Protecting and preserving dystrophic muscle: The balance between exercise and contraction-induced muscle injury

Symposium at the Muscular Dystrophy Association (MDA) Clinical & Scientific Conference

Orlando, FL

Monday March 4, 2024

Edgewise THERAPEUTICS

Program overview

- **Introduction by Joanne Donovan**

- **John Vissing, MD, PhD**, Director, Neuromuscular Clinic and Research Unit, Department of Neurology, University of Copenhagen
  Physical Exercise and Muscle Damage in BMD

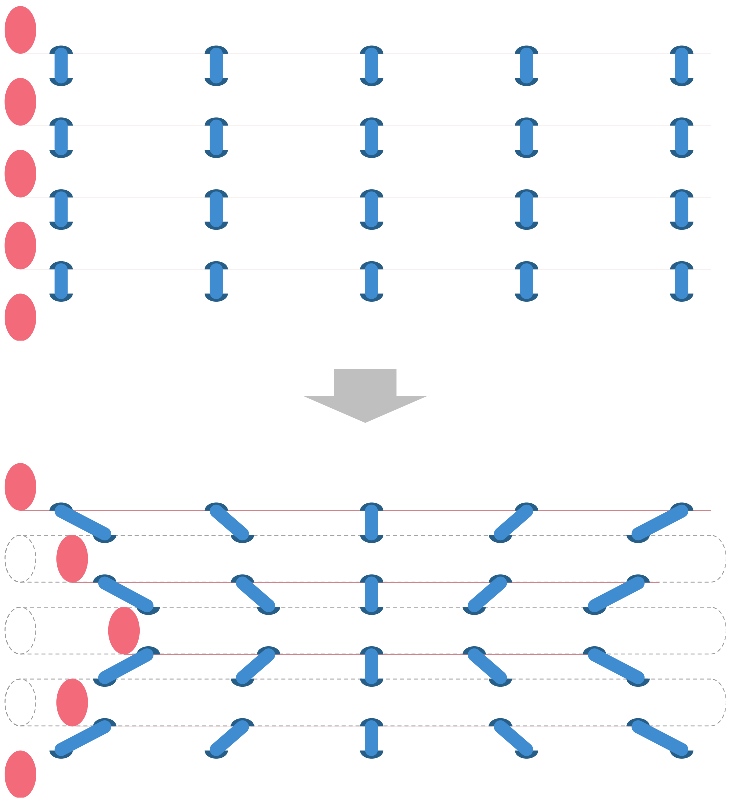
- **Tanja Taivassalo, PhD**, Associate Professor, Department of Physiology and Aging, University of Florida
  Overview of Physical Exercise in Boys with Duchenne Muscular Dystrophy

- **Joanne Donovan, MD, PhD**, Chief Medical Officer, Edgewise Therapeutics
  Targeting Protection Against Contraction-Induced Injury in BMD: An Overview of the Sevasemten (EDG-5506) Clinical Program

- **Panel Questions and Discussion**

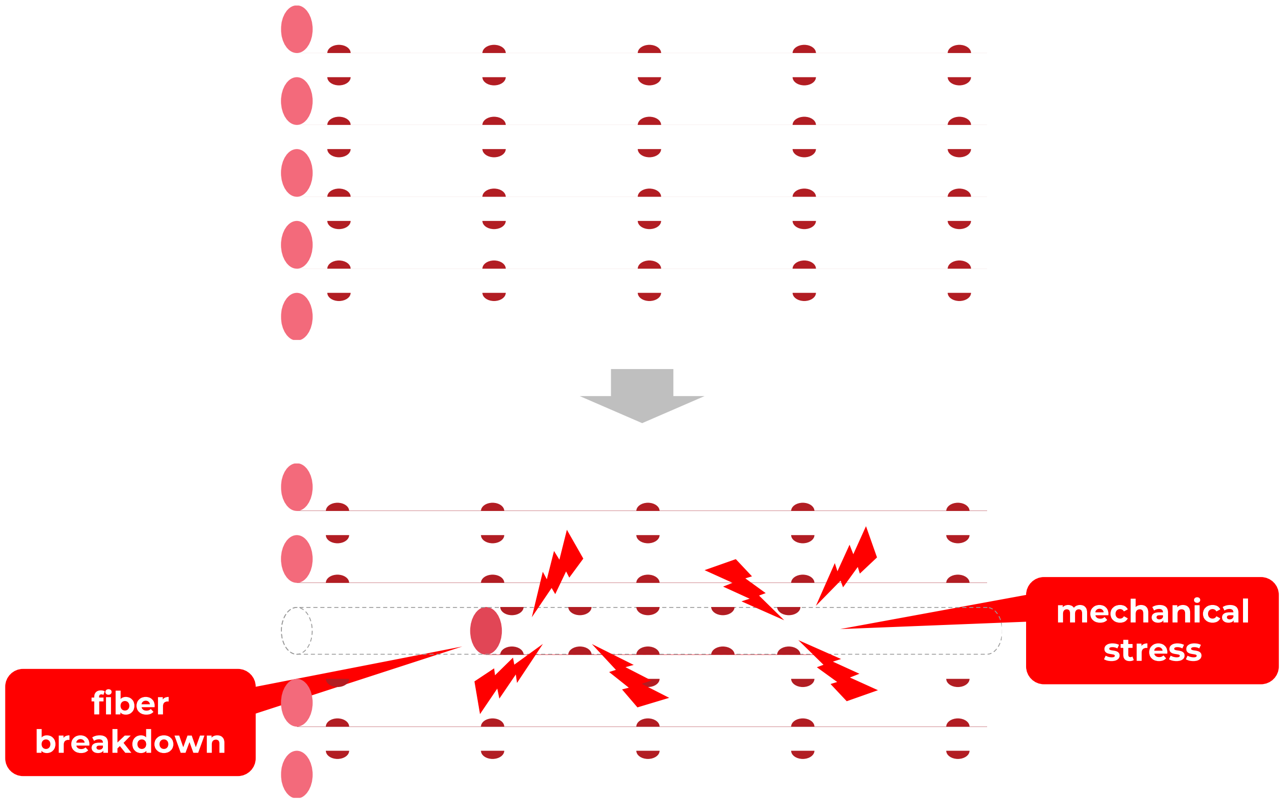
In dystrophinopathy, contraction leads to muscle damage

Healthy muscle contraction



Dystrophin connects contractile proteins to the membrane and surrounding matrix to protect against contraction-induced injury.

Dystrophic muscle contraction



Contraction-induced muscle injuries occur in the absence of full-length dystrophin.

