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ORIGINAL ARTICLE

Exercise training attenuates insulin resistance and improves β-cell function in patients with systemic autoimmune myopathies: a pilot study

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Abstract

Introduction/objectives To assess the effects of exercise training on insulin resistance and β-cell function in patients with systemic autoimmune myopathies (SAMs).

Method This quasi-experimental, prospective study includes 9 patients with SAMs (six with dermatomyositis, two with antisynthetase syndrome, and one with polymyositis). Patients were submitted to a 12-week, twice a week, exercise training program comprising aerobic and resistance exercises. Baseline and after the intervention, we evaluated disease status, aerobic capacity, muscle strength, body composition, insulin resistance, and β-cell function parameters.

Results The patients have a mean age of 46.7 years and stable disease. No clinical or laboratory parameter impairment was observed after the intervention. Compared with baseline, aerobic capacity, muscle strength, and function increased after 12 weeks ($P < 0.05$), while no changes were observed for body composition. Data from the oral glucose tolerance test showed that exercise did not change glucose area under the curve (AUC), whereas insulin and C-peptide AUC decreased significantly ($P < 0.05$). Furthermore, Matsuda index and HOMA2 percentage (both surrogates of insulin resistance) also improved ($P < 0.05$).

Conclusion Exercise training improved aerobic capacity, muscle strength, and muscle function in patients with SAMs. In addition, exercise training led to an attenuation of insulin resistance and improvements in β-cell function parameters. These data indicate that exercise training can mitigate metabolic impairments, attenuating the cardiovascular risk in SAMs.

Key Points

- *Exercise training improved aerobic capacity, muscle strength, and function without disease impairment*
- *Exercise training was capable of improve insulin resistance and β-cell function in patients with SAM*
- *These results suggest that exercise can mitigate metabolic impairments in patients with SAM, attenuating the cardiovascular risk*

Keywords Exercise training · Insulin resistance · Myositis · Physical exercise · β-Cell function

Introduction

Systemic autoimmune myopathies (SAMs) are a heterogeneous group of diseases that are clinically characterized by progressive predominantly proximal skeletal muscle weakness in the limbs. Patients with SAMs can also experience extramuscular manifestations in the skin, lungs, and/or joints [1, 2]. The SAMs include dermatomyositis, polymyositis, immune-mediated necrotizing myopathies, and inclusion-body myositis [2].

Several studies have described a high prevalence of metabolic syndrome in patients with SAMs [3–6]. This disorder is associated with higher risk factors for cardiovascular diseases. Insulin resistance (IR) plays a major role in the progression of metabolic syndrome by impairing both lipid and glucose homeostasis in insulin-sensitive tissues, such as adipocytes, liver cells, and skeletal muscle cells [7]. In patients with SAMs, IR is correlated with weight, body mass index, and waist circumference, suggesting that being overweight or obese impairs insulin action in these patients [8]. Other factors, such as

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chronic inflammation and glucocorticoid use, can also contribute to IR in patients with SAMs [8].

Exercise training is a therapeutic important tool in patients with SAMs, as it can increase muscle strength, function, and aerobic capacity, and attenuate inflammation markers [9–11]. Furthermore, similar to type 2 diabetes mellitus [12], exercise training can improve IR and β-cell function in systemic autoimmune diseases [13]. However, there is paucity of studies in SAMs.

The main objective of this study was to investigate the effect of a supervised, exercise training program on IR and in β-cell function parameters in patients with SAMs.

Patients and methods

This was a quasi-experimental prospective study, conducted between 2016 and 2019. The patients with dermatomyositis and polymyositis fulfilled the classification criteria of European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2017 [14], whereas the patients with antisynthetase syndrome fulfilled classification set out by Connors et al. [15].

The study was approved by the local ethics committee and was registered at ClinicalTrials.gov (identifier number: NCT03092167).

