AKADEMISKA SJUKHUSET

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PHYSICAL TRAINING AND EXERCISE AS TREATMENT FOR MG?

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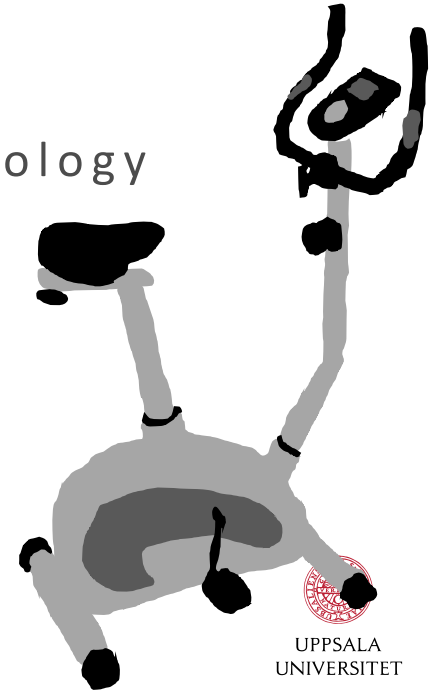

Overall health benefits

- Physical exercise reduces the risk of premature mortality and chronic disease with at least 20-30% *(Warburton,* Curr Opin Cardiol, *2017)*
- Physical inactivity related to higher mortality *(WHO 2009)*
- Beneficial effects in several autoimmune diseases and part of the treatment regimen, for example in rheumatoid arthritis

(Perandini 2012, Spruit 2013, Giesser 2015; Stavropoulos-Kalinoglou 2013, Hochberg 2012, Alexanderson 2012, Zainuldin 2011, Kennedy 2013, Nielsen 2006, Mancia 2013 Chetlin 2004; Voet N 2014)

How about Myasthenia Gravis?

Potential benefits of physical activity in MG?

- Physical exercise influences the **immune response**, with a rise in T regulatory cells, decreased immunoglobulin secretion and decreased Th1 cell production
- Release of the myokine IL-6, which induces an **anti-inflammatory** response through IL10 secretion and IL-1b inhibition
- Exercise enhances aerobic capacity, improves muscle function, and reduces disability in other neuromuscular disorders, also in MG?

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Challenges of measuring fatigue in MG: relevant for physical activity intervention studies

- Fatigue is both *performance fatigability* and *fatigue perception*
- **Fatigue may be best assessed using multiple measures**
- Clinical MG scores: quantitative MG score (QMG) and MG composite scale (MGC)
- Neurophysiological examination: repetitive nerve stimulation (RNS)
- Fatigue severity scale (FSS); developed primarily for multiple sclerosis
- Functional evaluations: 6 min or 2 min walk tests
- Subjective evaluation forms

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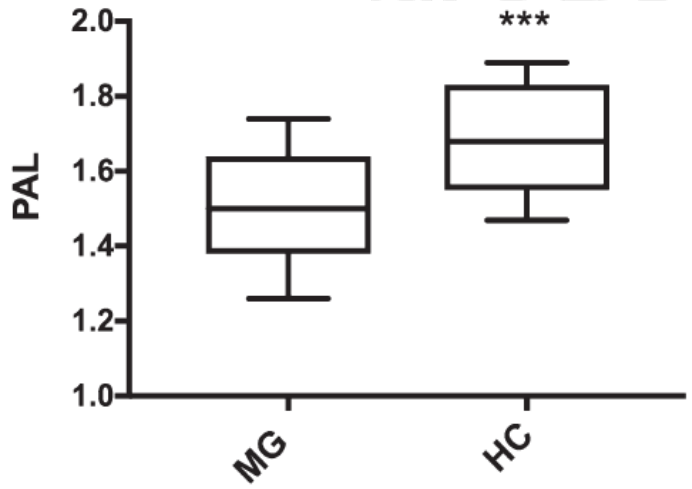
Reviewed in: O´Connor, Front Neurol, 2020

Pattern of habitual exercise in MG patients?