Optimizing the level of physical activity is a delicate balance in muscular dystrophies

Prescribed exercise

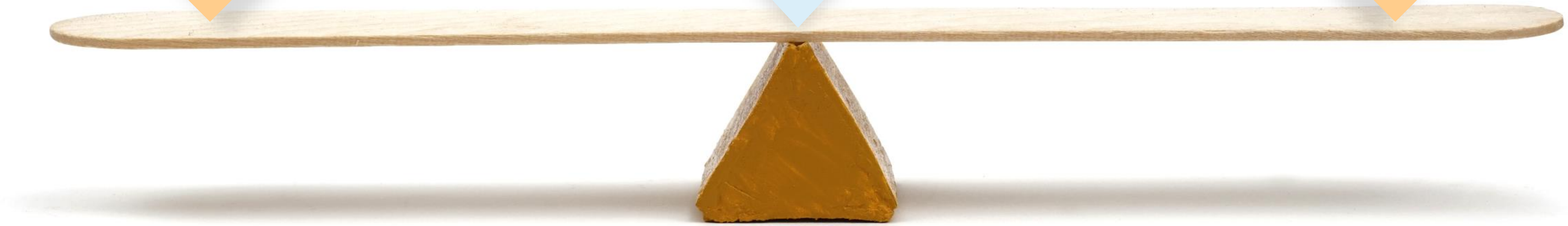
Limited muscle damage

Total immobilization

Little to no muscle damage

Excessive exercise

Injurious muscle damage



Key questions

- Since lack of dystrophin leads to contraction-induced damage in dystrophinopathies, is all muscle fiber contraction "bad" in muscular dystrophies?
- How can circulating biomarkers of muscle injury provide an understanding of contraction-induced injury in muscular dystrophies?
- Are there benefits to prescribed exercise in muscular dystrophies?
- Can targeting contraction-induced injury in muscular dystrophies with sevasemten (EDG-5506), a fast myosin inhibitor be an effective pharmacological approach in DMD and BMD?

Physical Exercise and Muscle Damage in Becker Muscular Dystrophy

John Vissing, MD, PhD

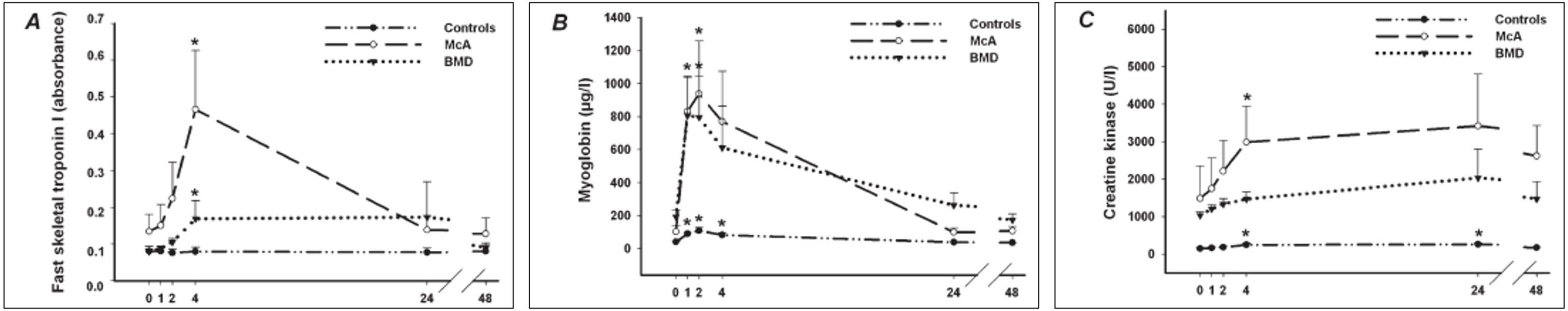
Director, Copenhagen Neuromuscular Center
Department of Neurology, University of Copenhagen

Disclosures for John Vissing

- Consultant on advisory boards for **Edgewise Therapeutics**, Roche, Sanofi Genzyme, Sarepta Therapeutics, Novartis Pharma AG, Fulcrum Therapeutics, Biogen, Lupin, Amicus, Zogenix, Regeneron, Argenx BVBA, UCB Biopharma SPRL, Arvinas, ML Biopharma, Atamyo, Horizon Therapeutics, Dyne Therapeutics
- Research, travel support, and/or speaker honoraria from Sanofi Genzyme, Alexion Pharmaceuticals, **Edgewise Therapeutics**, Fulcrum Therapeutics, and UCB Biopharma SPRL
- Principal investigator in clinical trials for **Edgewise Therapeutics**, Sanofi Genzyme, Roche, Horizon Therapeutics, Argenx BVBA, Novartis Pharma AG, Alexion Pharmaceuticals, UCB Biopharma SPRL, Genethon, ML Biopharma, Reneo Pharma, Pharnext, Janssen Pharmaceutical, Khondrion, Regeneron, and Dynacure SAS, Janssen

Injury biomarkers with exercise in Becker and McArdle disease

20 mins, 95% VO_2 Max bike exercise followed by 40 leg presses at 80% 1-RM max



Source: Figure adapted from Dahlqvist JR, Voss LG, Lauridsen T, Krag TO, Vissing J. A pilot study of muscle plasma protein changes after exercise. *Muscle Nerve*. 2014;49(2):261-266. doi:10.1002/mus.23909

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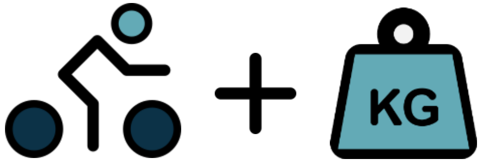
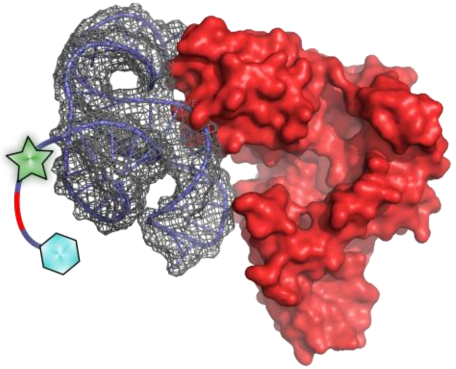
Methodology: Exercise challenge and SomaScan® analysis