The exclusion criteria were overlapped myositis, infection, established diabetes mellitus, uncontrolled systemic arterial hypertension, use of statins and/or fibrates, any disorder that could preclude the participation in the exercise training, use of more than 10 mg/day of prednisone in the last 3 months, engagement in exercise programs in the last 6 months, and reactivation of the disease. One hundred thirty-eight consecutive patients with defined SAMs were screened. Thirty-eight patients met the inclusion criteria. However, 29 were not included because of lack of interest in participating in the study, malignancy, and work. Thus, nine patients were enrolled in the intervention.

Patients engaged in a 12-week exercise program that took place twice a week. All sessions started with resistance training comprising six exercises: horizontal leg-press, horizontal bench-press, let pull down, narrow-grip seated row, weighted knee extension, seated hamstring curl, and lying leg raise. Patients performed sets of 8 to 12 maximum effort repetitions, with a 1-min rest between sets. We implemented an overload progression when the subject could perform more than 12 repetitions of the last training set for two consecutive workouts.

After the strength exercises, patients performed a walking or jogging exercise on a treadmill. This consisted of a 5-min warm up, followed by 30 to 50 min of moderate-intensity walking or running and a 5-min cool-down period. The duration gradually increased every 4 weeks, starting at 30 min and reaching 50 min. The intensity of the exercise sessions was set to target a heart rate corresponding in the interval between the ventilatory anaerobic threshold (VAT) and respiratory compensation point (RCP). Finally, each session ended with 5 min of global static stretching. We registered the participants' adherence to the exercise training at each session, and all sessions were supervised by a trained professional. In addition, a rheumatologist was present at all sessions to report any adverse events.

The patients also underwent a maximal-graded, treadmill, cardiopulmonary exercise test to determine the peak oxygen uptake volume (VO_2 peak). Their cardiopulmonary effort was considered to be maximal when one of the following criteria was met: VO_2 plateau (i.e., < 150 mL/min increase between consecutive stages), heart rate no less than 10 beats below the age-predicted maximal heart rate, or respiratory-exchange ratio above 1.10. VO_2 peak was considered as the average of the final 30 s of the test [16]. We determined the VAT and RCP as described previously [16].

We also tested dynamic and isometric muscle strength and function both before and after training. Dynamic muscle strength was assessed using one-repetition maximum (RM) on leg-press and bench-press [17] and isometric muscle strength was evaluated using handgrip test [18]. Muscle function was evaluated by timed-up-and-go [19] and timed-stands tests [20]. To avoid learning effects, the patients underwent two familiarization sessions, at least 48 h apart, for all strength and functional tests. The coefficients of variation for these tests were ≤ 5%.

Before and after exercise training, fat mass, body fat, free-fat mass, and total mass were measured by dual energy X-ray absorptiometry (DXA), using a Hologic QDR 4500A densitometry equipment (Discovery model, MA, USA).

To evaluate IR, the patients underwent a 2-h oral glucose tolerance test (OGTT) both before and after training [21], and the area under the curve (AUC) for glucose, insulin, and C-peptide was assessed. We also evaluated surrogates of insulin resistance using the Matsuda index (reference value ≥ 2.5 arbitrary units (AU)), insulinogenic index (≥ 0.4 AU), homeostatic model assessment (HOMA) for IR (HOMA1 IR (≤ 1.6 AU) and HOMA2 IR (≤ 1.45 AU)), B cell function (HOMA2 %B (≤ 175 AU)), and insulin sensitivity (HOMA2 %S (≤ 68.9 AU)) [22–24].

The disease status was assessed according to the International Myositis Assessment & Clinical Studies Group (IMACS) core measures, which involve the following: manual muscular testing (MMT)-8, visual analog scales (VAS) for global disease activity from the point of view of the patient and the physician, Myositis Disease Activity Assessment VAS (MYOACT) scoring, and Health Assessment Questionnaire (HAQ) [25]. Furthermore, serum levels of creatine phosphokinase (reference value ≤ 167 U/L), aspartate aminotransferase (≤ 31 U/L), alanine aminotransferase (≤ 31 U/L), and

Table 1 General features, disease status, drug usage, body composition, and lipid parameters of 9 patients submitted to the exercise training