- 27 MG patients had an accelerometer for 7 days
- **Physical activity level (PAL) was lower in MG patients**

  (1.5±0.14) than in healthy controls(1.7±0.15) ($p<0.00001$)

- MG patients had a sedentary behavior during 78 % of the day; with only 22% (all women) achieving the recommended level of 10 000 steps/day.
- Interestingly: no correlation between MG severity and PAL (R=0.33; p=0.26)

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O´Connor et al, J Neuromusc Dis 2019

Study	Design	Aim to define:	Participants	Training protocol
Rahbek et al, 2017	2 arms randomized and stratified, supervised; 8 weeks	-Feasibility of AT and RT - Muscle strength, psychological wellbeing	15 MGFA class II+III 3 dropouts (2 unrelated) 6 completed AT 6 completed RT	• AT: mod-high intensity, cycle test • RT: progressive increase in resistance exercises
Westerberg et al, 2017	Prospective pilot study, supervised; 12 weeks	- Safety and efficacy of physical exercise training in MG	10 MGFA class I+II (8 AChR+, 2 AChR-) No dropouts	• AT: bicycle interval training • RT: resistance exercises • Balance training
Westerberg et al, 2018	Non-blinded observational study, supervised; 12 weeks	- Effects of physical exercise on functional muscle parameters	14 MGFA class I-IV 3 dropouts (all unrelated) 8 AChR+, 2 AChR-/MuSK-; 5 EOMG and 6 EOMG	AT: bicycle interval training RT: resistance exercises
Lohi et al, 1993	Pilot study, 10 weeks	- Evaluate muscle force and fatigue resistance	11 patients with mild-moderate MG	Unilateral strength training one arm and one leg

EXERCISE IN MYASTHENIA GRAVIS: A FEASIBILITY STUDY OF AEROBIC AND RESISTANCE TRAINING

MARTIN AMADEUS RAHBEK, MSc,[1] ERIK ELGAARD MIKKELSEN, MSc,[1] KRISTIAN OVERGAARD, PhD,[1]
LOTTE VINGE, MD, PhD,[2] HENNING ANDERSEN, MD, PhD,[2] and ULRIK DALGAS, PhD[1]

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- Screening of 150 MG patients; 15 included; 12 patients (11 mild and 1 moderate MG) fulfilled the exercise

- Both groups reported adverse events, including bulbar symptoms (n=2) and increased fatigue (n=3), QMG score was unchanged

- The RT group showed increases in maximal strength and functional capacity

- Eight weeks of moderate to high intensity AT and PRT were feasible for most patients with mild MG. Maximal strength and functional capacity increased in the RT group

Westerberg et al x 2: study design

County of Jönköping
n = 70

County of Uppsala
n = 73

3
Discontinued

10 completed
participation rate 71-95%

4 women
65±14 years
6 EOMG

11 completed
participation rate 75-96%

6 women
60±18 years
5 EOMG

STUDY I

STUDY II

Each patient served as his/her own control (before vs after training)

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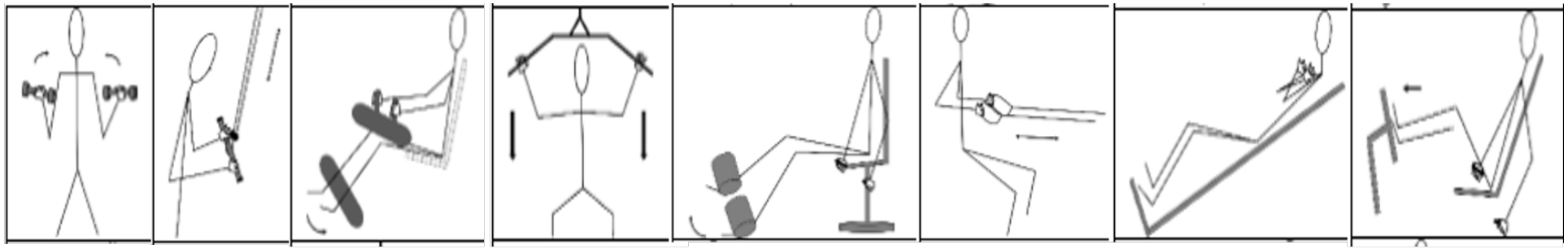
Exercise regimen

Twice a week for 12 weeks, under physioteraphy supervision, 75 min per session:

- **30 min aerobic training** on stationary bicycles

--5 minutes warming up
--seven sets of
2 minutes “maximum cycling”
1 minute “recovery cycling”
--5 minutes cooling down

- **8 different muscle resistance exercises**, 2 sets 10 repetition maximums
- Balance



