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The Short- and Long-Term Impact of Pulmonary Rehabilitation in Subjects with Sarcoidosis: A Prospective Study and Review of the Literature

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Keywords
Sarcoidosis · Exercise · Rehabilitation · VO_2max · Interstitial lung disease

Abstract
Background: Sarcoidosis is a heterogeneous multisystemic disorder of unknown etiology. Dyspnea and fatigue are two of the most common and debilitating symptoms experienced by subjects with sarcoidosis. There is limited evidence regarding the short- and long-term impact of pulmonary rehabilitation (PR) on exercise capacity and fatigue in these individuals. ***Objective:*** To evaluate the benefit of PR in subjects with pulmonary sarcoidosis at different severity stages and to review the current literature about PR in sarcoidosis. ***Methods:*** PR included a 12-week training program of a twice-weekly 90-min workouts. Fifty-two subjects with stable pulmonary sarcoidosis were recruited. Maximal exercise capacity, defined as VO_2max, was measured using the cardiopulmonary exercise test (CPET). Pulmonary function tests, 6-min walking distance (6MWD), St. George's Respiratory Questionnaire (SGRQ), and the modified Medical Research Council (mMRC) and Hospital Anxiety and Depression Scale (HADS) questionnaires were given before and after PR and following 6 months (follow-up). ***Results:*** The PR program significantly increased the VO_2max (1.8 ± 2.3 mL/kg/min, $p = 0.002$), following 12 weeks. mMRC and SGRQ scores were also improved (−0.3 ± 0.8, $p = 0.03$, and −3.87 ± 10.4, $p = 0.03$, respectively). The impact of PR on VO_2max was more pronounced in subjects with pulmonary parenchymal involvement. The increase in VO_2max correlated with initial disease severity (indicated by FEV1/FVC, $p = 0.01$). Subjects with FEV1/FVC <70% showed greater improvement in 6MWD. 6MWD also improved in those with a transfer coefficient of the lung for CO (KCO) above 80% predicted ($p < 0.05$). At 6-month follow-up, the VO_2max, 6MWD, and SGRQ scores remained stable, thus suggesting lasting effects of PR. ***Conclusion:*** PR is a promising complementary therapeutic intervention for subjects with sarcoidosis. Further study is needed to validate these findings.

Elad Guber and Ori Wand contributed equally to this work.
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Introduction

Sarcoidosis is a heterogeneous multisystemic disorder of unknown etiology, which often presents with bilateral hilar lymphadenopathy and pulmonary infiltrates [1, 2]. Clinical manifestations often vary with the stage of the disease and degree of organ involvement [3–6]. As in chronic obstructive pulmonary disease and pulmonary hypertension, subjects with sarcoidosis experience limiting symptoms in daily life activities. They usually experience dyspnea, fatigue, and exercise intolerance, resulting in low physical activity levels and reduced quality of life [7–9]. These symptoms tend to persist despite optimal pharmacological treatment [10–12]. Moreover, reduced health status has been related to decreased pulmonary function, symptoms of depression, and respiratory muscle weakness [7–9].

Pulmonary rehabilitation (PR), where exercise training is a core component, is recommended as part of the comprehensive care for subjects with interstitial lung disease [13]. However, these recommendations are mostly based on studies done in idiopathic pulmonary fibrosis or heterogonous groups of subjects with interstitial lung disease [14–16]. So far, only a limited number of studies directly assessed the impact of PR on outcomes of sarcoidosis. Moreover, these studies mostly included brief PR programs with no long-term follow-up. Peak oxygen uptake (VO_2max), which is an objective and precise parameter of exercise capacity, was infrequently assessed [17, 18].

In the current study, we set forth to prospectively evaluate the short- and long-term impact of a formal PR program in subjects with sarcoidosis using an incremental cardiopulmonary exercise test (CPET), which is considered as the gold standard exercise capacity assessment tool. The St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) and the Hospital Anxiety and Depression Scale (HADS) questionnaires, 6-min walking distance (6MWD), and complete pulmonary function tests (PFTs) were also performed in each visit.

