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Effects of Exercise Training on Endothelial Function, Arterial Structure, and Physical Conditioning in Patients with Systemic Autoimmune Myopathies: A Case Series Study

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Abstract

Introduction. Exercise training has been effective in improving endothelial function and decreasing arterial stiffness in several systemic autoimmune diseases. However, to date, no studies have assessed patients with systemic autoimmune myopathies (SAM). **Methods**. Five female patients with definite SAM (3 dermatomyositis and 2 polymyositis) who underwent a 12-week, twice-a-week, exercise training program were assessed prospectively. The following parameters were assessed: endothelial function measured by flow-mediated dilatation (FMD), carotid femoral by pulse wave velocity (PWV), disease status by International Myositis Assessment & Clinical Studies Group (IMACS) set score, the ventilatory anaerobic threefold (VAT), respiratory compensation point (RCP), maximum effort (ME), maximal oxygen uptake (VO2max) measured by ergospyrometer, and strength and muscle function. **Results**. Mean age of the patients and duration of disease were 43.9 and 10.5 years, respectively. The median FMD and PWV were 10.2% and 7.1 m/s. After exercise training, important FMD reduction was observed in 4 out of 5 patients, whereas the PWV parameters decreased in only 2 out of 5 patients. The exercise training was safe, without clinical intercurrences or disease relapses. Moreover, an increase in strength and functionality was observed. Concerning aerobic capacity, there was a decrease in the VAT and an increase in ME, without alterations in the maximum oxygen consumption. **Conclusions**. In general, exercise training does not alter endothelial function and PWV values, but improves muscle strength and function and also, does

not lead to disease reactivation (Clinical Trials (NCT03092167)).

Keywords

Dermatomyositis, Endothelial Function, Exercise, Polymyositis, Pulse Wave Velocity

1. Introduction

Dermatomyositis (DM) and polymyositis (PM) are systemic autoimmune myopathies (SAM) and are commonly characterized by progressive, symmetric and predominantly proximal limb muscle weakness [1]. In DM, there are also classical cutaneous lesions, such as heliotrope rash and Gottron's papules [1].

In addition to muscle impairment, several studies have described the presence of heart rate variability, blood pressure dysfunction, and/or abnormal brachial artery reactivity in patients with SAM [2] [3]. These factors can contribute to increased morbidity and mortality for cardiovascular diseases, including heart failure, myocardium infarction, and cerebrovascular diseases [2] [3]. Moreover, cardiovascular diseases and their risk factors are frequently preceded by endothelial dysfunction and arterial stiffness [4] [5].

Endothelial dysfunction is characterized by an imbalance of relaxation and constriction in response to stimuli of nitric oxide, leading to arterial stiffness development and progressing to atherosclerosis [6]. Assessments of flow-mediated dilatation (FMD) and pulse wave velocity (PWV) are non-invasive techniques extensively used to evaluate the vascular function and structure in the general population and in patients with several rheumatic autoimmune diseases, including SAM [7]-[12].

In a solitary study on this topic, Vincze *et al.* [12] have shown decreased FMD and increased arterial stiffness in patients with DM, suggesting that this population may be predisposed to higher risks of atherosclerosis.

Exercise training has been considered a tool to minimize cardiovascular comorbidities and their risk factors, as well as to improve quality of life, strength and muscle function, including in SAM patients [13]-[18].

Moreover, some studies have shown that exercise training is effective in improving the endothelial function and decreasing arterial stiffness of patients with autoimmune rheumatic diseases, such as systemic lupus erythematosus and rheumatoid arthritis [19] [20].

However, to the best of our knowledge, there is no study assessing the effects of exercise training on the structural and functional properties of large arterial vessels in patients with SAM.

In this case series study, we reported on the effects of exercise training on endothelial function, arterial structure, and physical conditioning in 5 patients with SAM.

2. Subject and Methods

Study design. This is a single center study that prospectively assessed 5 female patients with definite SAM (3 patients with DM and 2 patients with PM), between 2017 and 2018. The study was approved by the local ethics committee and was registered in Clinical Trials (NCT03092167). The present study was approved by the local ethics committee. All participants signed an informed consent form.