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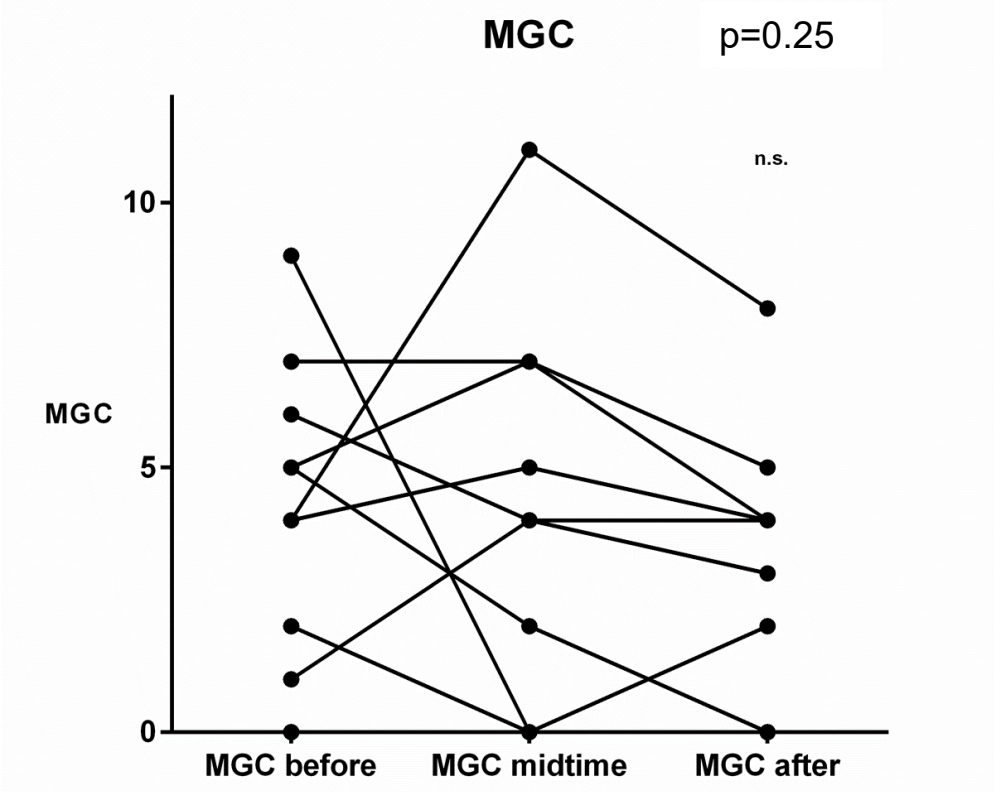
Westerberg et al, Muscle Nerve, 2017; Westerberg et al, Medicine 2018

No worsening in clinical status= no MG deterioration

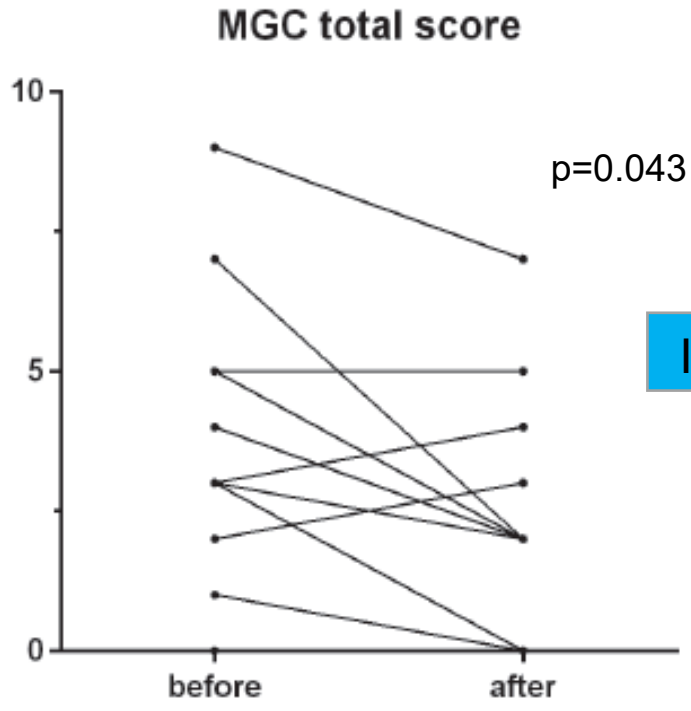
Study 1



MGC, median (range)	**4.5 (0-9)**	**4 (0-11)**	**3.5 (0-8)**

MG Composite Scale
0 = no symptoms
50 = pronounced weakness, ventilator

Study 2



Improvement!