	Baseline	Post	*P*	ES	Delta (95% CI)
General features					
Age (years)	46.7 ± 7.8	–	–	–	–
Female	6 (66.7)	–	–	–	–
Disease duration (years)	8.4 ± 4.5	–	–	–	–
Dermatomyositis	6 (66.7)	–	–	–	–
Antisynthetase syndrome	2 (22.2)	–	–	–	–
Polymyositis	1 (11.1)	–	–	–	–
Disease status					
Patient's VAS (0–10)	1.8 ± 2.4	0.0 ± 0.0	0.160	1.08	(− 0.0 to 3.6)
Physician's VAS (0–10)	0.3 ± 0.8	0.0 ± 0.0	0.363	0.57	(− 0.3 to 0.9)
MMT-8 (0–80)	80.0 ± 0.0	80.0 ± 0.0	0.999	–	–
MYOACT (0–60)	0.1 ± 0.2	0.0 ± 0.0	0.241	0.78	(− 0.0 to 0.2)
HAQ (0.00–3.00)	0.21 ± 0.30	0.42 ± 0.33	0.659	0.40	100 (− 0.0 to 0.4)
Creatine phosphokinase (U/L)	181.6 ± 145.0	131.7 ± 147.4	0.453	0.34	− 27.4 (71.1 to 293.0)
Aspartate aminotransferase (U/L)	21.8 ± 7.4	22.7 ± 10.9	0.862	0.09	4.1 (16.1 to 27.4)
Alanine aminotransferase (U/L)	22.9 ± 8.4	26.8 ± 18.2	0.536	0.27	17.0 (16.4 to 29.3)
Lactic dehydrogenase (U/L)	231.1 ± 59.4	213.7 ± 31.2	0.440	0.37	− 7.5 (185.4 to 276.7)
Drugs					
Prednisone					
Current use	1 (11.1)	–	–	–	–
Dose (mg/day)	5.0	–	–	–	–
Azathioprine	1 (11.1)	–	–	–	–
Methotrexate	2 (22.2)	–	–	–	–
Mycophenolate mofetil	6 (66.7)	–	–	–	–
Body composition					
Fat mass (kg)	29.8 ± 7.7	28.6 ± 7.7	0.746	0.15	− 4.0 (23.8 to 35.7)
Body fat	35.8 ± 7.7	34.8 ± 8.3	0.759	0.12	− 2.8 (29.8 to 41.7)
Free-fat mass (kg)	51.3 ± 10.9	51.9 ± 12.1	0.502	0.05	1.2 (42.9 to 59.6)
Weight (kg)	83.1 ± 14.5	82.0 ± 15.1	0.419	0.07	− 1.3 (71.9 to 94.2)
Body mass index (kg/m^2)	32.1 ± 4.3	31.7 ± 4.8	0.453	0.09	− 0.5 (28.7 to 35.4)
Lipid parameters					
Total cholesterol (mg/dL)	181.6 ± 145.3	131.7 ± 147.1	0.450	0.34	− 27.5 (69.9 to 293.2)
LDL cholesterol (mg/dL)	109.8 ± 24.1	113.4 ± 24.0	0.827	0.15	3.3 (91.2 to 128.3)
HDL cholesterol (mg/dL)	45.5 ± 11.0	42.8 ± 10.2	0.181	0.25	− 5.9 (37.0 to 53.9)
Triglycerides (mg/dL)	134.3 ± 40.5	120.3 ± 50.7	0.172	0.30	− 10.4 (103.1 to 165.4)

Results are expressed as mean ± standard deviation or percentage (%)

CI, coefficient interval; *ES*, effect size; *HAQ*, Health Assessment Questionnaire; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *MMT*, manual muscle testing; *MYOACT*, Myositis Disease Activity Assessment Visual Analog Scale; *VAS*, visual analog scale

lactic dehydrogenase (≤ 314 U/L) were evaluated. Blood lipids (i.e., total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were also assessed.

