Exercise Training Program Improves Endothelial Function and Physical Capacity in a Patient with Hereditary Inclusion Body Myopathy Linked to a Valosin-Containing Protein Pglyg97glu Gene Mutation

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Abstract

Background: To assess the effects of an exercise training program on endothelial function, arterial stiffness, disease status and physical capacity in a patient with hereditary inclusion body Myopathy linked to avalosin-containing proteinPglyg97Glue mutation.

Methods: A 51-year-old white female patient with only inclusion body Myopathy phenotype (without Paget disease of bone and frontotemporal dementia) was submitted to a 24-weeks aerobic and resistance training program.

Results: Endothelial function, aerobic capacity and muscle strength (i.e. bench press) were improved after 12-weeks. Aerobic capacity and endothelial function further improved after 24-weeks, whereas no alterations were observed for arterial stiffness. Moreover, there was no impairment on the clinical and laboratory parameters of the disease after 12- and 24-weeks.

Main Findings: Exercise training proves safe and effective for improving endothelial function and increasing aerobic capacity, muscle strength and function in the patient.

Keywords: Aerobic capacity; Exercise training; Inclusion body myopathy; Myopathy; Myositis

Introduction

Hereditary Inclusion Body Myopathies (h-IBM) are heterogeneous progressive muscle disorders that share clinical and histologic features with sporadic inclusion body myositis [1,2]. Patients with h-IBM present a hereditary/familial component, with huge phenotypic variety. A subgroup of h-IBM patients may be relate to genetic mutations, such as valosin-containing protein mutations, which, in addition to promoting progressive and irreversible muscular involvement, can lead to Paget disease of bone and frontotemporal dementia, a rare penetrant autosomal dominant disorder [3]. Therefore, unlike sporadic inclusion body myositis, h-IBM presents a systemic manifestation and is not restricted only to the muscular component. In general, myopathy associated with h-IBM affects both proximal and distal skeletal muscles [4]. Chronically, it is accompanied by difficulty raising the arms, inability to properly ambulate or climb stairs, hand weakness and reduction or absence of tendon reflexes, thus resembling limb girdle muscular dystrophies [5]. Two to three decades after diagnosis patients require a wheelchair for mobility [6]. Together, these features, could lead to sedentary behavior in these patients, which in turn has been associated with impaired physical capacity, increasing cardiovascular risk and worsening clinical symptoms in these patients.

To date, only a few studies have demonstrated that exercise training programs can be an important coadjuvant therapy in improving quality of life, muscle strength and aerobic capacity in patients with sporadic inclusion body myositis, a disease which has similar clinical manifestations as h-IBM [7-11]. Notably, no studies analyzing all of these parameters in patients with h-IBM phenotype has been conducted.

Furthermore, none of these longitudinal studies assessed arterial stiffness and endothelial function in response to exercise training programs in any of these diseases. Once that these outcomes
are earlier predictors of atherosclerosis and future cardiovascular events, and exercise training has been an important tool capable of counteract endothelial dysfunction and arterial stiffness, we believe that exercise could attenuate cardiovascular risk associated with these variables in these diseases.

Therefore, follow the rules of case report (CARE) guidelines [12], we assessed the impact of a exercise training program in a patient with h-IBM linked to a valosin-containing protein gene mutation, on disease status, physical function, muscle strength, aerobic capacity, endothelial function and arterial stiffness.

**Case Presentation**

This study was approved by the local Institutional Ethics Committee. The present study assessed a 51-year-old white female patient with defined hereditary inclusion body myopathy linked to the valosin-containing protein pGlyG97Glu gene mutation [13]. Hereditary findings of her family are described elsewhere [13]. The patient has no signs or symptoms of Paget disease of Bone (normal: whole body 18F-FDG PET/CT, skeletal scintigraphy screening, and serum level of alkaline phosphatase) or frontotemporal dementia phenotypes (normal brain magnetic resonance imaging, and score of 30 out of 30 on the Portuguese version of the Montreal Cognitive Assessment [14].

