Combined intensive resistance and endurance exercise in low-disease activity inflammatory myopathies : A Hospital vs. Community-Based prospective study

QUENTIN TOUMAZEAU[1], Léa DEBRUT[1, 2], Pauline SILVERSTIN[1], Alizée HEIT[1], Anne-Laure CHARLES[1], Bernard GENY[3], Margherita GIANNINI[1, 4], Alain MEYER[1, 4]

[1] *UR3072 Research Centre of Biomedicine Strasbourg, University of Strasbourg, Strasbourg, France*
,
[2] *Faculty of Sport Sciences, European Centre for Education, Research and Innovation in Exercise Physiology (CEERIPE), University of Strasbourg, Strasbourg, France,*
,
[3] *Physiology and Function Explorations Department, Strasbourg University Hospitals, Strasbourg, France,*
,
[4] *Physiology and Muscle Function Explorations Department, Referral Centre for Systemic Rare Autoimmune Diseases, Strasbourg University Hospitals, Strasbourg, France*

Background

Inflammatory myopathies (IM) are autoimmune diseases characterized by chronic skeletal muscle inflammation and weakness. Many IM patients feature persistent impairment in exercise capacity despite a low disease activity under immunosuppressants. Reduced exercise capacity is associated with fatigue, disability and mortality. Combined resistance and endurance exercise (REE) has been reported to improve exercise capacity. However, i) these results, obtained in a randomized controlled trial of 23 patients, have not been replicated, ii) was conducted in a hospital setting limiting patients access to the care, iii) the mechanism underlying the efficacy of exercise in IM has been scarcely investigated.

Objectives

This study aimed to validate the efficacy and safety of REE in patients with low disease activity IM, to compare hospital-based and community-based training programs and explore the underlying mechanisms.

Methods

Eighty patients with IM (2017 ACR/EULAR criteria) with a disease duration >12 months, CK serum levels <500IU/L and stable medication for ≥6months were prospectively included for a 36-session REE. The program consisted of 30min of aerobic exercise at 70% of VO_2max followed by 20min of resistance exercise at 30–40% of max strength; 3 sessions per week for 12 weeks with evaluations conducted before and after the intervention. Participants <50km from the hospital trained onsite(HB); others used local physiotherapists following specialist instructions (CB).

Results

At that point, twenty-five patients completed the protocol. At inclusion, mean CK was 154±182U/L, and physician VAS was 2.0±0.8, which remained unchanged after completion of the protocol (respectively, 174±196U/L and 1.3±1.0). VO_2max increased to a similar extent afte both the HB (Δ=1.68±1.50 mL/min/kg, p=0.0098) and CB (Δ=2.30±2.44 ml/min/kg, p=0.0033) REE. Strength evaluated by hand-held dynamometer (HB: Δ=14.43±14.48kgf, p=0.008; CB: Δ=9.05±13.32 kgf, p=0.019), 6-min walk distance (HB: Δ=28.64±33.78m, p=0.018; CB: Δ=30.43±54.52m, p=0.057) were similarly improved in both groups. Perceived fatigue (PROMIS7) decreased in the HB (Δ=–5.±1.52, p=0.002) as well as in the CB (Δ=– 5.75±1.26, p<0.001). Perceived disability (PROMIS20) decreased in the HB (Δ=–5.23±1.6, p=0.006), but not in CB (Δ=–0.38±1.31, p=0.95). REE had no impact on body composition and IMACS muscle damage score. PBMCs mitochondrial respiration improved as shown by complex IV activity (Δ=11.05± 23.72 pmol/s/10^6 cells, p=0.007).

Conclusions

In both hospital-based or community-based settings, REE is feasible, safe and effective for low disease activity IM patients. Improvement of exercise capacity, muscle strength, perceived disability, and fatigue were associated with an improvement in mitochondrial respiratory capacity that may play a role in the efficacy of this non-pharmacological treatment.
Topic/s: Muscle

GENERATION OF A PRE-CLINICAL IN VITRO MODEL OF MYOSITIS-RELATED DAMAGE AND IDENTICATION OF FABP3 AS A NEW BIOMARKEI OF DAMAGE

François-Xavier Muller[1], Léa Debrut[1, 2], Quentin Toumazeau[1], Alain Meyer[1, 4], Margherita Giannini[1]
4

[1] *UR3072 Research Centre of Biomedicine Strasbourg, University of Strasbourg, France*
,
[2] *Faculty of Sports Sciences, European Centre for Education, Research and Innovation in Exercise Physiology (CEERIPE), University of Strasbourg, Strasbourg, France*
,
[4] *Physiology and Muscle Function Explorations Department, Referral Centre for Systemic Rare Autoimmune Diseases, Strasbourg University Hospitals, Strasbourg, France*

Introduction: Inflammatory myopathies (IM) are autoimmune diseases characterised by chronic inflammation of the skeletal muscles, leading to muscle weakness. In many patients, physical performance remains impaired despite low disease activity on immunosuppression. This condition, termed ‘damage’, is common and associated with mortality (1). ‘Damage’ affects all IM subtypes and is characterised by muscle atrophy and mitochondrial dysfunction. However, n biomarker or treatment exists, and its pathophysiology remains unknown. To follow this condition, we have shown that, among a wide range of myokines, only fatty acid-binding protein 3 (FABP3) is elevated in patients’ serum and correlates with the global ‘damage’ score (2).

Our aim is to develop a preclinical in vitro damage model, based on activity models, to test new treatments.

Material and Methods: We treated LHCN-M2 myotubes with pro-inflammatory cytokines increased in muscles and blood of patients with IM (IFN-β: 50 U/mL, IFN-γ: 50 U/mL, IL-1β: 5 ng/mL, IL-6: 20 ng/mL, TNF-α: 5 ng/mL) on day 0 and day 3. On day 3, we added prednisone (100 nM), the first-line treatment for IM. On day 6, we tapered prednisone (50 nM) until day 9, as in clinical practice. We assessed muscle atrophy, MHC-I expression by immunofluorescence, and FABP3 production by ELISA and Western blotting at several time points.

Results: On day 3, muscle diameter had decreased by 42.98 ± 2.835% ($p < 0.0001$) following cytokines treatment, and this reduction persisted on day 6 (54.82% ± 5.524 ($p = 0.1333$)) and day 9 (70.17% ± 8.522 ($p = 0.9350$)) despite prednisone. On day 3, MHC-I expression was observed in the cytokines group, unlike in the control group, and persisted following prednisone administration on days 6 and 9. On day 3 and 6, no difference was observed in FABP3 production between the treated cells (0,68 ± 0,2441 and 0,9888 ± 0,284 ($p>0,9999$) and the control ones, but on day 9, a 6-fold increase was observed (5,741 ± 1,165 ($p<0,0001$)). Finally, on day 3, FABP3 secretion was unchanged between the cytokine group (8,506 ± 3,671 pg/mL) and the control group (8,642 ± 3,772 pg/mL) but decreased after prednisone on days 6 (6,325 ± 2,072 pg/mL) and 9 (6,930 ± 1,588 pg/mL).

Discussion/Conclusion: We have developed a potentially relevant model that replicates the characteristics of the damage, such atrophic myotubes and expression of MHC-I. We have also

shown an increase of FABP3 production and secretion.This model could be used to test therapeutic strategies.
Topic/s: Muscle