MGC, median (range)	**3 (2-5)**	**2 (2-5)**

Westerberg et al, Muscle Nerve, 2017
Westerberg et al, Medicine 2018

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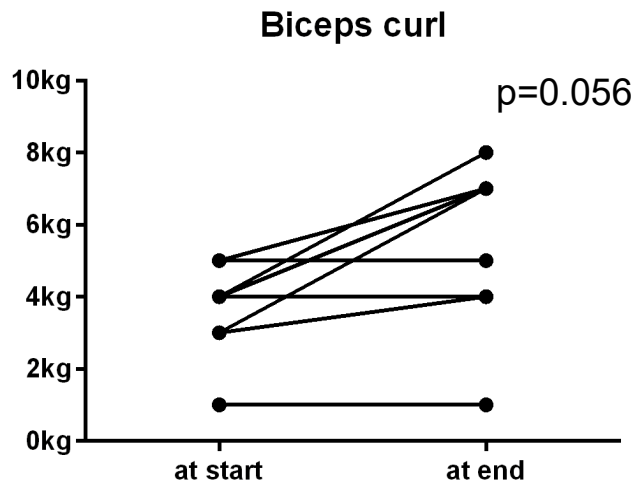
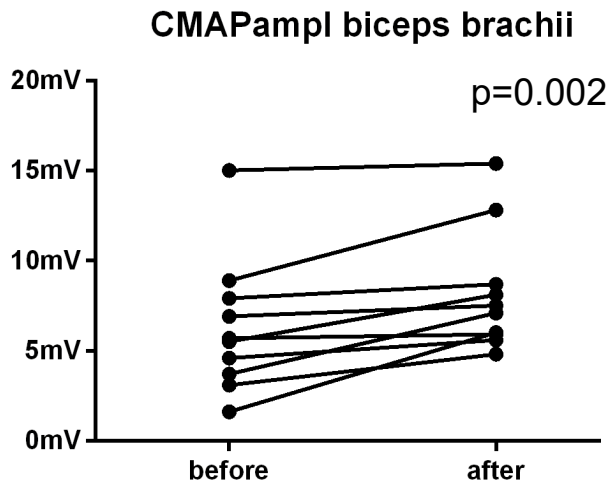
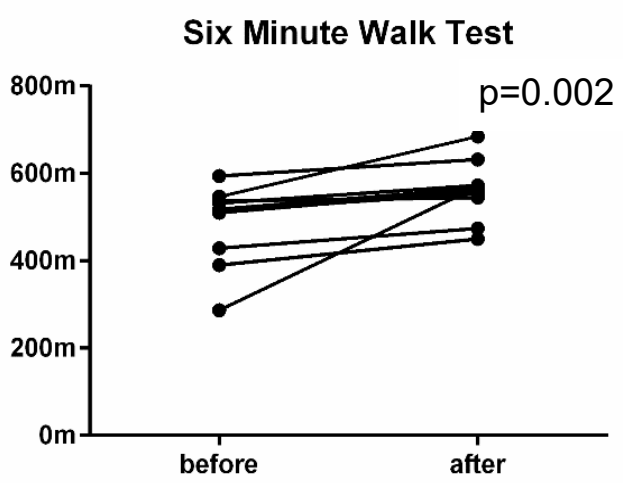
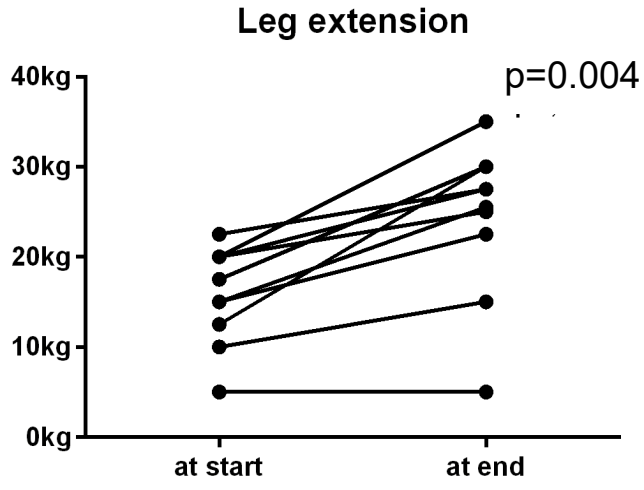
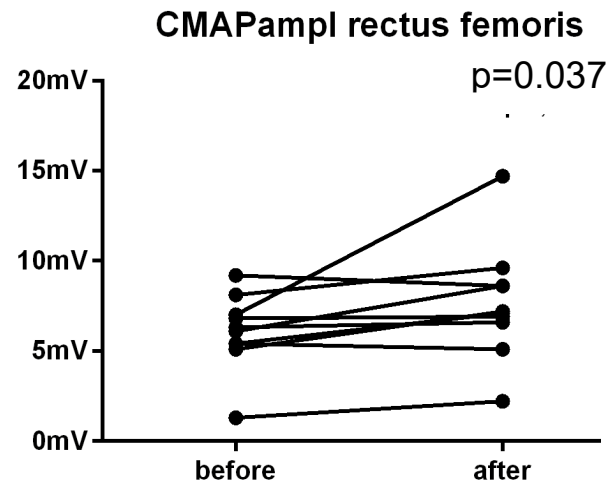
Improved muscle function

