Feasibility, safety and efficacy of exercise training in immune-mediated necrotising myopathies: a quasi-experimental prospective study

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Abstract

Objective

To evaluate the feasibility, safety and efficacy of exercise training in patients with immune-mediated necrotising myopathies (IMNM).

Methods

Eight consecutive sedentary patients with IMNM (5 anti-signal recognition particle and 3 anti-hydroxy-methyl-glutaryl coenzyme A reductase) were engaged in this study. Disease status was based on International Myositis Assessment and Clinical Studies Group (IMACS) core set measures. Physical performance was evaluated by cardiopulmonary exercise test, repetition maximum (RM) protocol, handgrip dynamometry, sit-to-stand (STS) and timed up-and-go (TUG) tests. All these parameters were measured at baseline and after a 12-week, twice-a-week, supervised exercise training comprising aerobic and strength exercises.

Results

Patients (aged 61 years on average) were very disabled at the beginning of the disease (mean duration of 17.7 months), but after being aggressively treated with a treat-to-target approach, they presented only mild symptoms that were well-controlled with oral immunosuppression and low disease status scores by the time of the exercise intervention. No disease relapsing, worsening of the IMACS set scores or adverse events were observed throughout the training period. Patients also increased aerobic capacity (e.g. time to achieve anaerobic threshold and time to achieve exhaustion), muscle strength (e.g. 1RM bench press) and function (e.g. STS test).

Conclusion

Supervised exercise training did not impair disease status and seemed to be feasible, safe and effective in patients with IMNM. Moreover, exercise training increased aerobic capacity, muscle strength and function, suggesting that this could be a novel potential coadjuvant therapy in IMNM.

Key words

exercise training, aerobic capacity, muscle strength, myositis, necrotising myopathies

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Introduction

Immune-mediated necrotising myopathies (IMNM) are a subgroup of systemic autoimmune diseases associated with acute/subacute onset muscle weakness and high levels of serum muscle enzymes. Histologic features involve the striking pattern of diffuse muscle necrosis with absence or scarcity of inflammatory cell infiltrates (1-4). In general, the natural disease course of the IMNM is very refractory, characterised by extensive muscular atrophy and fat replacement (5) and requiring a combination of glucocorticoids and multiple immunosuppressant drugs to counteract the symptoms, frequently with an unsatisfactory response (6-9).

To date, no studies have addressed physical performance in patients with IMNM. However, these patients may have diminished aerobic capacity, strength, muscle functionality and quality of life, as this disease resembles in several aspects other systemic autoimmune myopathies, such as dermatomyositis (DM) and polymyositis (PM) (10-12). Interestingly, many studies have shown the safety and benefits of exercise programmes in DM and PM (13-21), not only regarding muscle strength and functionality (15, 19, 20) but also aerobic capacity (13, 14, 20, 21). To our knowledge, the effects of exercise have not been examined in IMNM.

Thus, the goal of the present study is to evaluate the feasibility, safety and efficacy of supervised exercise training in patients with IMNM, particularly in relation to aerobic capacity, muscular strength and functionality.

Patients and methods

Study design

This prospective, single-cohort, quasi-experimental study initially included 24 consecutive adult patients with IMNM diagnosed according to the Myositis Study Group and the 119th European Neuromuscular Centre workshop criteria (22). Moreover, to improve the homogeneity of the sample pertaining to this study, only patients followed up at our outpatient clinic between 2013 and 2017 were assessed at baseline and after 12 weeks of an exercise training intervention.

Patients

At disease onset, all patients had been admitted to our tertiary centre to investigate the acute/subacute onset of proximal muscle weakness of the limbs, high levels of serum creatine phosphokinase, without apparent cause (*i.e.* neoplasms and infections), electroneuromyography with a predominant proximal myopathic pattern without a neurogenic pattern, and muscle biopsies (vastus lateralis) disclosing the presence of necrotic muscle fibres and an absence or scarcity of inflammatory cell infiltrates. All patients had positivity for autoantibody anti-signal recognition particle (anti-SRP) or anti-hydroxy-methyl-glutaryl coenzyme A reductase (anti-HMGCoAR).