Blood Plasma →



<u>SomaScan</u>
Modified aptamer-based assay for ~7000 circulating proteins

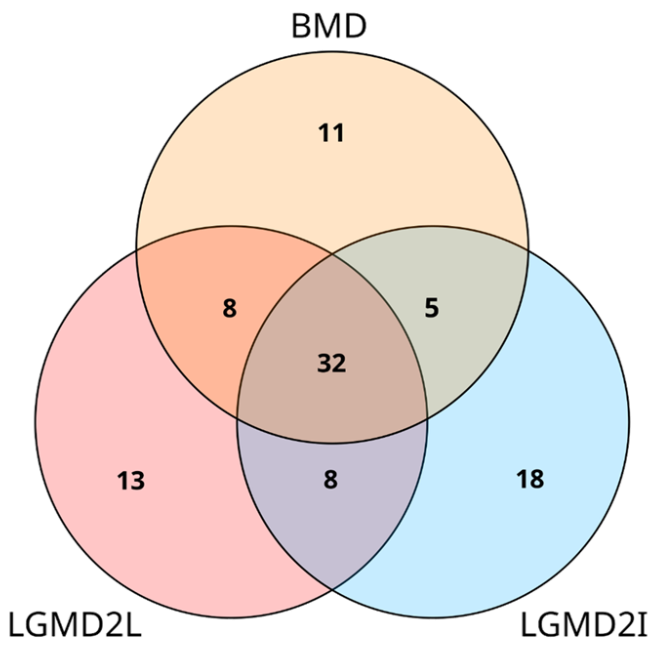
Assessment	10 min rest	Exercise Protocol	Post-Exercise Observation
VO_{2max} Test *Quadricep 1-rep max ID*		***Cycle*** *5x 4 min @ 95% VO_2max* ***Strength*** *4x, 10-rep @ 80% 1-rep max*	***0 hr*** · ***2 hr*** · ***4 hr*** · ***24 hr***

PI: Mads Stemmerik (CMRC, Rigshospitalet, Copenhagen)
Ben Barthel (Edgewise Therapeutics)

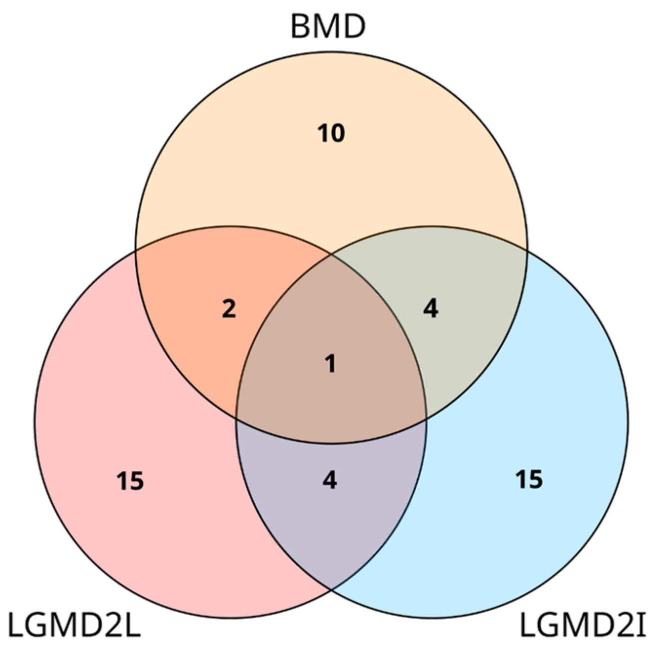
Participants and demographics

	N	% Male	Age (yrs)	BMI	$VO2_{Max}$ (mL min^{-1} kg^{-1})	WMax (J sec^{-1})	% HR_{Max}	1-RM (kg)
Control	9	77.8	44 ± 13	24.5 ± 2.4	38.8 ± 3.5	278 ± 53	100 ± 7.2	96 ± 26
BMD	9	100	33 ± 7	23.6 ± 2.9	22.9 ± 8.5	113 ± 107	94.4 ± 8.9	38 ± 41
LGMD2I	8	12.5	30 ± 10	22.6 ± 2.7	26.1 ± 8.5	132 ± 71	95.4 ± 5.3	49 ± 29
LGMD2L	9	66.7	52 ± 9	27.1 ± 4.4	27.6 ± 11.4	176 ± 89	96.6 ± 9.8	70 ± 44

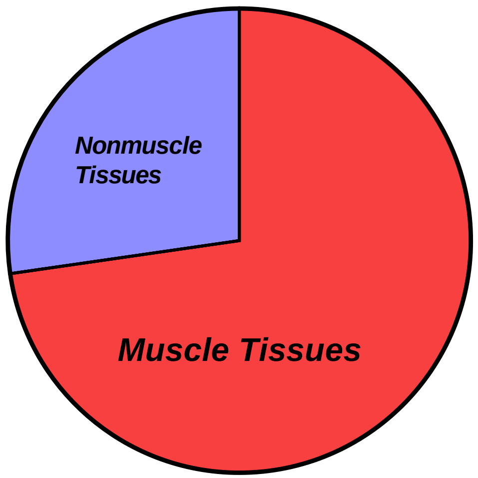
Identification of a shared pre-exercise baseline signature