Materials and Methods

Study Participants

Individuals with stable pulmonary sarcoidosis (i.e., no new symptoms in the last year and stable PFT in the last 3 months) and 18 years of age or older with no change in medications during the previous 3 months were recruited (from March 1, 2018, until February 1, 2020). Sarcoidosis was diagnosed according to the latest American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) statement [19]. Subjects with significant pulmonary/other comorbidity (e.g., previous lung surgery, advanced heart failure [NYHA III–IV], or malignancy in the last 3 years) that might affect exercise tolerance, chronic steroid treatment equivalent to >10 mg/day of prednisone, and those unable to perform CPET were excluded.

Study Design

This was a prospective, interventional before/after study, assessing the impact of PR in subjects with sarcoidosis. Each subject served as his own control in a before-after design (i.e., for each subject, the "after" was compared to the "before" for each parameter). Demographics, medical history, and clinical data were recorded by a pulmonary physician. On the first day (baseline, time 0), a set of measurements were obtained. Weight and height were measured, and BMI was calculated. Complete PFTs, including 6MWD and CPET, were performed at baseline, at the end of the 12-week PR program, and after 6 months. In addition, subjects were asked to fill out 3 questionnaires during each visit (see below). The primary outcome measure was the difference in mean VO_2max between time 0 and following the PR program. Secondary outcomes were difference in the measured variables between time 0 and 12 weeks, as well as the difference in those variables between time 0 and 6 months.

Pulmonary Function Tests and Six-Minute Walk Distance (6MWD)

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and total lung capacity were measured by spirometry and plethysmography with a Jaeger-Masterlab cabin (Vyaire Medical, Germany). Single-breath diffusing capacity of the lung for carbon monoxide (DLCO, in mL CO/min/mm Hg) and transfer coefficient of the lung for CO (KCO, in CO/min/mm Hg/L) were measured and corrected for hemoglobin concentration. Reference equations for lung volumes KCO were used as previously described [20]. Values below normal (as per the ATS guidelines) were considered impaired. Maximum voluntary ventilation was measured by spirometry, according to the ATS guidelines [21]. Respiratory muscle strength was assessed by maximal inspiratory pressure (PIMAX) and maximal expiratory pressure (PEMAX) [22]. 6MWD test was performed according to the ATS guidelines [23].

Cardiopulmonary Exercise Test (CPET)

Peak exercise capacity was assessed by a maximal incremental cycle exercise test. Peak external work rate, maximal heart rate, systolic and diastolic blood pressure, and peak oxygen uptake (VO_2max) were normalized for height, age, and gender [24].

Questionnaires

Subjects completed the following questionnaires at baseline, 12 weeks (i.e., after), and at 6 months (i.e., follow-up). (1) Health status and dyspnea assessments were measured using the St. George's Respiratory Questionnaire (SGRQ) [25], (2) the modified Medical Research Council (mMRC) [26] was used to assess respiratory disability, and (3) the Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression, in which a score of 8–10 (on a scale of 0–21) is indicative of uncertain symptoms and a score >11 is indicative of clinically relevant symptoms [27].

The PR Program

A personalized exercise program of moderate intensity was provided by a physiologist based on the initial physical examination, CPET results, and individual capabilities. Maximal heart rate was set at 70%, as calculated by the Karvonen formula and by the anaerobic threshold on CPET. Target intensity was set at 12–14 on the Borg Rating of Perceived Exertion (RPE), which is considered a moderate level. The program included twice-weekly sessions, 90 min each, with each session consisting of 3 parts. The first part included 20 min of balance, weight, flexibility, and range of motion exercises. The second part included 40 min of aerobic exercises on a variety of ergometers (10–15 min each). The third part included 30 min of strength exercises on 11 major muscles groups (2–3 sets of 10–15 repeats/min each). The weights were chosen based on subjects' ability to maintain the needed number of repeats (at least 10 repeats/min). Heart rate and blood pressure were measured at each session while at rest and at maximal exercise load.

Statistical Analysis

Statistical analysis was done with SPSS-23 software (IBM, Armonk, NY, USA). In order to demonstrate a significant difference between time 0 and following the 12-week program, ensuring a statistical power of at least 80% and a level of confidence of 5%, a sample group of 50 subjects was calculated, according to the primary outcome (i.e., VO_2max). Results are presented as mean (±SD), median, or percent. A 2-tailed paired *t* test (continuous), a Mann-Whitney U test, or a χ^2 test (binomial) was used to determine differences between variables in the beginning and the end of the PR. Significance was set at $p \leq 0.05$. Pearson correlation (continuous, *r*) or Spearman rank correlation (r_S) was used to determine relationships.