Exclusion criteria were: coexisting neoplasms, current engagement in an exercise or rehabilitation routine and inability to adhere to the protocol (*e.g.* distant dwelling and time unavailability).

As an internal protocol from our Service, all patients with IMNM received pulse therapy with methylprednisolone (1 g/day, for three consecutive days) and/or intravenous human immunoglobulin (2 g/kg, spread out over 2 to 5 consecutive days). Then, prednisone (1 mg/kg/day) was used and tapered according to clinical and laboratory results. With regard to prednisone sparing agents, the following immunosuppressant drugs were used: azathioprine (2–3 mg/kg/day), methotrexate (10–25 mg/week) and mycophenolate mofetil (3 g/day).

During the selection phase, 13 out of 24 patients were excluded due to: diagnosis of cancer (n=2), unavailability to engage in the protocol (n=6) and inability to contact (n=5). Also, three died during this phase from events unrelated to the myopathy. Thus, 8 out of 24 patients were effectively included in the protocol.

The study was approved by the Local Ethics Committee and informed written consent was given by the patients.

Evaluation protocol

Demographic, clinical, laboratory and therapeutic data were obtained by means of a review of the electronic medical records, which contained previously standardised and parameterised data.

The following parameters were analysed: age, gender, ethnicity, total disease time, body mass index and use of glucocorticoids (current and cumulative) and other immunosuppressant drugs. Anti-SRP antibodies were determined using a commercial solid-phase immunoblotting kit, a qualitative immunoassay line for detection of 11 human immunoglobulin G (IgG) autoantibodies against specific or associated myositis antigens in serum or plasma. In order to increase the specificity of the method, the manufacturer's protocol was followed. Reaction positivity was defined according to a previously published study (23). Anti-HMGCoAR antibody was assayed by enzyme-linked immunosorbent assay (ELISA), using recombinant HMGCoAR protein and anti-HMGCoAR polyclonal antibody (MyBioSource, CA, USA). For the purposes of this study, patients with anti-HMGCoAR values of more than three standard deviations of the mean of 8 healthy individuals were considered positive.

Disease status was based on the International Myositis Assessment and Clinical Studies Group (IMACS) core set measures that were compounded by: Manual Muscular Testing (MMT-8; 24), visual analogue scales (VAS) for global disease activity from the point of view of the patient and the physician and for extramuscular activity(25-27, 31), Myositis Disease Activity Assessment VAS (MYOACT) scoring (28), Health Assessment Questionnaire (HAQ; 29, 30), and serum levels of creatine phosphokinase (normal range: 24–173 U/L). Disease improvement was measured by the 2016 European League Against Rheumatism/American College of Rheumatology (ACR/EULAR) criteria for clinical response in adult DM and PM (31).

Patients underwent a treadmill (Centurion 200, Micromed, Brazil) maximal cardiorespiratory test, with increments in velocity and inclination at every minute until volitional exhaustion. Oxygen consumption (VO_2) and carbon dioxide output were obtained through breath-by-breath sampling and expressed as a 30-second average using an indirect calorimetry system (Cortex - model Metalyzer III B, Leipzig, Germany). HR was continuously recorded at rest, during exercise and at recovery, using a 12-lead electrocardiogram (Ergo PC Elite, InC. Micromed, Brazil). The peak oxygen consumption (VO_{2max}) and the time until anaerobic threshold (AT), respiratory compensation (RCP) and maximum effort (ME) were evaluated.

The dynamic [1RM for the leg-press and the bench-press exercises (32)] and isometric [handgrip for the dominant arm (33)] strength were assessed at baseline and after the intervention. Muscle function was evaluated through the 30-second sit-to-stand (34) and the timed up-and-go test (35). To avoid learning effects, the patients underwent two familiarisation sessions, at least 48h apart, for all strength and functional tests. The coefficients of variation for these tests were ≤0.5%.