Patients. Patients from our outpatient clinic that fulfilled the European League against Rheumatism/American College of Rheumatology 2017 classification criteria of SAM [21].

Endothelial function. The procedures were performed according to a guideline [4]. In brief, the assessment was performed in the morning after 12 hours fasting period. The assessment room was silent, with low luminosity, and temperature between 20˚C and 25˚C. Images of the right brachial artery located 7 cm above the medial humeral epicondyle, were recorded for measurements of blood flow velocity and arterial resting diameter. To register FMD (*i.e.*, the endothelium-dependent function), a sphygmomanometer was placed on the forearm and inflated to a pressure of at least 50 mmHg above systemic pressure for 5 minutes, inducing the reactive hyperemia maneuver. Images were captured for 3 minutes after cuff release. The diameter of the artery was measured through ultrasound equipment (Sequoia Echocardiography System®, version 6.0, Acuson, Siemens, CA, USA). The analysis of images was realized by the software Cardiovascular Suite (Quipu®, Pisa, Italy). The different phases of the examination were recorded on a computer for later analysis. FMD% (endothelium-dependent) was calculated according to the formula: FMD% = [(diameter after hyperemia − resting diameter) × 100]/resting diameter.

To evaluate inter-observer reproducibility, 6 healthy individuals were assessed twice by the same examiner, with an interval of 6 hours.

Aortic stiffness. The evaluation for aortic stiffness was performed according to previous publications

Maximal cardiopulmonary test. The aerobic capacity evaluation was performed by a cardiopulmonary treadmill (Centurion 200, Micromed) test, using a ramp protocol with increasing velocity and/or slope every minute in the work load until exhaustion. Electrocardiograms were performed to assess heart rate (HR) and blood pressure (BP) at 12 simultaneous monitoring during the exercise test: at rest and at the end of each minute and after 6 minutes of recovery. The maximal aerobic power was verified by means of the maximum oxygen consumption at the peak of the exercises (VO2max) through a sensor system that allows the measurement of pulmonary ventilation (VE) at each expiration (MetaLyzer model 3B/model; breath by breath). Metabolic thresholds were determined by the ventilatory equivalent (pulmonary ventilation VE/VO2 without loss of CO_2 production), and O_2 consumption (VE/VCO2) was considered for VAT. For respiratory compensation point (RCP) the linearly increase of VE/VO2

and VE/VCO2 was used. The metabolic thresholds were determined by a single measurer.

Muscle function. Muscle functions were measured by the Time Stand Test (TST) [22] and Timed Up-and-Go (TUG) test [23].

Muscle strength. Maximal muscle strength was assessed according to the descriptions of Brown and Weir [24]. For upper limbs, it was evaluated through the horizontal bench press, and for lower limbs by means of the horizontal leg press. Before the test two familiarizations were performed with a 48-hour interval. The coefficient of variation was >5%. The upper and lower tests were performed in two sets, the first one consisting of 8 repetitions with 50% of the estimated load at 1 repetition maximum (RM) in up to 5 attempts with 3-minute intervals between each attempt.

Laboratory data. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (DHL), and creatine phosphokinase (CPK) were analyzed by automated kinetic methods.

Clinical parameters and drug regimen. We assessed the disease status through the International Myositis Assessment & Clinical Studies Group (IMACS) set scores, which includes Manual Muscle Testing (MMT)-8 [25], Myositis Disease Activity Assessment Visual Analogue Scale (MYOACT) [26], global assessment of disease by physician and patient through the visual analogue scale (VAS) [27] [28], Health Assessment Questionnaire (HAQ) [29], and muscle enzymes (creatine phosphokinase; reference value 26 - 308 U/L). Duration of disease, current treatment, including glucocorticoid and immunosuppressive drugs were also recorded.