Results

Perceived Well-Being Is Improved following the PR Program

Fifty-eight subjects were screened for the study. Of them, 2 declined participation and 4 could not perform CPET. Thus, 52 subjects were recruited for the 12-week PR program. The mean age of the participants was 53.5 ± 11 years. Nearly half of the subjects were males (51.9%), mostly nonsmokers (72.4%). Twenty-two percent were treated with oral steroids. Sarcoidosis stages distribution according to Scadding criteria [28, 29] are presented in Figure 1. Overall, 42 subjects had radiographic evidence of pulmonary parenchymal involvement (81%) and 43 had thoracic lymphadenopathy (83%). Thirty-eight subjects returned for the follow-up visit after 6 months.

Since literature data demonstrated that subjects with extrapulmonary sarcoidosis are more symptomatic [30], patient files were reviewed regarding extrathoracic organ involvement, and there were 3 subjects with arthritis, one with skin involvement, one with uveitis, one with liver disease, and one with neurosarcoidosis. Additionally, 4 patients had multiorgan disease outside the thorax, including ocular and joint disease in 2 subjects, 1 subject had liver disease and peripheral neuropathy, and 1 had involvement of the liver, skin, and joints in addition to stage II pulmonary sarcoidosis. Only 2 subjects had echocardiographic signs of pulmonary hypertension.

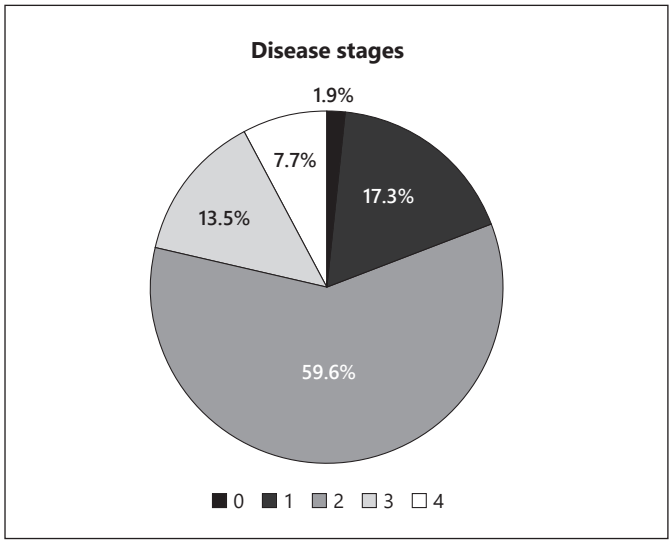

Fig. 1. Disease stage distribution within the cohort.

Following PR, the SGRQ and the mMRC questionnaire scores showed a significant decrease, indicating improved health-related quality of life and dyspnea (−3.87 ± 10.4, $p = 0.028$, and −0.3 ± 0.8, $p = 0.032$, respectively, shown in Fig. 2a, b). Scores were maintained at the follow-up only for SGRQ ($p = 0.01$, shown in Fig. 2b). No significant changes were noted in the HADS questionnaire following the PR although a trend of improvement was noted at the 6-month follow-up visit (shown in Fig. 2c).

Peak Exercise Capacity Is Improved following the PR Program

PFT and 6MWD results at baseline and following PR are shown in Table 1. Most subjects had normal or mildly impaired PFT at baseline. There were no significant changes in the PFT results following the PR. However, a modest, yet statistically significant, increase in 6MWD at the 12-week timepoint was found (15 m, $p = 0.03$, Table 1). The main outcome revealed a significant increase in VO_2max following the 12-week rehabilitation ($p = 0.001$, shown in Fig. 3a).