The patient had progressive proximal muscle weakness of the lower limbs since the age of 48. Serum creatine phosphokinase was between two and five times the upper limit of normality. Electromyographic studies revealed myopathic pattern in predominantly proximal muscle area of limbs. Vastus lateralis muscle biopsy showed fiber size variation, basophilic fibers with phagocytosis, some subsarcolemmal and rimmed vacuoles, inflammatory cell infiltrations in perivascular and perimysium tissues, increased endomysium and perimysium conjunctive tissue. Thigh muscle magnetic resonance imaging showed scattered fatty replacement and also mild thigh muscle atrophy (Figure 1). The patient had not been receiving any treatment to muscle decline.

The patient underwent 24-weeks, twice weekly, supervised exercise training program. The exercise training program was comprised by aerobic and resistance training. Aerobic sessions consisted of a 5 min warm-up followed by 30 to 50 min of treadmill walking, and a 5 min cooling-down period. Walking duration was gradually increased every four weeks, from 30 to 50 min. The intensity of the exercise sessions was set at the heart rate corresponding to the interval between the ventilatory anaerobic threshold and respiratory compensation point.

Shortly after the aerobic session, the patient performed the resistance training, which was consisted of seven exercises per session, including leg press, bench press, leg extension, pulley, leg flexion, seated rowing and abdominal exercises. The patient performed three sets of 12 repetitions, with a 1 min rest between sets. Stretching exercises were performed after the resistance training. Training intensity was adjusted according to the gradual increase in strength, such that the patient was able to perform no more than 12 repetition maximum. All sessions were monitored by at least two investigators. The patient was instructed to report any adverse event throughout the exercise training program.

Before and after the exercise training program, the patient completed a maximal graded treadmill cardiopulmonary exercise test to determine peak oxygen uptake (VO2peak). The cardiopulmonary exercise test was considered to be maximal when one of the following criteria was met: VO2 plateau (i.e., <150 ml/min increase between two consecutive stages), heart rate no less than 10 beats below age-predicted maximal HR and respiratory exchange ratio value above 1.10. VO2peak was considered as the average of the final 30 seconds of the test [15]. Ventilatory anaerobic threshold and Respiratory compensation point were determined as described previously [15]. Ventilatory anaerobic threshold was determined when ventilatory equivalent for VO2 (VE/VO2) increased without a concomitant increase in ventilatory equivalent for carbon dioxide (VE/VCO2). Respiratory compensation point was determined when VE/VO2 and VE/VCO2 increased simultaneously.

Additionally, muscle strength tests (assessed by one repetition maximum and handgrip test), functional performance assessed by the timed-up-and-go and timed-stands test, endothelial function assessed by ultrasound-based measurements of brachial reactivity, and arterial stiffness determined by carotid-femoral pulse wave velocity were evaluated as described previously [15,16]. The same examiner carried out the assessment of endothelial function and arterial stiffness. For endothelial function, the left brachial artery was measured at a longitudinal section above the antecubital fossa, using a high-resolution ultrasound system (Sequoia Echocardiography System, version 6.0, Acuson) equipped with a multi frequency linear transducer (7-12 MHz) to produce 2-dimensional images. This technique was use to evaluate the change in arterial diameter and blood flow after physical and pharmacologic stimulation. The reactive hyperemia maneuver was use as a physical stimulus to...
evaluate endothelium-dependent response. First, a resting image
was obtained and a pulsed Doppler velocity signal was recorded. The
artery was then occluded by inflating the blood pressure cuff to 50
mm Hg above the subject’s resting systolic blood pressure. The cuff
was kept inflated for 5 minutes and then rapidly deflated manually.
Brachial artery diameter was measured 1 minute after cuff release.
Reactive hyperemia was calculated as the percentage flow change
from baseline. Flow-mediated dilation measured at end diastole was
expressed as the percentage increase in lumen diameter from baseline.
Endothelium-independent response, also called non endothelium-
dependent vasodilation, was measured after a 10-minute rest period
following the reactive hyperemia assessment. A second baseline
scan was obtained for 2 minutes, and then the exogenous nitric
oxide donor nitroglycerine spray was administered (0.40 mg of
sublingual trinitrate by aerosol; NitraginPumpspray, Alpharma-
oxide donor nitroglycerine spray). The percentage change in brachial
artery diameter was measured 5 minutes after the administration of nitroglycerin. The percentage change in brachial artery diameter in response to nitroglycerin administration was used to assess endothelium-independent vasodilation (i.e., nitrate-induced dilation).