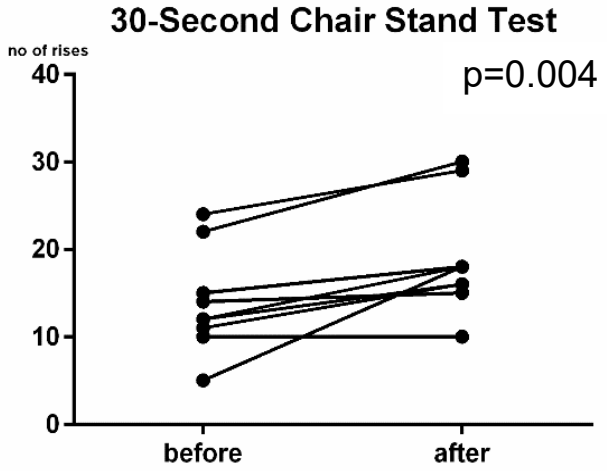












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Westerberg et al, Muscle Nerve, 2017

Improved funtional and general effects

- Improvement in 6 minute walk test (p=0.0039) and 30-Second Chair Stand Test (p=0.0078)
- Changed body composition: increased muscle mass and reduced fat mass (p=0.019)
- Improved ability to perform physical exercise (p=0.0078) according to ESES
- No change in body weight and BMI
- Reduced serum microRNA miR-150-5p and miR-21-5p
- No abnormal increase of muscle enzymes (CK, myoglobin)

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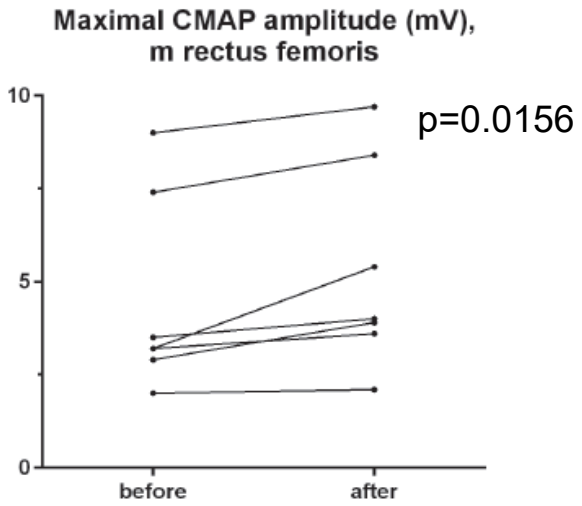
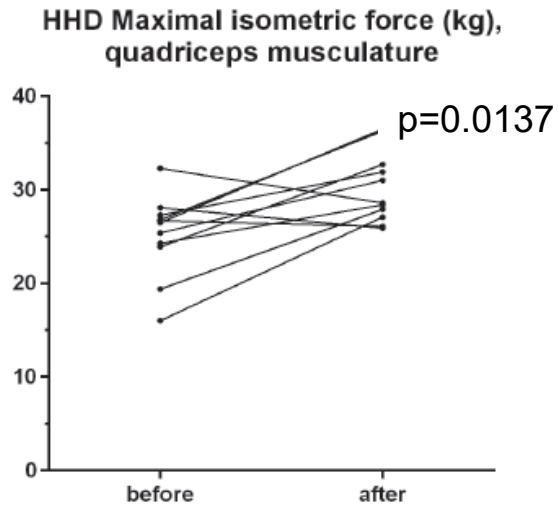
Westerberg et al, Muscle Nerve, 2017