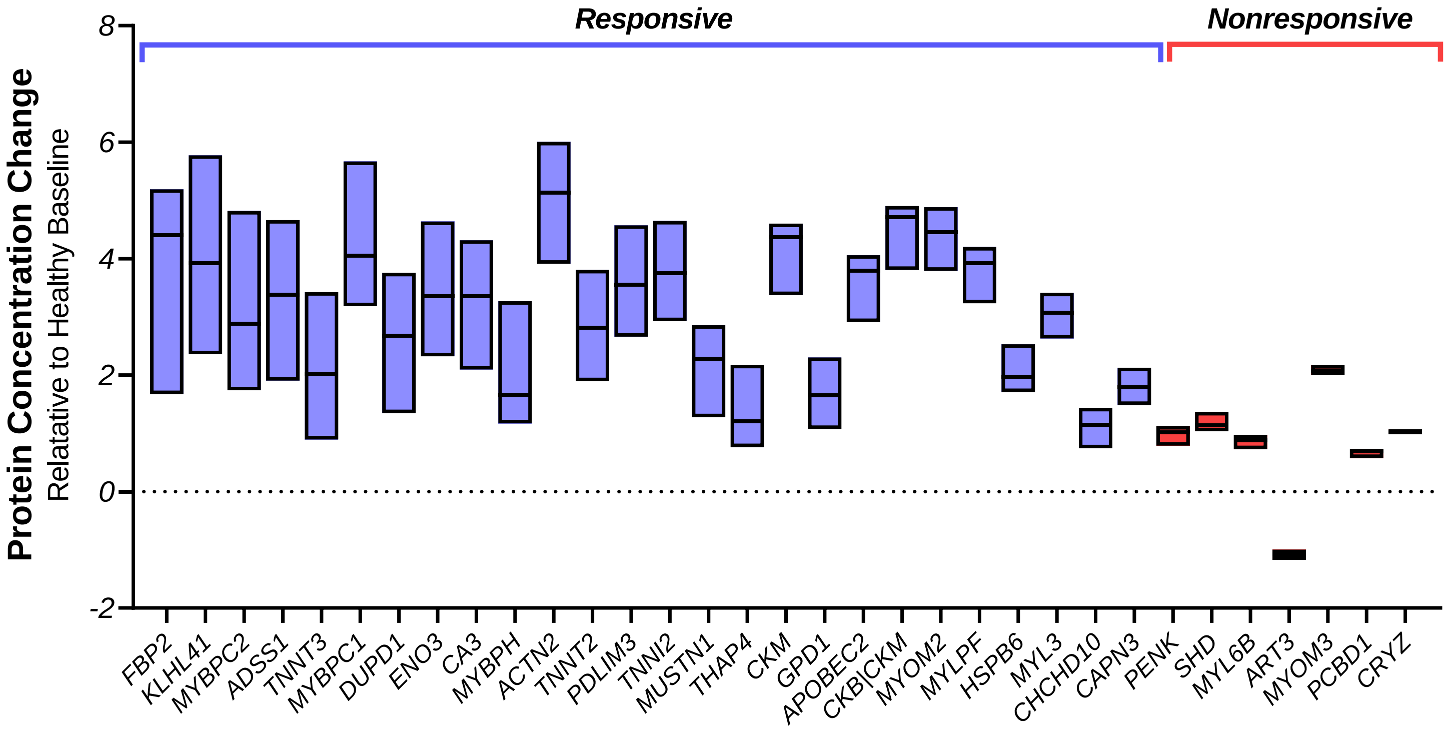
32 common elevated proteins



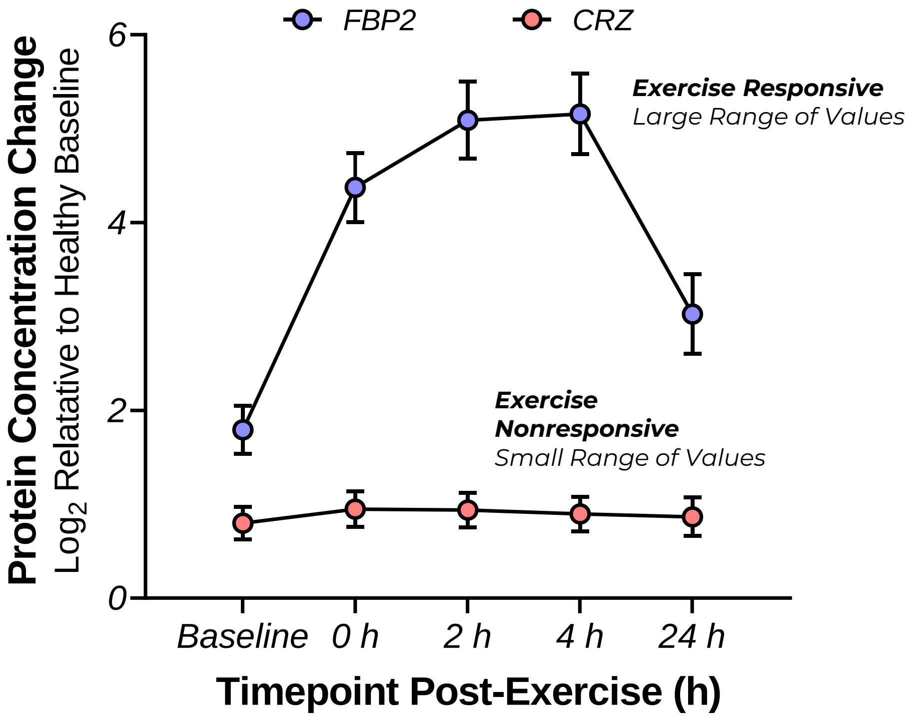
1 common decreased protein
(Ecto-ADP-Ribosyltransferase)



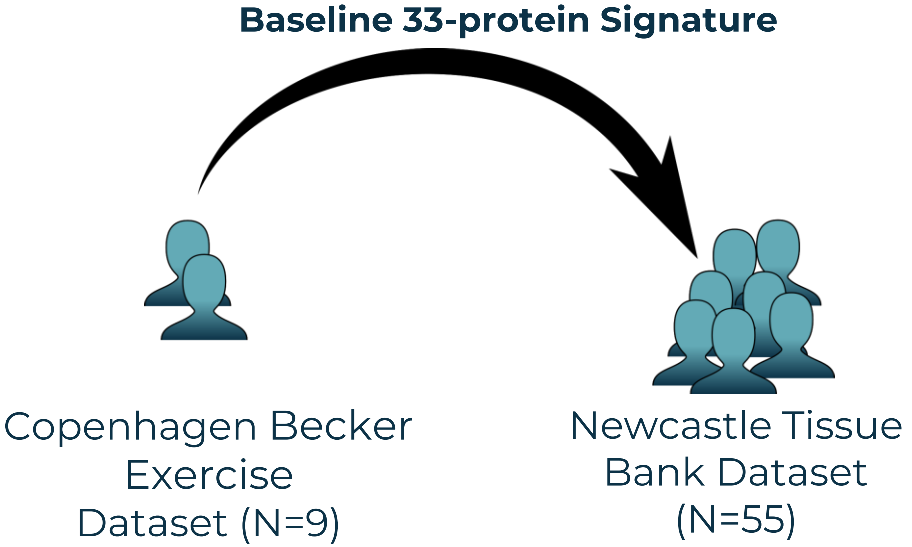
Exercise dynamics of baseline signature proteins