Statistical analysis Kolmogorov Smirnov test was used to test the data distribution. Independent samples were compared using unpaired *t* tests and Mann-Whitney *U* tests when data were parametric or non-parametric, respectively. Dependent samples were compared with paired *t* tests or Wilcoxon tests when data were parametric or non-parametric, respectively. Categorical variables were analyzed by Fisher's exact test. The AUC for glucose, insulin, and C-peptide was calculated in Graphpad prism 5.0. The effect size (ES), a measure of the magnitude of change (small ≤ 0.49; medium 0.49–0.79; large ≥ 0.80), was calculated using Cohen's *d*. Data are expressed as mean ± SD, percent delta, and 95% confidence interval (CI),

Table 2 Muscle strength, muscle function, and aerobic capacity parameters of the 9 patients submitted to the exercise training

	Baseline	Post	*P*	*ES*	Delta (95% CI)
Muscle strength and function					
1 RM leg-press (kg)	71.7 ± 14.8	82.9 ± 14.0	0.013	0.77	15.6 (60.3 to 80.1)
1 RM bench-press (kg)	28.6 ± 9.6	32.3 ± 10.5	0.002	0.37	12.9 (21.2 to 35.9)
Handgrip (kg)	24.0 ± 9.5	25.4 ± 11.3	0.253	0.13	5.8 (16.6 to 31.3)
30-s sit to stand test (n)	13.9 ± 2.8	16.0 ± 3.7	0.002	0.64	15.1 (11.7 to 16.0)
Timed-up-and-go test (s)	7.3 ± 1.1	6.7 ± 1.1	0.005	0.55	− 8.2 (6.4 to 8.1)
Aerobic capacity					
VO_2 maximal (L/min)	1.5 ± 0.4	1.7 ± 0.5	0.068	0.44	13.3 (1.1 to 1.8)
VO_2 maximal (mL/kg/min)	18.5 ± 4.1	20.9 ± 5.2	0.052	0.51	12.9 (15.3 to 21.6)
Time-to-achieve VAT (min)	4.8 ± 0.9	6.0 ± 1.5	0.064	0.44	25.0 (4.1 to 5.5)
Time-to-achieve RCP (min)	9.1 ± 1.3	10.7 ± 1.3	0.001	1.23	17.5 (8.1 to 10.0)
Time-to-achieve exhaustion (min)	10.6 ± 2.1	13.2 ± 1.8	0.000	1.33	24.5 (8.9 to 12.2)

Results are expressed as mean ± standard deviation

CI, coefficient interval; *ES*, effect size; *RCP*, time elapsed until respiratory compensation point; *RM*, repetition maximum; *VAT*, ventilatory anaerobic threshold; *VO_2 maximum*, maximum oxygen uptake

except as otherwise stated. $P \leq 0.05$ was considered to be statistically significant. All statistical analyses were performed using the software SPSS, version 15.0 (Chicago, IL, USA).

Results

Table 1 shows the main features of the patients, including disease status, body composition, blood lipids, and drug therapies.

The patients had a mean age of 46.7 years and a mean disease duration of 8.4 years. Six patients were female, and three were male. Six patients had dermatomyositis, two had antisynthetase syndrome, and one had polymyositis. All patients had a stable disease according to the IMACS scores, and all were using at least one immunosuppressive drug. Only one patient was using prednisone (at a dose of 5 mg/day). During the study, no patients had to change the drug regimens.

No impairments in disease status were observed during the intervention (Table 1). The patients had a high adherence to the exercise program (98%). Body composition improved during the trial, with a reduction in fat mass (29.8 ± 7.7 vs. 28.6 ± 7.7 kg, baseline and post, respectively; $P = 0.047$) and body fat (35.8 ± 7.7 vs. 34.8 ± 8.3%; $P = 0.027$), with no differences in free fat mass ($P > 0.05$). Blood lipids were similar before and after exercise training ($P > 0.05$).