Intervention protocol

Exercise sessions consisted of twice-a-week workout sessions fully assisted by accredited physical education professionals. All sessions started with strength training. Strength training was composed of 6 exercises using machines or assisting devices: horizontal leg press, horizontal bench press, let pull down, narrow-grip seated rows, weighted knee extensions and seated hamstring curl. Additionally, patients were asked to perform an assisted lying leg raise for core strengthening. For all exercises, 3 sets of 8-12 RM repetitions were performed, with a 60-second rest between sets. Overload progression was implemented when the subject could perform >12 repetitions on the last training set for two consecutive workouts. Strength training sessions lasted approximately 30 minutes.

After strength training, the patients performed aerobic exercises on a treadmill. The training sessions consisted of a 5-minute warm-up, followed by 30 to 50 minutes of moderate-intensity walk/running and a 5-minute cooling-down period. The walking duration was gradually increased every four weeks, from 30 to 50 minutes. The intensity of the exercise sessions was set at the heart rate corresponding to the interval between the AT and the RCP. Finally, each session ended with 5 minutes of global static stretching. The adherence to exercise training was registered at every session, and all sessions were supervised by a seasoned rheumatologist to report adverse events. The details of this intervention are present in the supplementary files.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables, which were expressed as mean ± standard deviation or median (interquartile 25^{th}–75^{th}). Categorical variables were expressed as percentages (%). Data normally-distributed were analysed by a paired *t*-student test, and data with a non-normal distribution were analysed by Wilcoxon's test. Categorical variables were analysed by Fisher's exact test. *p*-values ≤0.05 were considered to be statistically significant. The effect size (ES), a measure of the magnitude of change, was also calculated using Cohen's *d* for aerobic capacity and strength variables. All statistical analyses were performed using the software SPSS, v. 15.0 (Chicago, IL, USA).

Results

As outlined in Table I, the mean age of the 8 patients was 60.7, with a slight predominance of the female gender (55%) and no difference in ethnicity or body mass index distribution. The mean time between disease onset and the beginning of the study was 17.7 months.

Regarding disease parameters, 62% and 38% of the patients tested positive for autoantibody anti-SRP and anti-HMGCoAR, respectively.

All patients had important muscle weakness by the time of diagnosis, with four of them presenting bedridden and with dysphagia. As highlighted above, all of the patients received methylprednisolone pulses and/or immunoglobulin before the protocol, sometimes multiple times, pursuing remission induction, and were thereafter treated with oral immunosuppressant drugs until complete glucocorticoid withdrawal. By the time of enrolment, all patients were clinically stable or in remission. The mean cumulative dose of prednisone was 12.5

Table I. General data and disease activity for 8 patients with immune-mediated necrotising myopathy.

Parameters	12-weeks training		*p*-value
	Before	After	
General data			
Age (years)	60.7 ± 11.1	-	-
Disease duration (months)	17.7 ± 11.1	-	-
Female gender	5 (55)	-	-
Ethnicity: White	4 (50)	-	-
Body mass index (kg/m^2)	26.3 ± 5.2	-	-
Autoantibody anti-SRP	5 (62)	-	-
Autoantibody anti-HMGCoAR	3 (38)	-	-
Disease status			
Physician VAS (0–10)	0.0 [0.0–1.2]	0.0 [0.0–0.0]	0.40
Patient VAS (0–10)	1.6 [0.9–4.9]	1.5 [0.3–2.8]	0.40
HAQ (0.00–3.00)	0.50 [0.00–1.10]	0.18 [0.00–0.50]	0.30
MMT-8 (0–80)	80 [76–80]	80 [80–80]	1.00
MYOACT (0–10)	0.0 [0.0–2.2]	0.0 [0.0–0.0]	0.40
Creatine phosphokinase (U/L)	348 [178–1559]	195 [161–1644]	0.90
Treatment			
Glucocorticoid			
Current use	1 (12.5)	-	-
Cumulative dose (g)	12.4 ± 10.4	-	-
Immunosuppressant drugs*	8 (100)	-	-

Results expressed as percentage (%), mean ± standard deviation or median [25th–75th interquartile range]. HMGCoAR: hydroxy-methyl-glutaryl coenzyme A reductase; HAQ: Health Assessment Questionnaire; MMT: Manual Muscle Testing; MYOACT: Myositis Disease Activity Assessment VAS; SRP: signal recognition particle; VAS: visual analogue scale.
*Azathioprine (2–3 mg/kg/day); methotrexate (10–25 mg/week); mycophenolate mofetil (3 g/day).