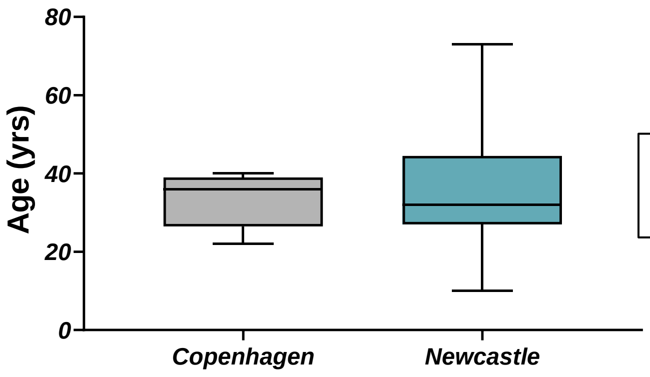


Most and least responsive proteins

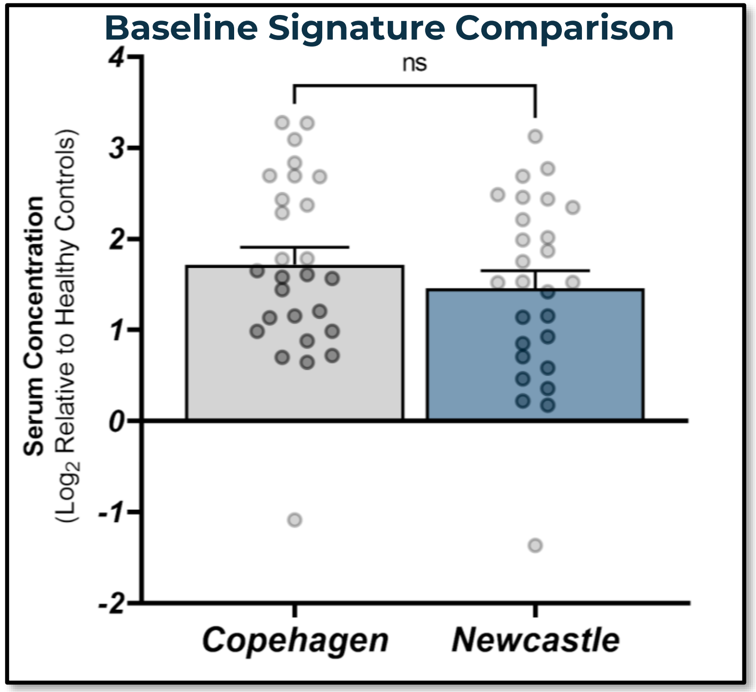


Validation of the universal baseline signature using Becker data





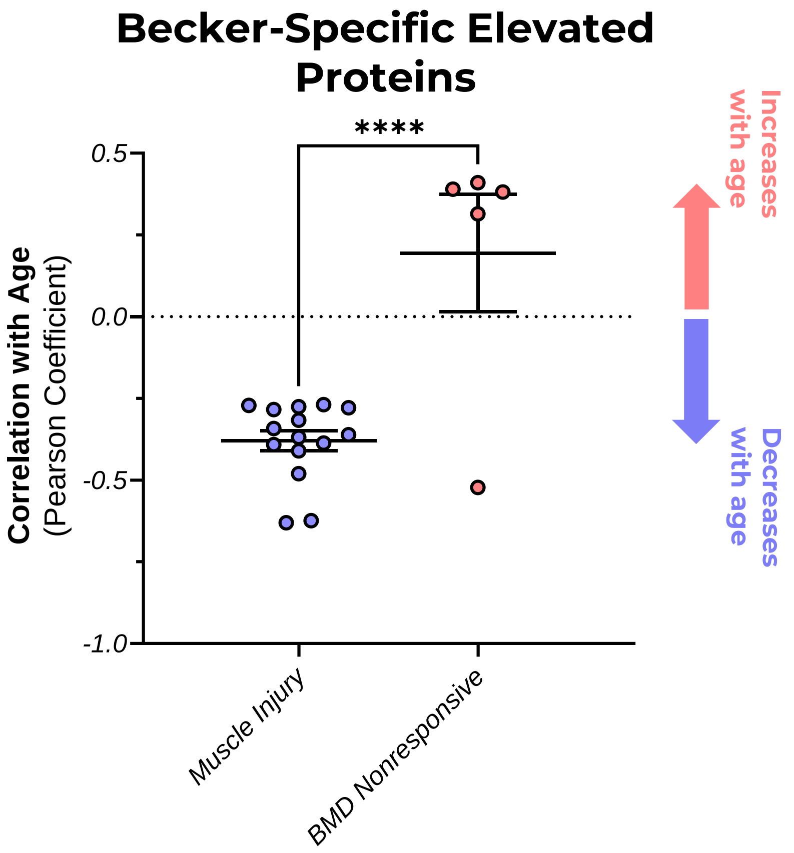
Larger age range in Newcastle set

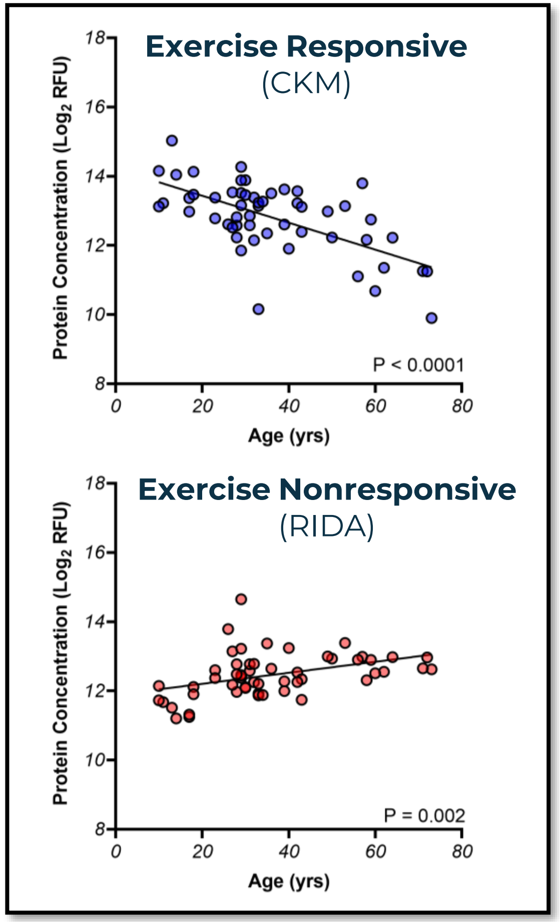


Similar pattern of elevation and decrease for universal signature

Exercise responsive and nonresponsive proteins show opposing age correlations

30 - 50% of responsive and nonresponsive proteins exhibit <u>significant correlations with age</u>



