



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 a valosin-containing protein PglyG97Glu gene 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 related 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 adjuvant 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

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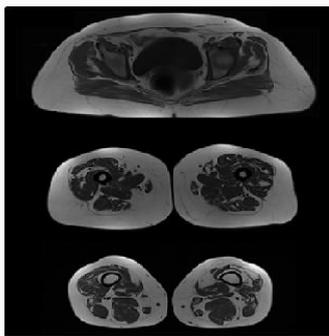


Figure 1: Magnetic resonance imaging of limb skeletal muscles of the patient from the present study.

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 ^{18}F -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 scatter fatty replacement and also mild thigh muscle hypotrophy (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 5min warm-up followed by 30 to 50 min of treadmill walking, and a 5min 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

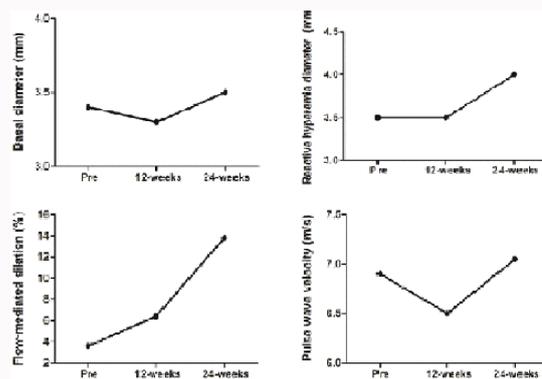


Figure 2: Endothelial function and arterial stiffness in patient at baseline and after 12- and 24-weeks exercise training program.

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 ($\text{VO}_{2\text{peak}}$). The cardiopulmonary exercise test was considered to be maximal when one of the following criteria was met: VO_2 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. VO_2 peak 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 VO_2 (VE/VO_2) increased without a concomitant increase in ventilatory equivalent for carbon dioxide (VE/VCO_2). Respiratory compensation point was determined when VE/VO_2 and VE/VCO_2 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 used to evaluate the change in arterial diameter and blood flow after physical and pharmacologic stimulation. The reactive hyperemia maneuver was used as a physical stimulus to

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.

	At baseline	After	
		12-weeks	24-weeks
Disease status			
Manual Muscle Testing - 8 (0-80)	73	78	78
Health Assessment Questionnaire (0.00-3.00)	1	0.86	0.86
Creatine phosphokinase (U/L)	317	-	269
Patient' visual analogue score (0-10 cm)	3	0	0
Physician' visual analogue score (0-10 cm)	3	0	0
Aerobic capacity			
Peak VO ₂ (L/min)	0.7	1	0.9
Peak VO ₂ (mL/kg/min)	15	16.7	14.3
Peak heart rate (bpm)	153	165	166
Peak respiratoryexchange rate	1.1	1.1	1.3
Ventilatory anaerobic threshold (min)	2.4	4.3	4
Respiratory compensation point (min)	5	9	11
Time-to-exhaustion (min)	6.4	11	14
Strengthandfunctionalcapacity			
Legpress 1RM (kg)	24	24	24
Benchpress 1RM (kg)	18	22	22
Handgrip (kg)	20.5	21.5	22
Timed-stands test (reps)	7	12	12
Timed-up-and-go (s)	9.1	7.2	7.2

RM: Repetition Maximum; Peak VO₂: peak oxygen uptake.

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 5minutes 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, AlphaPharma-Isis). 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 testand 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 help to maintaining the gaining in Peak VO₂. We also observed improvements in muscle function (demonstrated by improvements in timed-stands testand in timed-up-and-goafter 12-weeks, andstablewithin 24-weeks).

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 adjuvant 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 of results, where randomized clinical trials in a larger number of patients are required.

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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References