Table II. Aerobic capacity, strength and muscle functionality before and after exercise training.

Parameters	12–weeks training		*p-v*alue	ES
	Before	After		
Aerobic capacity				
VO_{2Max}(L/min)	1.3 ± 0.5	1.4 ± 0.6	0.90	0.14
VO_{2max} (mL/kg/min)	19.2 ± 3.7	19.4 ± 3.7	0.72	0.05
AT (min)*	4.2 ± 1.3	5.5 ± 0.7	0.02	1.24
RCP (min)*	7.0 ± 1.4	9.6 ± 1.8	<0.01	1.61
ME (min)*	9.2 ± 2.0	11.3 ± 1.7	<0.01	1.13
Muscle strength and function				
1 RM leg press (kg)	31 [26–50]	50 [30–53]	0.40	0.28
1 RM bench press (kg)	23.5 ± 11.5	27.0 ± 12.9	0.03	0.28
TUG (s)	7.5 ± 1.2	7.0 ± 1.3	0.11	0.40
STS (n)	12.5 ± 3.1	14.7 ± 3.2	<0.01	0.70
Hand grip (kgf)	26.5 ± 12.5	26.1 ± 11.0	0.80	0.03

Results expressed as percentage (%), mean ± standard deviation, median [25th–75th interquartile range]. AT: time elapsed until anaerobic threshold; ES: effect sse; ME: time elapsed until maximum effort (exhaustion); RCP: time elapsed until respiratory compensation point; RM: repetition maximum; STS: 30-second sit-to-stand test; TUG: Timed up-and-go test; VO_{2max}: maximum oxygen uptake.

g, and only one patient was still using prednisone (20 mg/day). Nevertheless, all patients were using at least one immunosuppressant drug: two patients were on azathioprine (2–3 mg/kg/day), three were on methotrexate (10–25 mg/week), two were on a combination of both, and one was on mycophenolate mofetil (3 g/day).

Even before training, patients had preserved muscle strength and no signs of disease activity, as summarised in Table I. Also, median HAQ and median patient's VAS suggested a low degree of disability. Median creatine phosphokinase, however, was 348 U/L, slightly elevated according to the method's cut-off. After the protocol, no variables concerning disease activity changed significantly. The EULAR/ACR response criteria score (31) summed 20 points, thus representing minimal improvement.

Patients showed a high adherence to the exercise training programme (95%), and no serious adverse event was reported. One patient presented with exercise-related pain in the calves after 4 sessions, but it subsided after optimisation of regional stretching. Another patient presented with back pain after 2 sessions that was easily controlled with analgesics and subsided with the progression of the protocol. No flares or relapses were identified, and no patient needed additional immunosuppressive drugs during the protocol.

Regarding aerobic capacity, there were significant improvements in the time to achieve AT (p=0.02, *ES*: 1.24), RCP (p<0.01, *ES*=1.61) and ME (p<0.01, *ES*=1.13; Table II, Fig. 1).

The performances in 1RM bench press (p=0.03, *ES*: 0.28) and STS test (p<0.01, *ES*=0.70) were also significantly improved (Table II, Fig. 2).

Discussion

To our knowledge, this is the first study to investigate the feasibility, safety and efficacy of exercise training in patients with IMNM. The main findings of the present study were: a) Exercise training in patients with IMNM seemed to be safe; b) Exercise training was capable of increasing aerobic capacity (*i.e.* time to achieve AT, RCP and ME), which represents improvements in cardiorespiratory parameters in IMNM, and c) Exercise training improved strength (*i.e.* 1RM bench press) and functionality (*i.e.* STS test), suggesting an attenuation of disease symptoms.