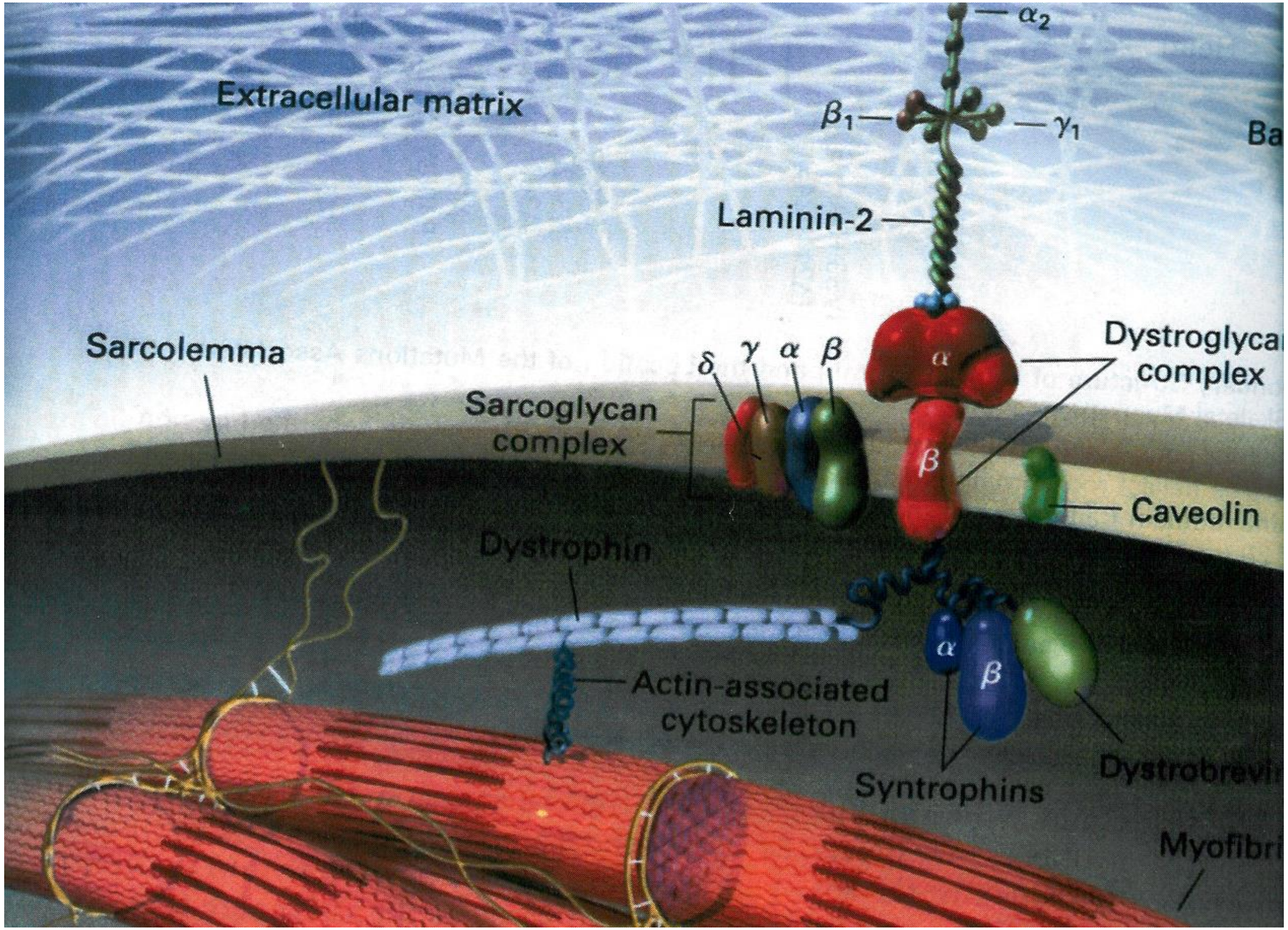


Conclusions and future questions

- We have identified and validated a common signature of biomarkers that are elevated in several muscular dystrophies, including Becker
- Exercise responsive and nonresponsive markers exhibit opposite directional correlations with age
- Can exercise nonresponsive biomarkers be leveraged as more stable indicators of disease progression and/or treatment effects over long time-frames?
- Can exercise responsive biomarkers be used as a more sensitive biomarker set to measure muscle injury in an interventional trial?

The findings show that you can certainly induce muscle damage by exercise in Becker, but does that mean that exercise should be avoided?

Training in dystrophinopathies

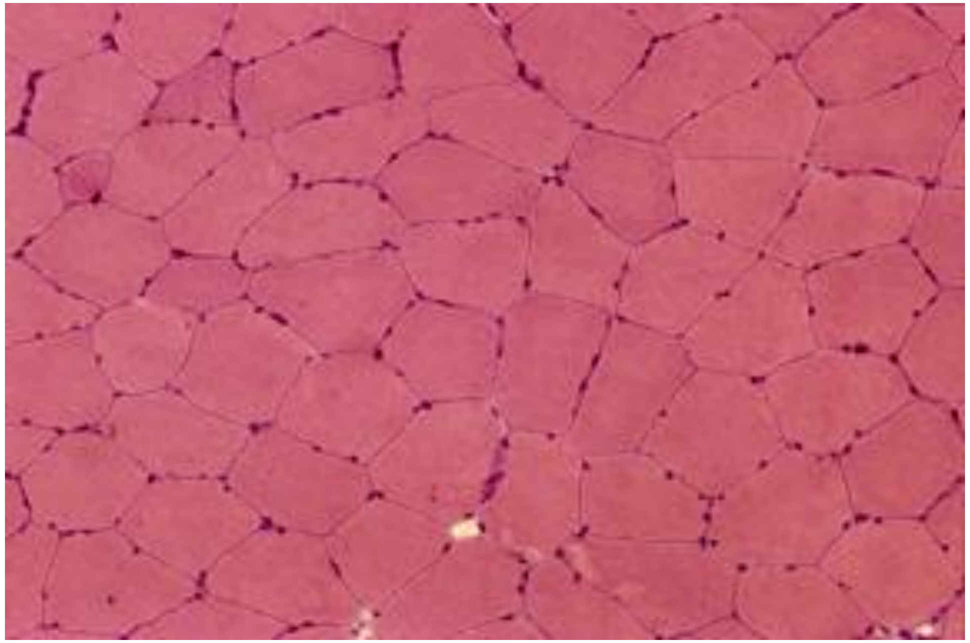
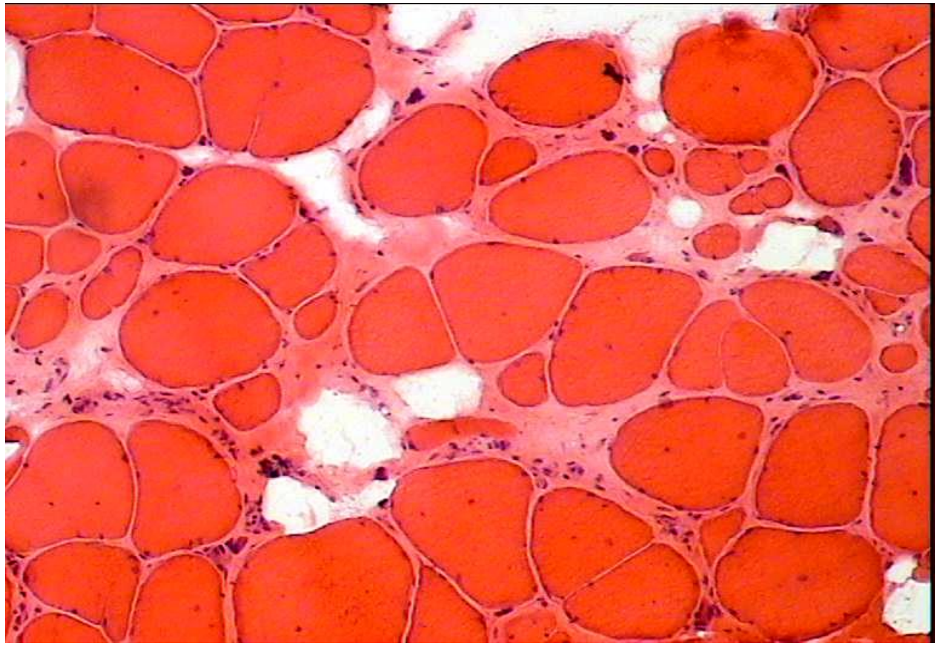