There were significant improvements in dynamic strength (Table 2), as demonstrated by improvements in 1 RM leg-press (71.7 ± 14.8 vs. 82.9 ± 14.0 kg; $P = 0.013$) and 1 RM bench-press (28.6 ± 9.6 vs. 32.3 ± 10.5 kg; $P = 0.002$), whereas no differences in isometric strength were observed. The patients also showed significant improvements in timed-

Table 3 Glucose, C-peptide, insulin, and B cell function parameters of the 9 patients submitted to the exercise training

	Baseline	Post	*P*	ES	Delta (95% CI)
Fasting blood glucose (mg/dL)	89.9 ± 16.1	90.4 ± 13.6	0.895	0.03	0.5 (77.5 to 102.2)
Fasting blood insulin (U/L)	16.5 ± 7.9	11.8 ± 5.5	0.052	0.69	− 28.4 (10.4 to 22.5)
Basal C-peptide (ng/mL)	3.7 ± 1.0	2.7 ± 0.6	0.015	1.21	− 27.0 (3.9 to 4.4)
Insulin and β-cell function parameters					
HOMA1 IR (≤ 1.6)	3.7 ± 1.8	3.0 ± 2.2	0.388	0.35	− 18.9 (2.3 to 5.0)
HOMA2 IR (≤ 1.45)	2.1 ± 1.0	1.7 ± 1.1	0.295	0.38	− 10.8 (1.3 to 2.8)
HOMA2 %B (≤ 175)	165.4 ± 58.9	136.5 ± 59.4	0.074	0.49	− 17.5 (120.1 to 210.6)
HOMA2 %S (≥ 68.9)	57.0 ± 23.9	83.1 ± 49.7	0.056	0.67	45.7 (38.3 to 75.3)
Matsuda index (≥ 2.5)	3.3 ± 2.2	5.9 ± 4.0	0.032	0.80	78.7 (1.6 to 4.9)
Insulinogenic index (≥ 0.4)	1.1 ± 0.5	1.0 ± 0.9	0.678	0.14	− 9.1 (0.7 to 1.5)

Results are expressed as mean ± standard deviation

AUC, area under curve; *CI*, coefficient interval; *ES*, effect size; *HOMA*, homeostatic model assessment; *OGTT*, oral glucose tolerance test