The data for baseline and after 12- and 24-weeks of exercise
interventions are given in Table 1. At baseline, the patient had a
creatine phosphokinase level of 317 U/L (reference: < 167 U/L); muscle
manual testing (MMT-8) [17] of 73 out of 80; health assessment
questionnaire [18] score of 1.00 out of 3.00; a patient’s visual analogue
score of 3.0 out of 10 cm; and physician’s visual analogue score of 3.0
out of 10 cm. Importantly, there was no impairment on the clinical
and laboratory parameters of the disease after 12- and 24-weeks.

In addition, our patient had an increase in aerobic capacity and
muscle function. The increase in aerobic capacity was observed in
peak VO₂ (relative and absolute) after 12-weeks, and in time to
achieve ventilatory anaerobic threshold, time to achieve respiratory
compensation point and time-to-exhaustion (after 12-weeks and
24-weeks) (Table 1). Increase in muscle strength was observed only for
the bench press exercise at 12-weeks, with stabilization at 24-weeks.
Muscle function was improved after 12-weeks in the timed-stands
test in timed-up-and-go, stabilizing at 24-weeks.

Finally, endothelial function improved after 12-weeks and further
improved after 24-weeks, as demonstrated by increase in flow-
mediated dilation. No alterations were observed for arterial stiffness
(Figure 2).

Discussion

To the best of our knowledge, this is the first study to investigate
the effects of a exercise training program in a patient with h-IBM.
The patient showed an important improvement in endothelial
function, increase in aerobic capacity, muscle strength and function
parameters, without disease status impairment.

Patients with h-IBM have major skeletal muscle wasting as a
consequence of the disease. Moreover, the progressive atrophy
found in h-IBM patients, impairs muscle strength and function,
and, consequently, to an impairment in quality of life. Together,
these outcomes could increase sedentary behaviour in these patients.
Sedentary behaviour in patients with several diseases characterized
by myopathy is associated with impaired aerobic capacity and
increased cardiovascular risks [19]. Moreover, sedentary behaviour is
associated with skeletal muscle wasting, which can worsen the clinical
symptoms of these diseases [20]. Thus, strategies that can improve
these symptoms and attenuate muscle loss should be employed
in these patients. In this scenario, and, as evidenced in the present
study, exercise training emerges as an effective and safe strategy to
counteract these outcomes in h-IBM patients.

The increase in muscle strength found in this study was observed
only for the bench press exercise, while no such increase was seen for
the leg press exercise. The study of Spector et al. [11], demonstrate that
the most marked benefits were seen in the least weakened muscles in
sporadic inclusion body myositis patients submitted to exercise
training. In the patient with h-IBM engaged in this study, quadriceps
muscles were the most affected by the disease, even though clinical
and imaging muscle impairment of this particular patient seem quite
mild (Table 1, Figure 1). Thus, studies involving patients with more
severe disease will help to corroborate the findings of the present
study.

Patients with sporadic inclusion body myositis have impaired
aerobic capacity and muscle function, which can be improved with
exercise training [7,8]. We showed that our patient had a significant
increase in aerobic capacity (demonstrated by a higher time to
achieve ventilatory anaerobic threshold, respiratory compensation
point and time-to-exhaustion). The peak VO₂ has only increased after
12-weeks, following by a decrease within 24-weeks. Peak VO₂ has a
multi factorial nature, and since the patient has only been engaged
in a twice-a-week exercise training program, we believe that higher
volume exercise training in a week will be helpful to maintaining the
gaining in Peak VO₂. We also observed improvements in muscle
function (demonstrated by improvements in timed-stands test in
timed-up-and-goafter 12-weeks, andstablewithin 24-weeks).