Our cohort consisted of individuals with different disease severities. When considering only the 42 subjects with lung parenchymal involvement, the improvement in

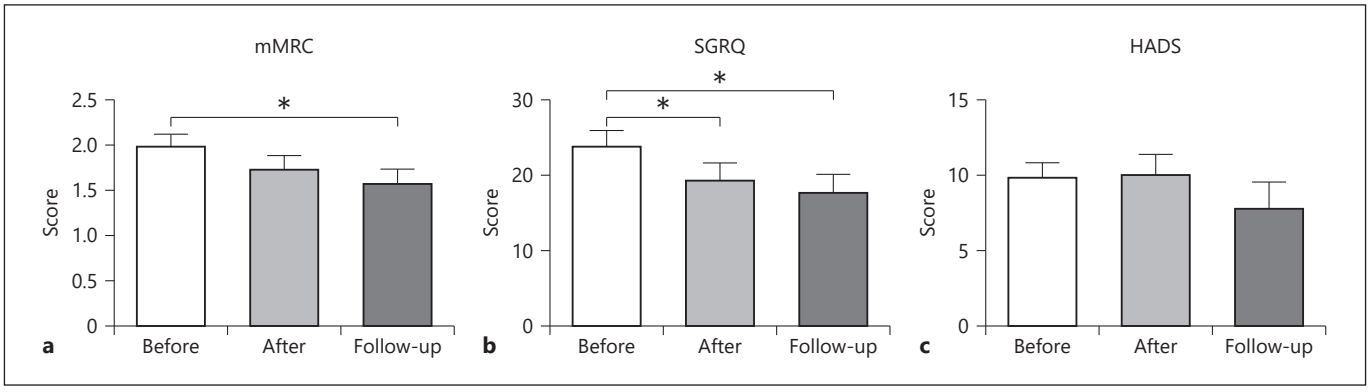

Fig. 2. mMRC (**a**), SGRQ (**b**), and HADS (**c**) scores at baseline (before), at the end of the 12-week program (after), and at the 6-month follow-up. HADS, Hospital Anxiety and Depression Scale; SGRQ, St. George's Respiratory Questionnaire; mMRC, modified Medical Research Council Questionnaire. *$p < 0.05$.

Table 1. Summary of outcome results

Pulmonary function tests	Before (±SD)	After (±SD)	*p* value	FU (±SD)	*p* value
FEV1, %	93.3±19.5	92.1±17.1	0.27	92.5±8.5	0.917
FEV1, L	2.51±0.88	2.46±0.82	0.06	2.4±0.44	0.192
FVC, %	106.3±18	102±22.5	0.18	100.7±18	0.96
FVC, L	3.4±0.9	3.4±0.9	0.29	3.3±0.6	0.81
TLC, L	5.3±1.2	5.25±1.2	0.5	5.13±0.8	0.66
MVV	84.8±29	88.6±29	0.11	87.4±21.6	0.867
FEV1/FVC, %	73.2±9.2	73.2±8.8	0.88	73.1±7.8	0.855
KCO, %	79.9±14	81.1±13.3	0.35	80±14	0.775
Resting O_2 SAT, %	96.5±1.7	96.9±1.6	0.08	97.3±1.2	0.267
RV/TLC	36.1±11.2	35.6±7	0.79	36.6±6.7	0.782
PIMAX, %	76.7±26	91±29	0.027	75.6±36	0.11
PEMAX, %	90.8±25	99.6±32	0.04	97.9±42	0.694
Peak heart rate	137.8±16	134.2±21	0.27	142±25	0.26
Systolic blood pressure	160±16	159.8±18	0.84	163.75±14	0.86
Diastolic blood pressure	80±7.7	76.8±7	0.03	80±8.8	1
6MWD	523.3±92	538.1±75	0.03	529.2±40	0.4

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; MVV, maximal voluntary ventilation; DLCO, diffusing capacity; 6MWD, 6-min walking distance; RV/TLC, residual volume of total lung capacity; PIMAX, maximal inspiratory pressure; PEMAX, maximal expiratory pressure; KCO, transfer coefficient of the lung for CO.

VO_2max was even more pronounced than for the full cohort (+1.8, $p < 0.001$). Moreover, a significant correlation was found between the change in VO_2max and the subjects' baseline FEV1/FVC ($r = -0.453$, $p = 0.018$, shown in Fig. 3b).

When analyzing the effect of rehabilitation, we found that the group with an FEV1/FVC value below 70% gained benefit as indicated by a significant improvement in the 6MWD ($p = 0.03$, shown in Fig. 4a) and a significant increase in PIMAX ($p = 0.01$). Subgroup analysis based on KCO levels showed that 6MWD was statistically improved in patients with normal KCO (values ≥80% predicted) (shown in Fig. 4b). At the 6-month follow-up visit, the 6MWD and the VO_2max were maintained at the post-PR level. In addition, the questionnaire scores were also maintained at post-PR levels (shown in Fig. 2), further suggesting that the effects of PR are long lasting.