Exercise training. Five patients agreed to participate in an exercise training program twice a week for 12 weeks. Each session started with resistance training, composed by 6 exercises: horizontal leg press, horizontal bench press, let pull down, narrow-grip seated rows, weighted knee extensions, and seated hamstring curl. Patients were instructed to perform 8 to 12 repetitions maximum; when patients were able perform more than 12 repetitions, the load was increased.

Subsequently, the patients were submitted to aerobic training. The intensity was determined through the ergospyrometer test, respecting the metabolic thresholds between the ventilatory anaerobic threshold (VAT) and respiratory compensation point (RCP). Load control was monitored by heart rate and also through subjective perception of effort (6 - 20 scale). The duration of the aerobic training was initially 30 minutes at the fourth week, progressing to 40 minutes, and in eighth week in 60 minutes. Finally, the session was finalized with 5 minutes of flexibilities exercises.

3. Results

Interobserver reproducibility of FMD. There was no difference between the resting diameter (4.5 ± 0.4 *vs.* 4.5 ± 0.4 mm; $P = 0.920$), hyperemia diameter (4.5 ± 0.3 *vs.* 4.5 ± 0.4 mm; $P = 0.911$) and FMD (1.2 ± 1.0 *vs.* 1.4 ± 2.0%; $P = 0.919$). Moreover, there was no difference in variances between the 2 measurements of

resting diameter (P = 0.920), hyperemia diameter (P = 0.911) and FMD (P = 0.919).

General features of patients: No patients had overlapped syndrome, diabetes mellitus, uncontrolled systemic arterial hypertension or heart failure. None had used lipid-lowering agents or prednisone > 0.5 mg/kg/day in the last 3 months.

During the exercise training protocol, the medication regimen was not changed and there was no evidence of disease relapses or clinical intercurrences. Adherence to exercise training was 96.1%.

Individual responses:

1) Patient #1. After exercise training, was observed a reduction some clinical parameters, particularly, VAS (patients) (−100%); HAQ scores (−100%) and MYOACT (−100%), whereas the others clinical parameters remain unchanged. Regarding the endothelial function was observed decrease in FMD (−44.0%) and increase in PWV parameter (+15.0%) for patient #1, as shown in Figure 1 and Figure 2, respectively. Regarding muscle strength, there were increases in leg press (+15.4%) and in the supine (+6.7%). Corroborating these findings, there was improvement of muscle function in the TST (+7.1%) and decrease in TUG

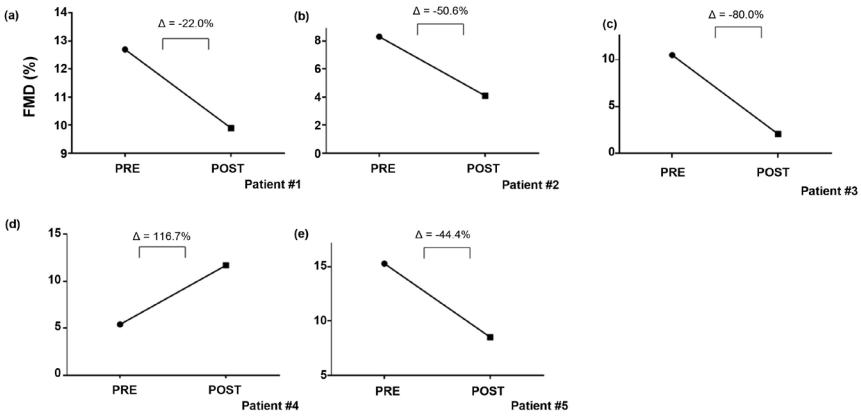

Figure 1. Endothelial function before and after exercise. FMD: flow mediated dilatation; Δ: percentage changes in relation to baseline parameter.