Albeit small, the study had a homogeneous group from a single centre, with narrow inclusion criteria, including only patients with serological evidence of IMNM and similar disease treatment and features. The intervention was standardised, controlled and supervised, ensuring high adherence (95%) and appropriate internal validity.

IMNM has been described only recently and is usually reported as devastating for the muscle. A previous study with

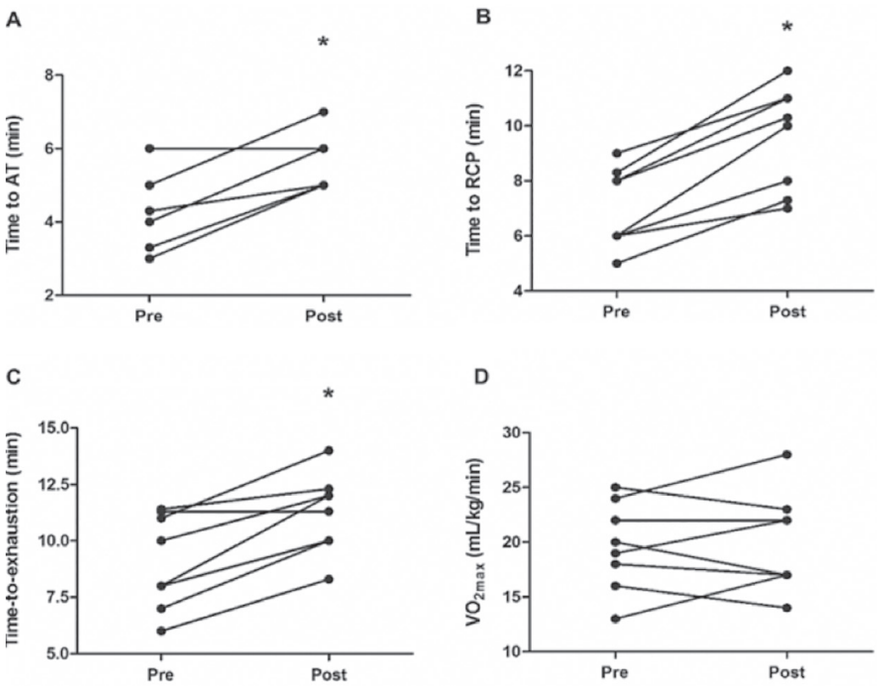

Fig. 1. Individual data of aerobic capacity before and after exercise training.
AT: anaerobic threshold; RCP: respiratory compensation point; VO_2 max: maximum oxygen uptake.
*p<0.05.