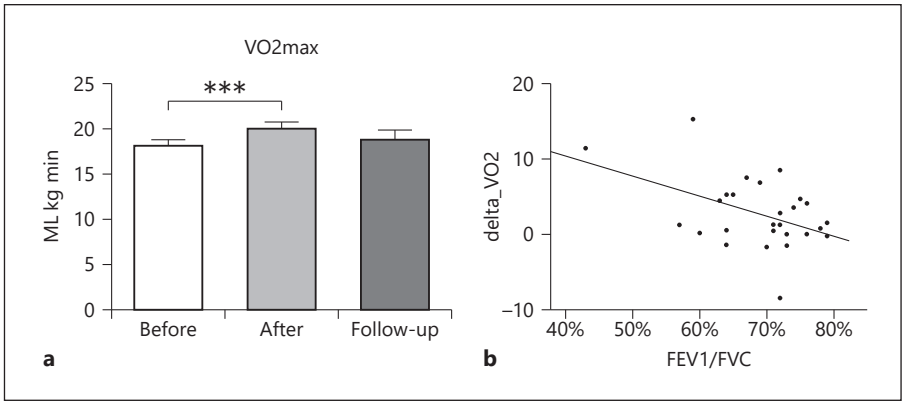

Fig. 3. a VO_2max was measured by CPET at baseline (before), at the end of the 12-week program (after), and at 6-month follow-up. **b** Correlation between baseline FEV1/FVC% and magnitude of change in VO_2max. CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Review of PR interventions among sarcoidosis patients

Study ref.	Design	*N*	PR program	Outcomes	Follow-up	Results
[34]	Retrospective comparative	90 (49 participated in PR)	12 weeks, outpatient	PFT, 6MWT, submaximal CPET, muscle strength, FAS, Borg scale	No	↑6MWT, ↓FAS ↑VO_2peak, ↑work rate, ↑elbow strength in PR group[a] No change in PFT, Borg scale
[35]	Prospective, single arm	18	13 weeks, outpatient	FAS, mMRC, VAS pain scale, muscle strength, WHOQOL-BREF	No	↑6MWT, ↓FAS, ↓mMRC, ↑quadriceps strength No change in pain scores, WHOQOL-BREF, elbow flexor muscle strength
[17]	RCT	18 patients with stages III–IV sarcoidosis (9 participated in PR)	12 weeks, outpatient	6MWT, PFT, MIP, MEP, FSS, mMRC, Borg scale, SGRQ, SF36, HADS, muscle strength	No	↑6MWT, ↓FSS, ↓mMRC, ↓Borg, ↓SGRQ, ↑MIP, ↓HADS, ↑PaO_2, ↑leg muscle strength No change in PFT, SF36
[36]	Prospective, single arm	11	12 weeks, outpatient high-intensity resistance training and daily inspiratory muscle training	PFT, MIP, MEP, FSS, mMRC, SGRQ, muscle strength, BAL counts	5 months	↑MIP, ↑MEP, ↑muscle strength, ↓%BAL lymphocytes No change in SGRQ, mMRC, PFT ↓FSS only in first follow-up
[37]	Prospective, single arm	296	3 weeks, inpatient	6MWT, SGRQ, PFT, MIP, SF-36, FAS, HADS, mMRC	No	↑6MWT, ↓SGRQ, ↓FAS, ↓mMRC, ↑SF-36, ↓HADS, ↑MIP Clinically irrelevant small ↑FVC and ↑FEV1
[38]	Prospective, single arm	41	4 weeks, inpatient	CPET, 6MWT, FAS	No	↑VO_2peak, ↑6MWT, ↓FAS
[39]	RCT	38 patients with stage IV sarcoidosis (20 participated in PR)	8 weeks, outpatient	6MST, PFT, mMRC, FAS, HADS, VSRQ, daily life physical activity	12 months	↑6MWT, ↓mMRC, ↓VSRQ ↓FAS only at 12 months for some subjects No change in daily life physical activity parameters, PFT, HADS
Current study	Prospective, single arm	52	12 weeks, outpatient	CPET, PFT, 6MWT, mMRC, HADS, SGRQ	6 months	↑VO_2peak, ↓SGRQ, ↓mMRC ↑6MWT in some patients No change in PFT, HADS