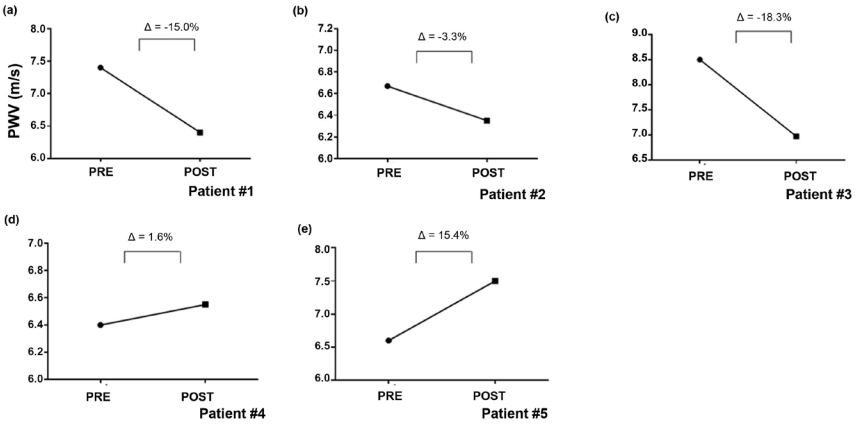

Figure 2. Structural properties of large arteries before and after exercise. PWV: pulse wave velocity; Δ: percentage changes in relation to baseline parameter.

test (−6.0%). Regarding the aerobic capacity, there was a reduction of VAT time (−40.0%), while RCP parameter increased (+9.1%).

2) Patient #2. Regarding the IMACS parameters was evidenced improve in VAS (physician and patients) (−100%) and HAQ (−100%) without changes in other clinical parameters. The FMD was reduced (−50.4%) for patient #2, whereas discrete changes were observed in PWV (+3.3%) parameters. The muscle strength improved in the leg press (+54.0%) and bench press (+6.7%). Muscle function also improved in the TUG test (−5.6%), whereas no changes were observed in the TST test (0%). Time to achieve the VAT (+37.7%) and RCP (+13.0%) improved, as well as observed time to exhaustion (+32.7%) and maximal oxygen consumption (+18.8%).

3) Patient #3. Clinically, the patient #3 shows unchanged IMACS parameters PRE and POST exercise training. A despite of FMD (−80.0%) and PWV (−18.8%) were reduced after the exercise. Muscular strength (+14.3%) in leg-press and bench press (+20.0%) increased. Similarly, the TST (+16.7%) increased, whereas the TUG (−13.0%) decreased. Concerning to the aerobic capacity, the VAT (−5.7%), RCP (−28.9%) and time to exhaustion maximum test time (−2.9%) reduced; in contrast, in addition, an increase in maximal oxygen consumption (+13.3%) was observed (Table 1).

4) Patient #4. The IMACS parameters remain without changes PRE and POST exercise training, whereas, the FMD (+116.7%) increased in patient #4, whereas trivial change was observed in PWV (+1.1%). In addition, there was an increase in bench press (+14.3%), with a slight improvement in leg press (+4.5%). In relation to muscle function, improvements in the TST test (+23.5%) and TUG test (−12.5%) were observed. Concerning aerobic capacity, reduced time to VAT (−43.4%) and RCP (−28.8%) were observed, with no changes in time to exhaustion maximum test time (0%). An increase of the maximum oxygen consumption (+37.5%) was also observed.

5) Patient #5. In clinical point of view, not changes were observed after exercise training. However, the FMD (−44.4%) was reduced in patient #5, whereas PWV increased (+15.4%). There was an increase in strength in leg press (+23.0%) and bench press (+20.0%), as well as functionality in the TST (+14.0%) and TUG (−3.0%) tests. Regarding aerobic capacity, there were no changes in the VAT (0%), but there was a decrease in RCP (−15.4%) and an increase in the time to exhaustion (+23.1%). An increase in the maximum oxygen consumption (+23.1%) was also observed (Table 2 & Table 3).

Table 1. General features of five patients with systemic autoimmune myopathies. Demographic parameter comparisons between patients and control group.