Animal studies have suggested a potential deleterious effect of training in muscular dystrophies

Sacco P, Jones DA, Dick JR, Vrbová G. Contractile properties and susceptibility to exercise-induced damage of normal and mdx mouse tibialis anterior muscle. *Clin Sci (Lond).* 1992;82(2):227-236. doi:10.1042/cs0820227.

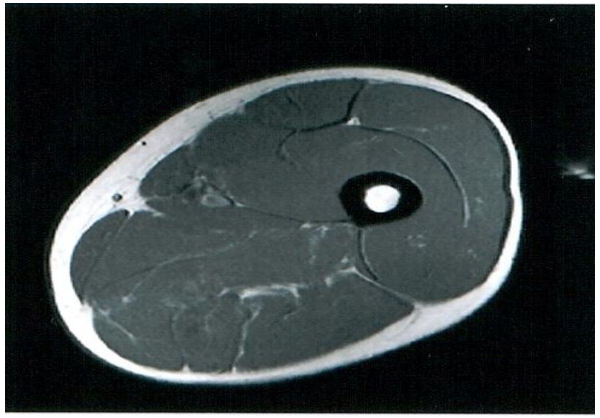
Carter GT, Abresch RT, Fowler WM Jr. Adaptations to exercise training and contraction-induced muscle injury in animal models of muscular dystrophy. *Am J Phys Med Rehabil.* 2002;81(11 Suppl):S151-S161. doi:10.1097/00002060-200211001-00016.

Is it safe to train a sick muscle?