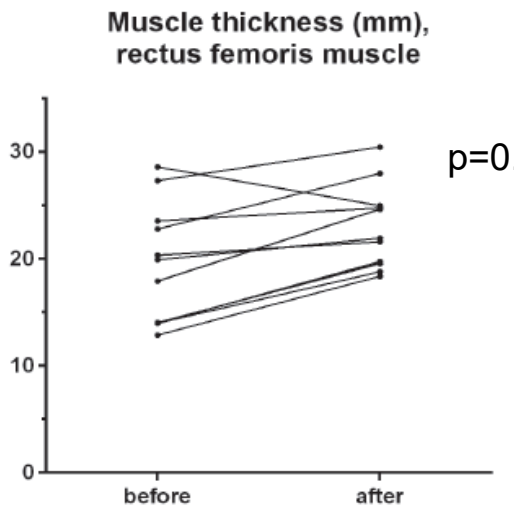
Improved leg muscle function



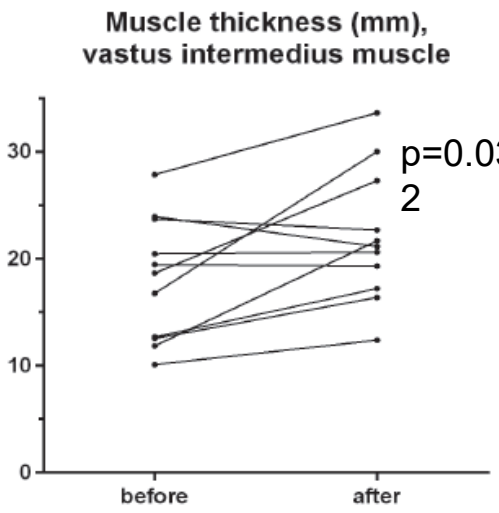
p=0.0156



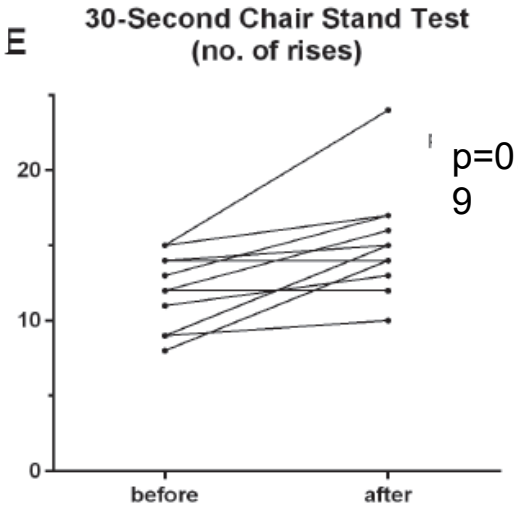
p=0.0137



p=0.0098



p=0.034
2



p=0.003
9

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Westerberg et al, Medicine, 2018

The first randomized controlled trial of exercise in MG

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 31 (2021) 726–735

www.elsevier.com/locate/nmd

Home-based exercise in autoimmune myasthenia gravis: A randomized controlled trial

S Birnbaum[a], R Porcher[b], P Portero[c], B Clair[d], S Demeret[d], B Eymard[c], M Gargiulo[a], E Louët[a], S Berrih-Aknin[a], R Le Panse[c], P Aegerter[d], JY Hogrel[a], T Sharshar[f,*], the MGEX Study Group[#]

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- The aim of this study was to determine whether exercise as an adjunct therapy is well tolerated and can improve health-related quality of life (HRQoL) in stabilized, generalized autoimmune myasthenia gravis (gMG).

- Parallel-group, multi-center prospective RCT using computer-generated block randomization.

- Adults with stabilized, generalized MG, and no contra-indication to exercise, were eligible.

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Birnbaum et al, Neuromus Dism 2021

