. *European Journal of Physical and Rehabilitation Medicine*, *58*(6), 857–863. [PubMed]
44. Ferraro, F., Calafiore, D., Dambruoso, F., Guidarini, S., & de Sire, A. (**2021**). COVID-19 related fatigue: Which role for rehabilitation in post-COVID-19 patients? A case series. *Journal of Medical Virology*, *93*(4), 1896–1899. [PubMed]
45. Daynes, E., Gerlis, C., Chaplin, E., Gardiner, N., & Singh, S. J. (**2021**). Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition – A cohort study. *Chronic Respiratory Disease*, *18*, 14799731211015691. [PubMed]
46. Wootton, S. L., King, M., Alison, J. A., Mahadev, S., & Chan, A. S. L. (**2020**). COVID-19 rehabilitation delivered via a telehealth pulmonary rehabilitation model: a case series. *Respirology Case Reports*, *8*(8). [PubMed]
47. Tozato, C., Fernandes Costa Ferreira, B., Pereira Dalavina, J., & Vitelli Molinari, C. (**2021**). Cardiopulmonary rehabilitation in post-COVID-19 patients: case series. *Revista Brasileira de Terapia Intensiva*, *33*(1). [PubMed]
48. Ahmed, I., Inam, A. Bin, Belli, S., Ahmad, J., Khalil, W., & Jafar, M. M. (**2022**). Effectiveness of aerobic exercise training program on cardio-respiratory fitness and quality of life in patients recovered from COVID-19. *European Journal of Physiotherapy*, *24*(6), 358–363. [CrossRef]
49. Bickton, F. M., Chisati, E., Rylance, J., & Morton, B. (**2021**). An Improved Pulmonary Telerehabilitation Program for Postacute COVID-19 Patients Would Be Feasible and Acceptable in a Low-Resource Setting. *American Journal of Physical Medicine & Rehabilitation*, *100*(3), 209–212. [PubMed]
50. WHO. (n.d.). WHO Coronavirus. [CrossRef]
51. Flaskamp, L., Roubal, C., Uddin, S., Sotzny, F., Kedor, C., Bauer, S., Seifert, M. (**2022**). Serum of Post-COVID-19 Syndrome Patients with or without ME/CFS Differentially Affects Endothelial Cell Function In Vitro. *Cells*, *11*(15). [PubMed]