RCT, randomized controlled trial; PFT, pulmonary function tests; FAS, Fatigue Assessment Scale; 6MWT, six-minute walk test; CPET, cardiopulmonary exercise test; mMRC, modified Medical Research Council dyspnea scale; WHOQOL-BREF, World Health Organization Quality of Life-BREF assessment instrument; VAS, Visual Analog Scale; SGRQ, St George's Respiratory Questionnaire; SF36, SF-36 Health-Related Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; PR, pulmonary rehabilitation; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; VSRQ, Visual Simplified Respiratory Questionnaire. [a] While VO_2max and elbow muscle flexor strength increased in patients who underwent PR, there was no significant difference from patients who did not participate in PR.

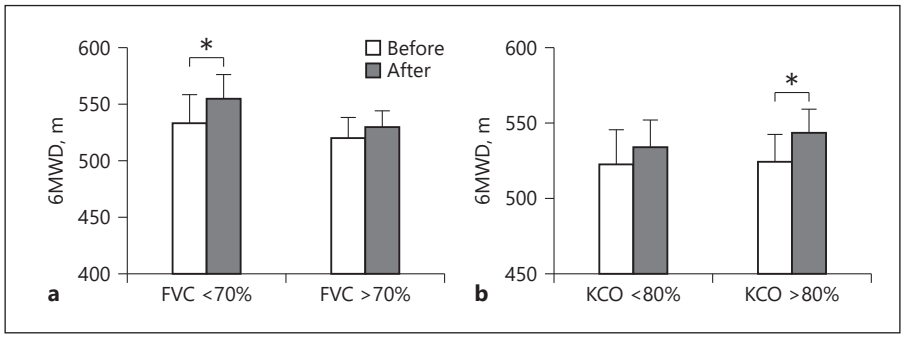

Fig. 4. a Six-minute walking distance (6MWD) at baseline (before) and at the end of the 12-week program (after), based on initial FEV1/FVC% status (FVC) or on DLCO/VA (**b**). *$p < 0.05$. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Discussion/Conclusion

Dyspnea and fatigue are two of the most common and debilitating symptoms experienced by subjects with sarcoidosis [31, 32]. These disabling symptoms influence the daily activities of patients and are associated with reduced quality of life, decreased exercise capacity, and muscle weakness [10–12]. As in any chronic illness, physical inactivity by itself can induce deconditioning, thus perpetuating a vicious cycle of further physical inactivity [32].

Medical therapeutic options for such systemic conditions are often limited, reflecting the complex nature and heterogeneous pathophysiologic origins [33]. Limited data in the medical literature have shown a beneficial effect of PR intervention among individuals with sarcoidosis resulting in an improvement of fatigue and dyspnea symptoms as well as improved exercise capacity and quality of life. Nevertheless, these data are based on a handful of studies, as summarized in Table 2 [17, 34–39].

In the present study, a 12-week outpatient PR program benefited subjects with pulmonary sarcoidosis both subjectively and objectively. Regarding subjective outcomes, PR was associated with improvement in dyspnea scores, as indicated by the SGRQ and mMRC questionnaire, similar to previous reports [34, 35, 37, 39]. The benefit of PR, as reflected in the SGRQ, was durable for additional 3-month postintervention, as indicated by a stable questionnaire score.

The most important objective outcome was the significant increase in exercise capacity as reflected by VO_2max on CPET, commonly considered the "gold standard" measurement of cardiorespiratory capacity [40]. The effect of PR on VO_2max in subjects with sarcoidosis has only been assessed prospectively once [38]. In that study, subjects were admitted for an intensive 4-week inpatient PR, a program that is not available in many parts of the world. Our results, using a more commonly available outpatient PR protocol, demonstrate a benefit of similar magnitude. An improvement of the VO_2max was also retrospectively observed by Strookape et al. [34] although in that study a submaximal CPET protocol was utilized.