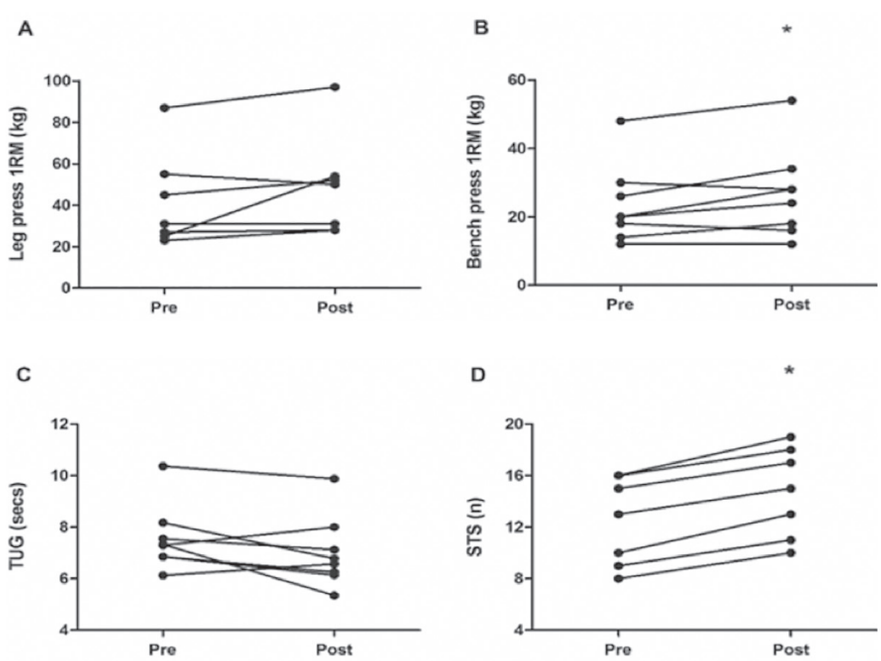

Fig. 2. Individual data of muscle strength and functional capacity before and after training.
RM: repetition maximum; STS: 30-second sit-to-stand test; TUG: Timed up-and-go test. *p<0.05.

19 positive anti-SRP IMNM patients showed an elevated prevalence of severe muscle weakness (described as incapability to perform daily life activities without help) statistically different from patients with PM. Authors also found significant differences concerning muscle atrophy, which was present in 80% of the subjects at the disease onset, compared to 43% in PM (7). Another study involving anti-SRP IMNM patients corroborated these later findings and extended this evidence to show a 70% rate of recurrence by the time of immunosuppression withdrawal (8). Moreover, a study indicated that only 4 out of 25 patients were able to recover full strength during the 8-year follow-up (9), and two studies with magnetic resonance imaging highlighted a striking elevated rate of muscle atrophy and fat replacement (5, 36), which is significantly different from what is seen in DM and PM (5).

In contrast to these findings, our patients were somewhat less severe than those described in the literature regarding muscle status and disability, presumably due to the treat-to-target induction of remission approach, which has already been partially reported by De Souza *et al*. within our population (37). However, facing such a potentially morbid scenario, new measures to mitigate weakness and improve quality of life are necessary.

Motivated by the many studies that reported the safety and benefits of exercise interventions in DM and PM (13-21), the present study extended these observations to IMNM patients. Importantly, there were no reports of disease relapses, important adverse events or functionality deterioration throughout the intervention.

By calculating the response criteria score (ACR/EULAR, 2016), we found only minimal improvement, but it is important to highlight that our patients started the protocol already with minimal disease activity. In fact, we did observe 51% absolute percent change on the patient VAS and 41% change on HAQ, which may suggest improvements in the patients' perceptions of quality of life.

Changes in muscle strength in response to training varied according to the muscle group. It is important to highlight, though, that one patient could not have his post-protocol 1RM leg press measured properly because his strength improved so much during the protocol that he could comfortably lift all of the machine's available weights. Since we observed increase in strength on both the bench press 1RM test and the STS test, which particularly require lower body strength, we hypothesised that, if we had more subjects, we would have also found a statistically relevant difference on the leg press 1RM test.

Concerning muscle functionality, all

patients improved on the STS test. The TUG test presented contradictory results that we attributed mainly to a ceiling effect. Since the patients engaged in this study presented preserved muscle strength, they performed a good TUG test at the beginning of the protocol, leaving little room for improvement on the post-exercise TUG test.

Finally, regarding aerobic capacity, almost all patients improved all three threshold times (*i.e.* AT, RCP and ME), indicating an undeniable increase in functional aerobic performance. The present study could not demonstrate an increase in $VO2_{max}$, presumably due to its multifactorial nature. Since the subjects trained only twice a week, we believe that a protocol with higher volume within a week would most likely produce the expected results.

This study has some limitations. First, we were not able to evaluate mechanisms behind the exercise-induced adaptations. In patients with other systemic autoimmune myopathies, such as DM and PM, there is an important impairment in aerobic capacity which is associated with a low proportion of oxidative, slow-twitch type I fibres (38); decreased muscle mitochondrial enzyme activities (39) and low capillarity density (40), with these parameters being improved after exercise (39, 40). Further studies are necessary to examine the effects of exercise in IMNM from a molecular and histological point of view. Additionally, our study had a relatively low sample size, a short follow-up period as well as a lack of control groups (*i.e.* composed by untrained healthy individuals or even by patients in a standard outpatient physiotherapy routine). Efforts should be made to tackle these limitations in the future, possibly through multicentre collaborative studies.