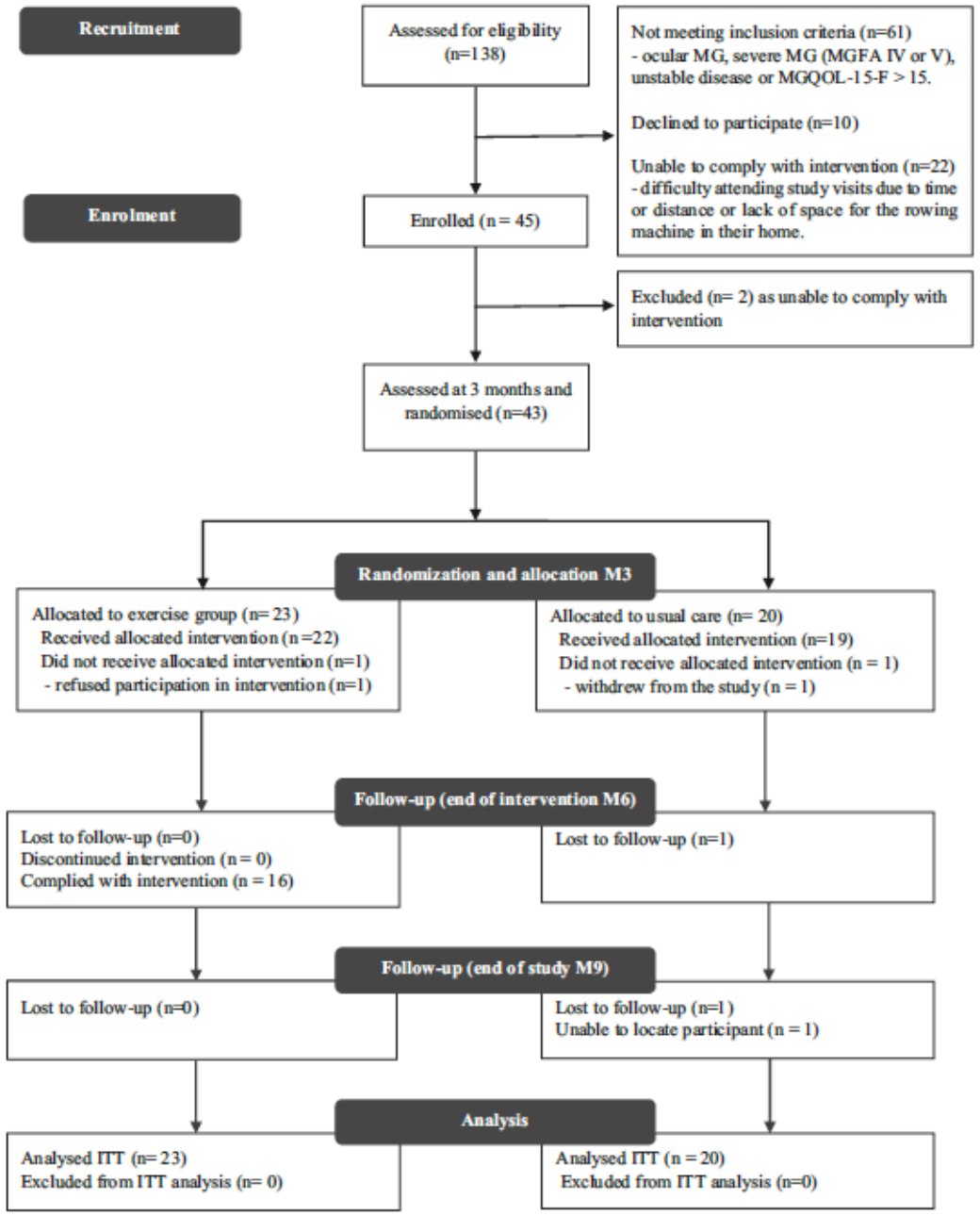

Fig. 1. Participant flow CONSORT diagram. ITT: intention-to-treat.

- Participants received usual care alone or usual care and exercise.
- The exercise intervention consisted of 3-weekly 40 min sessions of an unsupervised, moderate-intensity home rowing program over 3 months.

Birnbaum et al, Neuromusc Dis 2021

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RESULTS

- The primary endpoint was the change in health-related quality of life from randomization to post-intervention.

- Although exercise was well tolerated, the intention-to-treat analysis revealed no evidence of improved health-related quality of life compared to usual care

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Birnbaum et al, Neuromusc Dis 2021

Pragmatic study of tailored gym training for generalized MG

- Pilot study 6 months with personal trainer (PT)
- 8 patients with generalized MG
- Each patient obtained an individualized physical exercise program designed by PT, in a public gym

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AR Punga et al, manuscript

PAT #	SEX/AGE	DUR (Y)	WEIGHT/ BMI	MGFA CLASS	ANTIBODY SUBTYPE	MG MEDICATIONS	CONCOMITANT DISORDERS
1	F/32	4	59/ 19.7	IIB	AChR	Mestinon	None
2	F/71	5	67/ 25.2	IIA	AChR	Mestinon prednisolon 10 mg	Hypertension, astma
3	M/84	22	85/ 26.5	IIA	AChR	Mestinon	Spinal stenosis, cardiovascular disease
4	M/76	34	77/ 24.3	IIA	Seroneg	Prednisolon 10 mg	Osteoporosis
5	F/58	12	87/ 30.8	IIA	MuSK	Rituximab Prednisolon 5 mg	Diabetes type II
6	F/31	15	64/ 21.9	IIB	AChR	Terbutaline Prednisolon 5 mg	None
7	F/34	8	80/ 26.7	IIA	AChR	None	None

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Examples of patients

Patient	Medication	Symptoms at start	Personal goal with pt	Obtained goals
Woman3 2 y	Mestinon	Poor core strength Restricted thoracic flexibility Weak buttock muscles	Restore balance by improving mobility of the thoracic spine, reduce exaggerated lordotic posture by strengthening the core, buttock and thigh muscles.	Fully obtained
Man 76 y	Prednisolon 10 mgx1	Very weak buttock and thigh muscles, quadriceps and hamstrings. Unable to perform lunges/squats	Rebuild lower limb muscle strength.	Fully obtained

Patient	Thoughts at baseline	Thoughts at 3 months	Thoughts at 6 months
Woman 32 y	"Stiff body, feeling old, pain in the upper and lower back, weak legs, difficulty taking deep breaths"	"The entire back region feels so much better. My neck worsened temporarily but then the issue resolved. Stronger legs and no problem with deep breathing"	"The entire back region still feels better. The neck feels good and strong, legs are stronger, no problem with deep breathing"
Man 76 y	"Leg muscles are very weak. Poor fitness, cannot get my pulse up"	"My leg muscles feels stronger".	"My leg muscles are considerably stronger".