	Patients				
Parameters	#1	#2	#3	#4	#5
Disease	DM	DM	DM	PM	PM
Current age (years)	38.0	45.0	52.0	38.0	48.0

Continued

Disease duration (years)	11.0	1.0	4.0	13.0	8.0
Weight (kg)	93.0	69.0	73.0	67.6	77.5
Height (cm)	158.0	153.0	150.0	161.0	166.5
BMI (kg/m^2)	37.3	29.6	32.4	26.1	33.5
Treatment					
Glucocorticoid					
Current using	No	Yes	No	Yes	No
Dairy dose (mg/day)	-	15	-	20	-
Immunosuppressive drugs	MMF	MTX	MMF	MTX	Aza

Aza: azathioprine; BMI: body mass index; DM: dermatomyositis; MMF: mycophenolate mofetil; MTX: methotrexate; PM: polymyositis.

Table 2. Laboratory and physical capacity parameters.

	Patients														
	#1			#2			#3			#4			#5		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
IMACS scores															
Physician VAS (0 - 10)	0.0	0.0	0	2.0	0.0	−−100	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0
Patients VAS (0 - 10)	3.0	0.0	−100	6.0	0.0	−100	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0
HAQ (0.00 - 3.00)	0.13	0.00	−100	0.45	0.00	−100	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0
MMT (0 - 80)	80	80	0	80	80	0	80	80	0	80	80	0	80	80	0
MYOACT	0.13	0.00	−100	0.75	0.00	100	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0
CK (U/L)	177	95	−46.3	26	30	15.4	96	43	−55.2	85	95	11.8	214	226	5.6
LDH (U/L)	206	191	−7.3	210	198	−5.7	214	266	24.3	161	200	24.2	161	177	9.9
ALT (U/L)	18	16	−11.1	15	8	−46.7	24	66	175.0	14	11	−21.4	14	19	35.7
AST (U/L)	17	15	−11.8	17	15	−11.8	16	46	187.5	16	11	−31.3	13	17	30.8
Muscle strength															
Leg press (kg)	78	90	15.4	42	65	54.8	70	80	14.3	67	70	4.5	43	53	23.3
Bench press (kg)	30	32	6.7	20	22	10	30	36	20	14	16	14.3	20	24	20
Muscle function															
TST (reps)	14	15	7.1	11	11	0.00	12	14	16.7	17	21	23.5	14	16	14.3
TUG (s)	8.44	7.93	−6.0	8.72	8.23	−5.6	7.44	6.47	−13.0	5.56	4.87	−12.4	5.65	5.48	−3.0
Aerobic capacity															
VAT (min)	5.0	3.0	−40.0	5.3	7.3	37.7	5.3	5.0	−5.7	5.3	3.0	−43.4	5.3	5.3	0
RCP (min)	11.0	12.0	9.1	10.0	11.3	13	9.3	9.0	−3.2	13.0	9.3	−28.5	13.0	11.0	−15.4
ME (min)	12.0	14.0	16.7	11.3	15.0	32.7	10.3	10.0	−2.9	15.0	15.0	0	13.0	16.0	23.1
VO2 (mL/kg/min)	17.0	17.3	1.8	16.0	19.0	18.8	15.0	17.0	13.3	24.0	15.0	−35.7	19.9	24.5	23.1

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine phosphokinase; IMACS: International Myositis Assessment & Clinical Studies; LDH: lactate dehydrogenase; ME: maximum effort; MMT: Manual Muscle Testing; MYOACT: Myositis Disease Activity Assessment; RCP: respiratory compensation point; TST: time stand test; TUG: timed up-and-go; VAT: ventilatory anaerobic threefold; VO2max: maximal oxygen uptake. Δ: percentage changes in relation to baseline parameter.

Table 3. Vascular function and structural parameters.