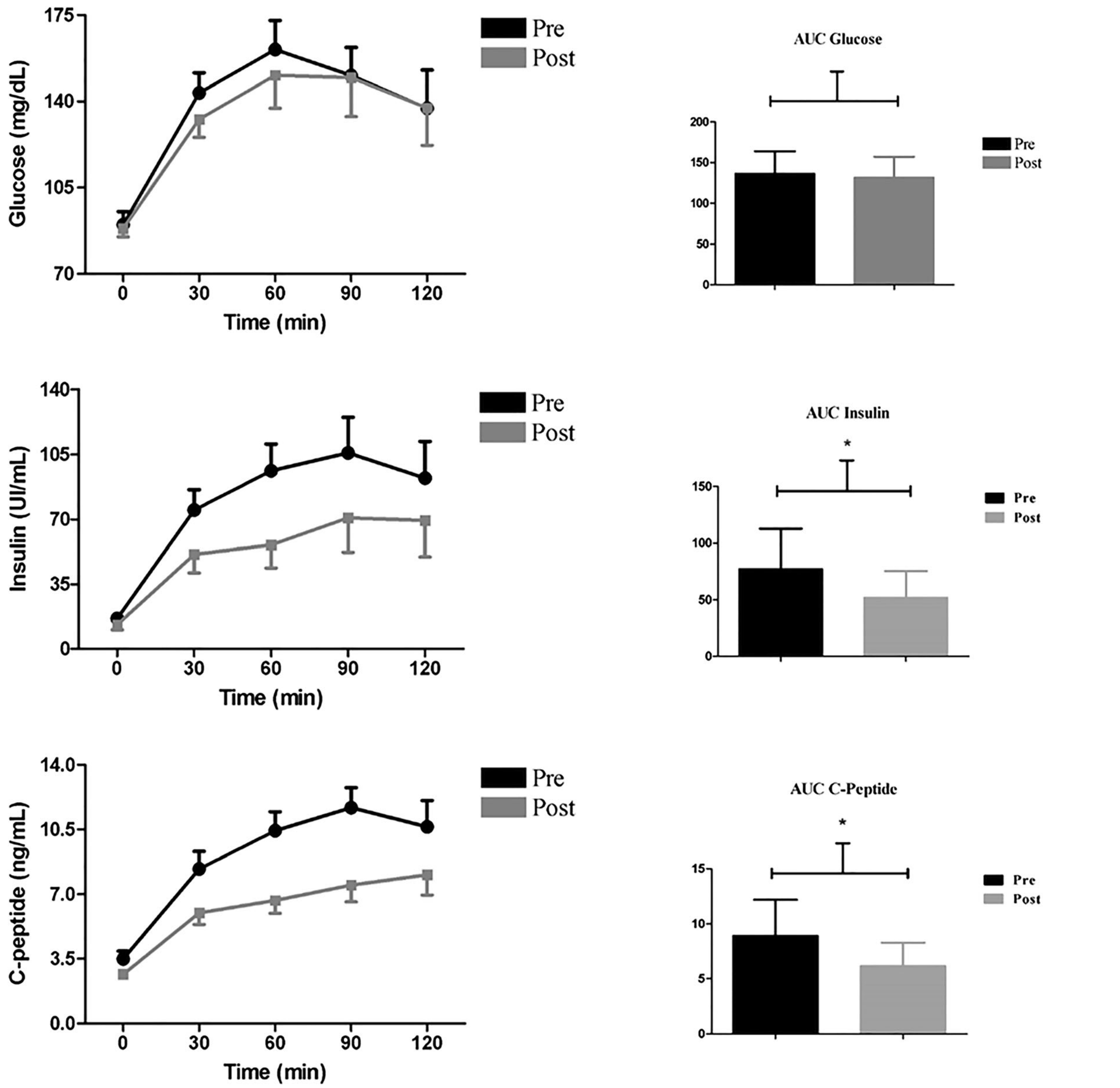

Fig. 1 Oral glucose tolerance test and area under curve of glucose, insulin, and C-peptide before and after exercise training. AUC: area under curve of glucose; OGTT: oral glucose tolerance test. *$P < 0.05$

stands test (13.9 ± 2.8 vs. 16.0 ± 3.7 times; $P = 0.002$), and timed-up-and-go test (7.3 ± 1.1 vs. 6.7 ± 1.1 s; $P = 0.005$).

Regarding aerobic capacity (Table 2), the patients showed a tendency toward improvement in absolute VO_{2max} ($P = 0.068$) and the time-to-achieve VAT ($P = 0.064$). The patients also showed a significant improvement in the time-to-achieve the RCP (9.1 ± 1.3 vs. 10.7 ± 1.3 min; $P = 0.001$) and time-to-achieve exhaustion (10.6 ± 2.1 vs. 13.2 ± 1.8 min; $P = 0.001$).

Regarding IR, after the intervention, patients showed a tendency toward lower fasting blood insulin (16.5 ± 7.9 vs. 11.8 ± 5.5 U/L; $P = 0.052$), as well as a significant reduction in basal C-peptide (3.7 ± 1.0 vs. 2.7 ± 0.6 ng/mL; $P = 0.015$) (Table 3). The patients also showed a tendency toward lower HOMA2 %S (57.0 ± 23.9 vs. 83.1 ± 49.7; $P = 0.056$), as well as a significant reduction in Matsuda index (3.3 ± 2.2 vs. 5.9 ± 4.0; $P = 0.034$). We observed no differences for the other parameters (Table 3). We found no differences for glucose AUC (Table 3; Fig. 1). However, insulin AUC (77.1 ± 35.7 vs. 52.1 ± 23.4; $P = 0.016$) and C-peptide AUC (8.9 ± 3.3 vs. 6.1 ± 2.1; $P = 0.009$) decreased after the intervention (Fig. 1).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of exercise training on IR and β-cell function parameters among patients with SAMs. The main findings of the present study were as follows: (a) Patients showed decreased in fasting basal insulin and basal C-peptide, as well as lower Matsuda index and lower AUC for insulin and C-peptide in OGTT; suggesting an attenuation of IR and improvements in β-cell function; (b) Patients showed improved aerobic capacity, muscle strength, and muscle function, without impairments in disease status.