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AR Punga et al, manuscript

Example of program

Program						
Cycling	Level 7	6-10 min	Level 7	6 min	Level 8	6 min
Rowing machine			level 4	5 min	Level 5	5 min
Crosstrainer			Level 5	6 min		
Kneebend against wall	3	10 sek	3	10sek		
Knee bend	2x6	TRX	2x5	5kg	3x6	6kg
Reverse plank						
Small lunge	2x6		2x3/leg	4kg		
Sit-up						
Push-up			2x4-10			
Excentric push-up			5			
Sitting row	2x6	23kg	3x8	43kg	4x8	43 kg
Lats pull						
Chest press, straight	2x6	18kg	3x8	36kg	4x10	36 kg
Chest press, upwards					2x8	23 kg
Pectoral fly maskin					4x10	16 kg
Reverse Pec-dec					3x10	23 kg
Bicepscurl			3x10	23kg	3x10	23 kg
Triceps press			3x10	23kg	3x10	23 kg
Standing rotation cable					4x10	23 kg
Leg kick			3x10	23kg	4x10	23 kg
Quadriceps curl			3x10	23kg	4x10	23-25 kg
Crunches			4x8	46kg	3x10	50 kg
Sitting leg press					3x10	82 kg

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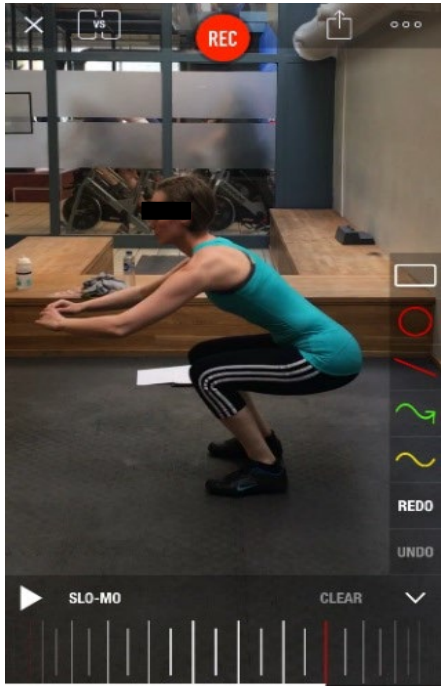

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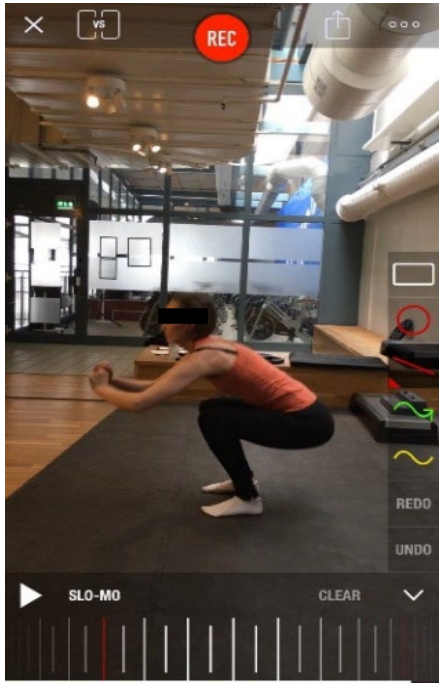

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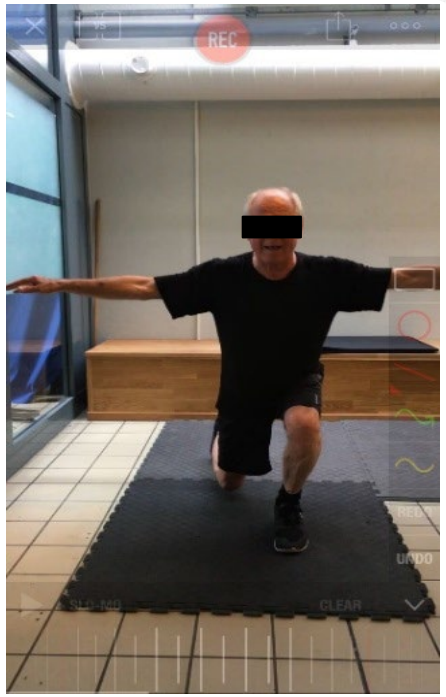

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TAKE HOME MESSAGE

- Patients with well-controlled MG can adhere safely to general exercise recommendations, including resistance training and aerobic training, without deterioration
- MG patients can indeed improve their functional muscle status as a result of aerobic and high-resistance strength training that can be individually tailored also in a gym setting
- This knowledge is important in order to establish collective as well as personalized guidelines on physical exercise for MG patients
- Simply being more active and reducing overall sedentary time is just as important

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Thank you for the attention!!

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