In summary, the 12-week supervised exercise training programme was safe and effective in improving aerobic capacity, muscle strength and function in patients with IMNM, shedding a glimpse of light on a yet unexplored matter. These preliminary results suggest that in the future we could have enough evidence to consider exercise training as a therapeutic tool in IMNM.

Supplementary file

As described in the intervention protocol in the present article, exercise training consisted of twice-a-week workout sessions fully assisted by accredited physical education professionals. All sessions started with strength training. Strength training was composed of 6 exercises using machines or assisting devices:

Horizontal leg press: The patients sit down on a horizontal leg press machine and place their legs on the platform directly in front of them at a medium (shoulder width) foot stance then pushing the platform all the way up until their legs are fully extended in front of them.

Horizontal bench press: The patients performing the exercise lie on their back on a bench with a loaded barbell grasped with both hands. They push the weight upwards until their arms are extended, not allowing the elbows to lock. They then lower the weight to chest level.

Lat pull down: The patients grasp a bar using a wide grip and sit down maintaining the upper body in an upright position, slightly leaning back from the hips. Then they pull the bar in front of their face to the top of their chest and pause. Slowly they release the bar back to the starting position by straightening his arms.

Narrow-grip seated rows: The patients sit down on the machine and place their feet on the front platform or crossbar provided making sure that their knees are slightly bent and not locked. The patients lean over as they keep the natural alignment of their back and grab the V-bar handles. With their arms extended pull back until their torso is at a 90-degree angle from their legs. Their back should be slightly arched and their chest should be sticking out. Then, keeping the torso stationary, they pull the handles back towards their torso while keeping the arms close to it until them touch the abdominals. They must breathe out as they perform that movement. At that point they should be squeezing their back muscles hard. Then, they hold that contraction for a second and slowly go back to the original position while breathing in.

Weighted knee extensions: The patients sit on a machine with his legs under a pad (feet pointed forward) and the hands holding side bars. This is the starting position. Using their quadriceps, they must extend their legs to the maximum as them exhale. The body remains stationary on the seat during the movement. Then the patients slowly lower the weight back to the original position as they inhale, ensuring that they do not go past the 90-degree angle limit.

Seated hamstring curl: We adjust the machine lever to fit the patient height and sit on the machine with his back against the back support pad. Then we place the back of lower leg on top of padded lever (just a few inches under the calves) and secure the lap pad against their thighs, just above the knees. Then they grasp the side handles on the machine as they point their toes straight and ensure that the legs are fully straight right in front of them. This is the starting position. As exhaling, they must pull the machine lever as far as possible to the back of their thighs by flexing the knees. They must keep their torso stationary at all times. They must hold the contracted position for a second and then slowly return to the starting position as they breathe in.

Additionally, the patients execute the lying leg raise, for core strengthening. To do so, the patients lie with their back flat on a bench and their legs extended in front of them off the end. Then, they place their hands either under their glutes with their palms down or by the sides holding on to the bench. This is their starting position. As they keep their legs extended, they must, as straight as possible with their knees slightly bent but locked, raise their legs until they make a 90-degree angle with the floor.

For all exercises, 3 sets of 8-12RM repetitions were performed, with a 60-second rest between sets. Overload progression was implemented when the subject could perform > 12 repetitions on the last training set for two consecutive workouts. Strength training sessions lasted approximately 30 minutes.

After strength training, the patients performed aerobic exercises on a treadmill. The training sessions consisted of a 5-minute warm-up, followed by 30 to 50 minutes of moderate-intensity walk/running and a 5-minute cooling-down period. The walking duration was gradually increased every four weeks, from 30 to

50 minutes. The intensity of the exercise sessions was set at the heart rate corresponding to the interval between the AT and the RCP. Finally, each session ended with 5 minutes of global static stretching.

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