	Patients														
	#1			#2			#3			#4			#5		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
SBP (mmHg)	123	106	−13.8	114	105	−79	119	132	10.9	91	92	1.1	127	126	−0.8
DBP (mmHg)	80	60	−15.0	71	58	−18.3	77	94	22.6	63	62	−1.6	80	79	−1.3
PWV (m/s)	7.4	6.4	−13.5	6.1	6.3	3.3	8.5	6.9	−18.8	6.4	6.5	1.1	6.5	7.5	15.4
Basal diameter (mm)	3.2	3.4	6.2	3.1	3.6	16.1	3.4	3.5	2.9	2.7	2.7	0	2.6	2.7	3.8
Hyperemia diameter (mm)	3.6	3.7	2.8	3.4	3.8	11.8	3.7	3.6	−2.7	2.8	3.3	17.9	3.0	2.9	−3.3
FMD (%)	12.7	9.9	−22.0	8.3	4.1	−50.6	10.5	2.1	−80.0	5.4	11.7	116.7	15.3	8.5	−44.4

DBP: diastolic blood pressure; FMD: flow mediated dilatation; PWV: pulse wave velocity; SBP: systolic blood pressure; Δ: percentage changes in relation to baseline parameter.

4. Discussion

To date, this is the first study to evaluate the effect of exercise training on endothelial function and the structural features of the large arterial vessels in patients with SAM. In general, the exercise training led to a decrease in FMD, with inconsistent changes in PWV.

Despite being a small-scale study, the patients were relatively homogenous (only female patients and with low disease activity). Moreover, none of them had overlapping syndromes, diabetes mellitus, uncontrolled systemic arterial hypertension, or heart failure, nor did they use lipid-lowering agents or prednisone > 0.5 mg/kg/day. As all of these parameters could have interfered in the outcomes, we believe we managed to relatively isolate the effects of exercise. Also, the FMD method was proven to be highly reliable, allowing detecting small changes in this parameter as a result of the intervention.

In the present study, the FMD and PWV values at baseline were similar with health individuals from the literature. In contrast, in a previous study, Vincze *et al.* [12] showed a reduction of FMD and increase of PWV values in patients with DM, when compared to a control group. However, in contrast to our study, Vincze *et al.* [12] did not evaluate the clinical and laboratory parameters, nor were the matching criteria described, limiting the authors' conclusions and a direct comparison to our data.

Several studies have shown that exercise training can promote a benign vascular remodeling characterized by changes in basal arterial diameter [30] [31]. In the present study, the basal arterial diameter increased 6.8% after exercise training. Interestingly, one patient had improved endothelial function.

Furthermore, reductions in PWV values were observed in 2 patients, whereas 2 had no changes and 1 had increases in the parameter. Similar findings have been observed in studies that used combined exercise training protocols in these PWV [32]. Particularly, the main changes in PWV are seen in studies with aerobic exercise programs [32]. However, in the present study, combined resistance

training and aerobic training were used. It is evidence of divergent results from the effects of combined training on arterial stiffness, corroborating the present study [33] [34].

Patients with SAM have reduced muscle strength and functional capacity [14] [16] [17] [18] [35]. Previous studies have shown that exercise training has been effective in increasing muscle strength and improving function, which correlates with an increase in quality of life [18] [36]. However, since our patients had a stable disease, there were significant alterations in muscle strength and functional capacity. These factors can be directly related to a possible ceiling effect, characterized by the patients presenting higher values before exercise training, leading to lower values after exercise training. Similar findings were also observed in all ergospyrometer parameters.

Importantly, no changes were observed in the clinical and laboratory parameters after exercise training, nor there were disease relapses or exercise-related adverse events. These findings further support the notion that exercise is well tolerable and safe for patients with SAM [14] [16] [17] [18] [35].

This study has some limitations. First, this is a small-scale study with a low sample size. Second, only women with low disease activity were assessed, therefore the conclusions should not be generalized to patients with different characteristics. Third, as SAM is a rare disease, we were not able to include a non-trained control group, which weakens the cause-and-effect relationships stablished in this study. Further larger-sample, controlled trials are necessary to confirm the current data.

5. Conclusion

In conclusion, exercise training may not change endothelial function, although this intervention does improve muscle and aerobic conditioning in SAM patients. Also, exercise was well tolerable and safe for all patients.

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Conflicts of Interest

All authors declare no conflict of interest.

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