We demonstrated that exercise training leads to improvements in insulin sensitivity and β-cell function in patients with SAMs. Metabolic syndrome is a highly prevalent clinical condition among these patients [3–6], and IR is a major component of this syndrome [8]. In other systemic autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, IR is correlated with chronic inflammatory state, physical inactivity, obesity, disease activity, atherosclerosis, metabolic syndrome, and, finally, increased cardiometabolic risk [26–31]. Therefore, exercise-induced improvements in IR and, hence, metabolic syndrome, could prevent the risk for cardiovascular diseases in SAMs.

Several factors may have contributed to the improved IR observed in this study [7, 32–35]. Exercise training is a powerful therapeutic tool for patients with IR conditions because it increases glucose transporter-4 (GLUT-4) translocation through insulin-independent pathways, which leads to increased glucose uptake in the skeletal muscle, the tissue responsible for taking up roughly 80% of circulating glucose [7]. Besides the increase in GLUT-4 translocation, in patients with systemic lupus erythematosus, a 12-week moderate-intensity aerobic exercise training program improved insulin sensitivity by increasing skeletal muscle AMPK phosphorylation after training [12], suggesting a potential underlying mechanism by exercise improves IR in patients with rheumatologic autoimmune diseases. However, more studies are necessary to highlight the molecular mechanisms behind these improvements.

There is also an important association between greater aerobic capacity and greater insulin sensitivity [32]. In fact, it is well-known that athletes and physically active individuals normally show better insulin sensitivity than sedentary individuals [33–35]. Corroborating this finding, in systemic autoimmune diseases such as rheumatoid arthritis, increased body fat and IR are associated with low VO_{2max} and 10-year cardiovascular risk [31], demonstrating the need for developing effective behavioral interventions to attenuate these outcomes. Therefore, the increase in aerobic capacity observed in this study may have contributed to the improvement in insulin sensitivity.

In other rheumatologic autoimmune diseases, such as rheumatoid arthritis, obesity is considered the main determinant of IR [30]. Recently, we also demonstrated that in patients with SAMs, IR is correlated with weight, body mass index, and waist circumference [8]. Furthermore, in these patients, increased body fat and decreased lean mass are associated with their disease duration, inflammatory status, skeletal muscle involvement, and physical activity [36], corroborating that a worst body composition in rheumatologic autoimmune disease corroborates to impairs insulin signaling. It is well described in the literature that a higher body fat, especially visceral fat, can impair IR through suppressing the insulin signaling [37]. However, in the present study, we fail to demonstrate improvements in body composition after intervention. Studies assessing a higher volume or intensity of exercise training could help to demonstrate benefits in these parameters in patients with SAMs.

This study had some limitations. First, due to the heterogeneity of these diseases, we were unable to include a control group. Further efforts should be done to replicate these data in randomized controlled trials. Second, the study included only patients with stable diseases. In addition, our patients had low frequency of metabolic syndrome; possibly because we did not include patients using statin or fibrate, as these drugs can interfere with insulin resistance parameters. Caution should be exercised in extrapolating these data to patients with more severe disease or a higher risk for metabolic syndrome. Once visceral adipose tissue is more strongly associated with insulin resistance compared with subcutaneous adipose tissue, the use of DXA for body composition analysis (which cannot discriminate between the two adipose depots) is also a limitation of the present study. Finally, we did not evaluate the expression of genes and proteins related to IR, hampering any conclusion on the molecular mechanisms underlying our findings.

In conclusion, exercise training was a safe and an effective strategy to improve insulin resistance and β-cell function parameters in patients with SAMs. This response is possibly mediated by the increase in aerobic capacity found in the present study. Therefore, we advocate that exercise training should be recommended to patients with SAMs to reduce insulin resistance and mitigate their cardiometabolic risk.

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Compliance with ethical standards

Disclosures None.

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