<table>
<thead>
<tr>
<th>Table 1: Disease status, aerobic capacity, strength and functional capacity in patient, at baseline and after 12 and 24 weeks of the exercise training program.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease status</strong></td>
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<tr>
<td>Manual Muscle Testing - 8 (0-80)</td>
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<tr>
<td>Health Assessment Questionnaire (0.00-3.00)</td>
</tr>
<tr>
<td>Creatine phosphokinase (U/L)</td>
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<tr>
<td>Patient’s visual analogue score (0-10 cm)</td>
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<tr>
<td>Physician’s visual analogue score (0-10 cm)</td>
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<tr>
<td><strong>Aerobic capacity</strong></td>
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<tr>
<td>Peak VO₂ (L/min)</td>
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<tr>
<td>Peak VO₂ (mL/kg/min)</td>
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<tr>
<td>Peak heart rate (bpm)</td>
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<td>Peak respiratory exchange rate</td>
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<tr>
<td>Ventilatory anaerobic threshold (min)</td>
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<td>Respiratory compensation point (min)</td>
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<tr>
<td>Time-to-exhaustion (min)</td>
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<tr>
<td><strong>Strength and functional capacity</strong></td>
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<tr>
<td>Legpress 1RM (kg)</td>
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<tr>
<td>Benchpress 1RM (kg)</td>
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<tr>
<td>Handgrip (kg)</td>
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<tr>
<td>Timed-stands test (reps)</td>
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<td>Timed-up-and-go (s)</td>
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RM: Repetition Maximum; Peak VO₂: peak oxygen uptake.
In patients with sporadic inclusion body myositis, the functional disability seems to be the most important predictor of quality of life in these patients [20], suggesting that exercise training program can represent an important coadjuvant for improving quality of life in patients with sporadic inclusion body myositis, and, possible, in h-IBM.

In an experimental model of valosin-containing protein disease, a progressive uphill exercise in valosin-containing protein mice lead to a significant improvement in muscle strength and performance evaluated by grip strength and Rotarod analyses when compared to sedentary mice [21]. Histologically, the uphill exercised mice displayed an improvement in muscle atrophy, and decreased levels of expression of ubiquitin and autophagy markers, suggesting an alleviation of disease-induced myopathy phenotypes [21]. The results of the present study are in line with these findings; however, further studies are needed to evaluate the implication of exercise training program for histological parameters in h-IBM patients.

After a 12-weeks and 24-week exercise training program, our patient exhibited significant important improvement in endothelial function (Figure 2). Patients with myopathies have impaired endothelial function, which is associated with early signs of atherosclerosis, leading to a high cardiovascular risk in these diseases [22]. In this context, exercise training emerges as a potential strategy for attenuating the endothelial dysfunction found in the disease, thereby, reducing cardiovascular risk.

There has always been a concern that higher intensity exercise training in patients with systemic autoimmune myopathies could worsen inflammation and subsequently exacerbate clinical symptoms [22]. In this regard, some authors have proposed resistance training with vascular occlusion as an alternative to high intensity exercise training in sporadic inclusion body myositis patients [9,10]. However, practical application of this training is difficult, since it requires prior knowledge by the professional on its application. In the present study, we showed that higher intensity exercise training in our patient was safe (with no impairment in diseases status), suggesting that patients with h-IBM should be engaged in exercise training programs to improve clinical symptoms of the disease. Although the data in this study are promising, these findings do not allow extrapolation to sedentary mice [21]. In this context, exercise training emerges as a potential strategy for attenuating the endothelial dysfunction found in the disease, thereby, reducing cardiovascular risk.

In summary, the 24-week exercise training program proves safe and effective in improve endothelial function and increase aerobic capacity, muscle strength and function in a patient with h-IBM, with no worsening of clinical parameters. These data suggest that exercise training can improve physical capacity and attenuate cardiovascular risk. Further studies are needed to confirm these findings.

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