- Amato AA, Barohn RJ. Inclusion body myositis: old and new concepts. *J Neurol* and its future therapy. *Neurotherapeutics*. 2008;5:633-7.
- Broccolini A, Mirabella M. Hereditary inclusion-body myopathies. *Biochim Biophys Acta*. 2015;1852(4):644-50.
- Kovach MJ, Waggoner B, Leal SM, Gelber D, Khardori R, Levenstien MA, et al. Clinical delineation and localization to chromosome 9p13.3-p12 of a unique dominant disorder in four families: hereditary inclusion body myopathy, Paget disease of bone, and frontotemporal dementia. *Mol Genet Metab*. 2001;74(4):458-75.
- Argov Z, Mitrani-Rosenbaum S. The hereditary inclusion body myopathy enigma and its future therapy. *Neurotherapeutics*. 2008;5(4):633-7.
- Fanganiello RD, Kimonis VE, Côrte CC, Nitrini R, Passos-Bueno MR. A Brazilian family with hereditary inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia. *Braz J Med Biol Res*. 2011;44(4):374-80.
- Huizing M, Krasnewich DM. Hereditary inclusion body myopathy: a decade of progress. *Biochim Biophys Acta*. 2009;1792(9):881-7.
- Arnardottir S, Borg K, Ansved T. Sporadic inclusion body myositis: morphology, regeneration, and cytoskeletal structure of muscle fibres. *J Neurol Neurosurg Psychiatry*. 2004;75(6):917-20.
- Johnson LG, Collier KE, Edwards DJ, Philippe DL, Eastwood PR, Walters SE, et al. Improvement in aerobic capacity after an exercise program in sporadic inclusion body myositis. *J Clin Neuromuscul Dis*. 2009;10(4):178-84.
- Gualano B, Neves M, Lima FR, Pinto AL, Laurentino G, Borges C, et al. Resistance training with vascular occlusion in inclusion body myositis: a case study. *Med Sci Sports Exerc*. 2010;42(2):250-4.
- Jørgensen AN, Aagaard P, Nielsen JL, Frandsen U, Diederichsen LP. Effects of blood-flow-restricted resistance training on muscle function in a 74-year-old male with sporadic inclusion body myositis: a case report. *Clin Physiol Funct Imaging*. 2016;36(6):504-9.
- Spector SA, Lemmer JT, Koffman BM, Fleisher TA, Feuerstein IM, Hurley BF, et al. Safety and efficacy of strength training in patients with sporadic inclusion body myositis. *Muscle Nerve*. 1997;20(10):1242-8.
- Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, et al. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. *Glob Adv Health Med*. 2013;2(5):38-43.
- Shinjo SK, Oba-Shinjo SM, Lerario AM, Marie SKN. A Brazilian family with inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia linked to the VCP pGly97Glu mutation. *Clin Rheumatol*. 2017; 37(4):1129-36.
- Freitas S, Simões MR, Alves L, Duro D, Santana I. Montreal Cognitive Assessment (MoCA): validation study for frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 2012;25(3):146-54.
- Oliveira DS, Shinjo SK, Silva MG, de Sá-Pinto AL, Lima FR, Roschel H, et al. Exercise in Takayasu Arteritis: Effects on Inflammatory and Angiogenic Factors and Disease-Related Symptoms. *Arthritis Care Res (Hoboken)*. 2017;69(6):892-902.
- Caldas CA, Borba EF, Bortolotto LA, Medeiros DM, Bonfa E, Gonçalves CR. Increased arterial stiffness assessed by pulse wave velocity in Behçet's disease and its association with the lipid profile. *J Eur Acad Dermatol Venereol*. 2013;27(4):454-9.
- Rider LG, Koziol D, Giannini EH, Jain MS, Smith MR, Whitney-Mahoney K, et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. *Arthritis Care Res (Hoboken)*. 2010;62(4):465-72.
- Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Qual Life Outcomes*. 2003;1:20.
- Pinto AJ, Roschel H, de Sá Pinto AL, Lima FR, Pereira RMR, Silva CA, et al. Physical inactivity and sedentary behavior: Overlooked risk factors in autoimmune rheumatic diseases?. *Autoimmun Rev*. 2017;16(7):667-74.

20. Sadjadi R, Rose MR, Muscle Study Group. What determines quality of life in inclusion body myositis?. *J NeurolNeurosurg Psychiatry*. 2010;81(10):1164-6.
21. Nalbandian A, Nguyen C, Katheria V, Llewellyn KJ, Badadani M, Caiozzo V, et al. Exercise training reverses skeletal muscle atrophy in an experimental model of VCP disease. *PLoS One*. 2013;8:e76187.
22. Vincze M, Dér H, Kerekes G, Szodoray P, Zeher M, Dankó K, et al. Decreased flow-mediated dilatation with increased arterial stiffness and thickness as early signs of atherosclerosis in polymyositis and dermatomyositis patients. *Clin Rheumatol*. 2014;33(11):1635-41.
23. Partridge RE, Duthie JJ. Controlled trial of the effect of complete immobilization of the joints in rheumatoid arthritis. *Ann Rheum Dis*. 1963;22(2):91-9.