The optimal exercise regimen in PR is debatable. In the current study, exercise of moderate intensity was employed, similar to most previous reports. Although a more intense exercise program may be more effective and less time consuming, it is frequently avoided out of fear of worsening the existing fatigue, experienced by the patient. However, as recently demonstrated by Grongstad et al. [41], a single session of high-intensity interval training exercise was feasible in subjects with sarcoidosis, without worsening postexercise fatigue when compared to continuous moderate-intensity exercise. Thus, a prospective study is needed to evaluate to long-term benefit of high-intensity interval training versus moderate PR in these individuals.

The field of PR in sarcoidosis is actively evolving. In a randomized controlled study comparing an inspiratory muscle training program versus sham intervention among subjects with stages I–II sarcoidosis, muscle training was associated with improved functional capacity (as assessed by 6MWD), improved dyspnea scores, and increased respiratory muscle strength [42]. Hence, employing inspiratory muscle training as part of PR may further add to its efficacy.

Reduced exercise capacity in sarcoidosis is common and many times is of multifactorial etiology. Therefore, frequently, PFTs do not reflect pulmonary gas exchange impairment during exercise [43], while abnormalities on CPET are abundant [44]. VO_2max is decreased in the majority of subjects with sarcoidosis. Outcome measures of CPET were also found to predict decline in pulmonary function during a 5-year follow-up [45]. Whether improvement in exercise capacity, as reflected in VO_2max,

will have a prognostic effect is currently unknown, and the clinically relevant minimal difference of VO_2max also has not been established. The greatest benefit in VO_2max was observed in subjects with radiographic evidence of parenchymal involvement. Thus, we believe that subjects with pulmonary sarcoidosis are those which should be targeted for PR programs.

Of note, in the current study, 6MWD was improved especially in those with preserved KCO. While a possible explanation to the above finding could have been the existence of significant pulmonary hypertension among those individuals with a decreased KCO [46, 47], which could limit the benefits gained by PR, only 2 patients from the entire cohort had echocardiographic evidence of pulmonary hypertension. Another interesting observation was that a significant improvement in the 6MWD was mostly observed in subjects with decreased FVC at baseline. One could postulate that those with a low FVC value and diminished exercise capacity were mostly limited due to impaired ventilatory functions and therefore benefited most from the PR intervention program. The notion that PR benefits more those with severe ventilatory defects is also supported by the trial published by Naz et al. [17], which included only severe cases and showed that 6MWD was significantly improved. The broad inclusion criteria in our study further supports our conclusion that PR provides beneficial effects to a wide range of subjects with sarcoidosis.

The main limitation of our study was the lack of a control group. Nevertheless, each participant served as his own control. In a pre-post evaluation, we identified differences in outcomes (e.g., 6MWD), based on each subjects' baseline status (i.e., KCO and FEV1/FVC). Another limitation was that although proven important, the level of physical activity was not prospectively evaluated. Additional prospective studies comparing large subject groups from a wide range of disease severities are required to support our findings.

Subjects who were treated with corticosteroid dosage equivalent to over 10 mg of prednisone daily were excluded from the study for 2 main reasons. First, to limit the possibility of severe steroid-induced myopathy. Second, we anticipated that those subjects will require changes in medication, either prescription of additional "steroid-sparing" immunosuppressive treatments, or changes to the steroids dose. We preferred to exclude those subjects to avoid confounding of the results by higher steroid dosage.

The duration effect of the PR is not fully known. In our literature review, we found 2 other publications with 5- and 12-month follow-up following PR. The effects were preserved, however, only for some of the parameters (Table 2). Here, we observed that the 6MWD and the VO_2max were maintained at the post-PR level for additional 3 months following intervention. In addition, the questionnaire scores were also maintained at post-PR levels, further suggesting that the effects of PR are long lasting. These results support a long-lasting effect of a limited-time PR program. We thus believe that similar programs should be offered even when a prolonged program is not feasible. In conclusion, our study provides important data supporting the beneficial effects and durability of a PR intervention program on exercise capacity and quality of life measures in subjects with different stages of sarcoidosis.

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Statement of Ethics

The study was approved by the local ethics institutional review board (IRB) in accordance with the Declaration of Helsinki and with the Good Clinical Practice Guidelines (0019-11-MMC). Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding to disclose.

Author Contributions

O.W., E.G., and D.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. A.R. and G.E.S. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Availability of Data and Material

Any data can be supplemented on demand.

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