Healthy muscle

Dystrophic muscle

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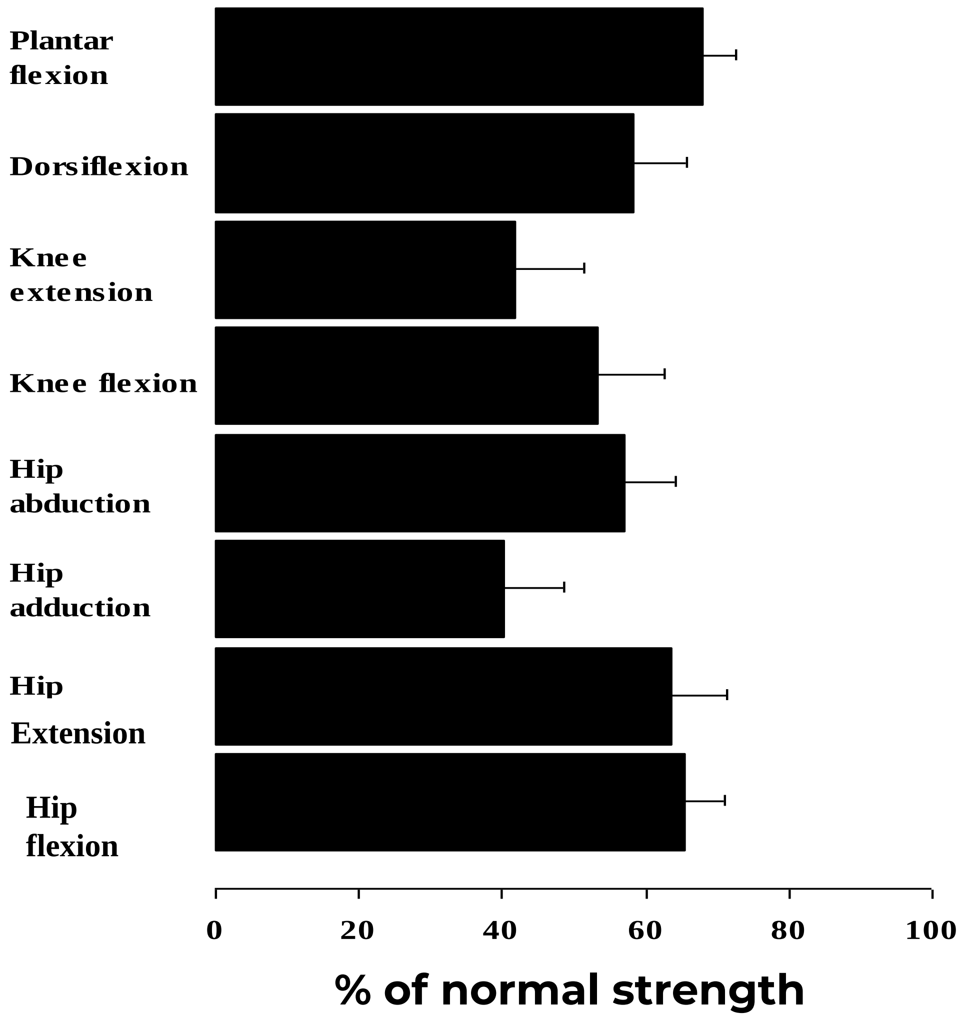
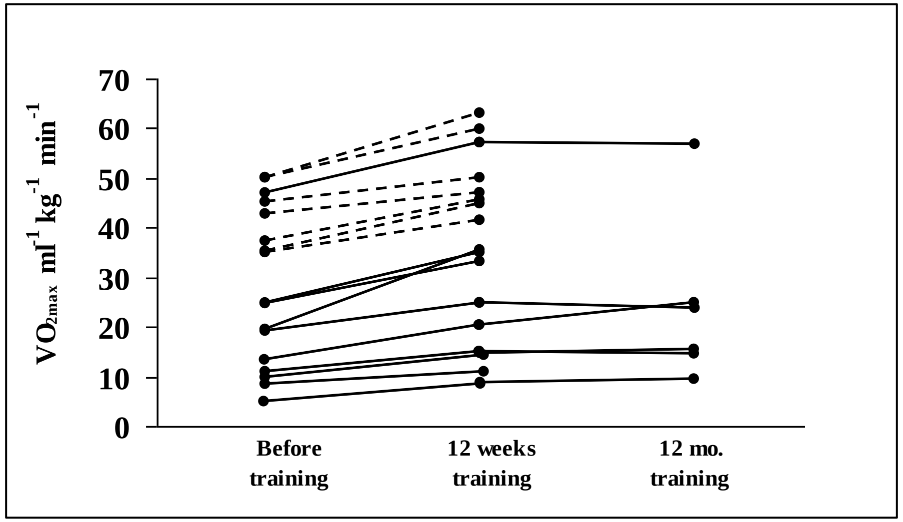
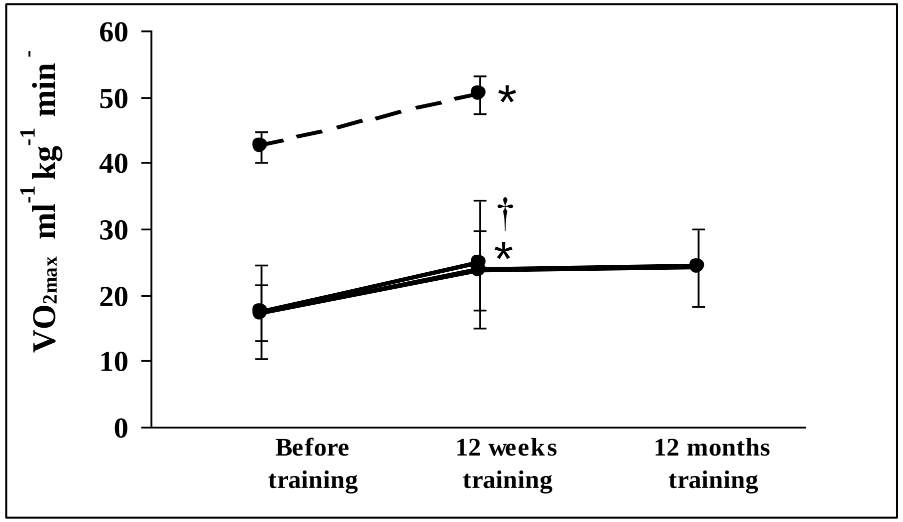
12-week and 1-year aerobic exercise training in 11 men with Becker

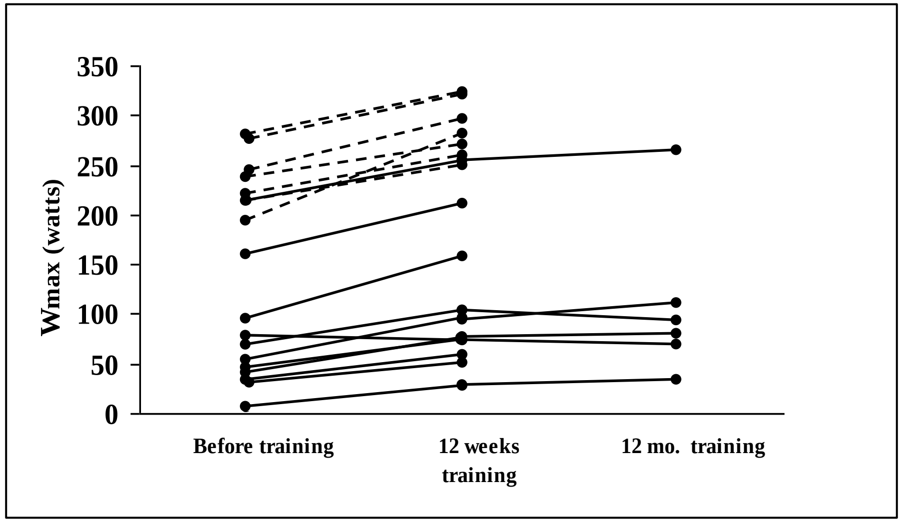
Patients included in this study had a relatively mild Becker phenotype

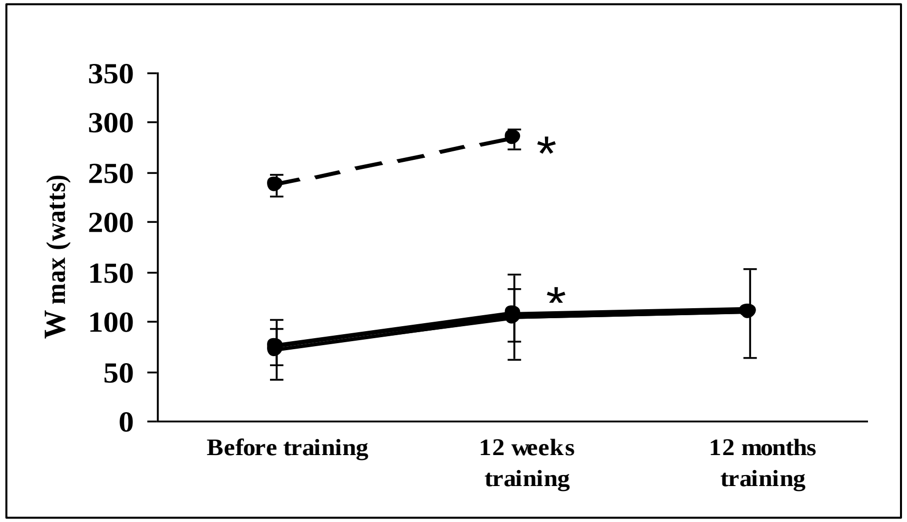


3-month and 12-month aerobic training in Becker









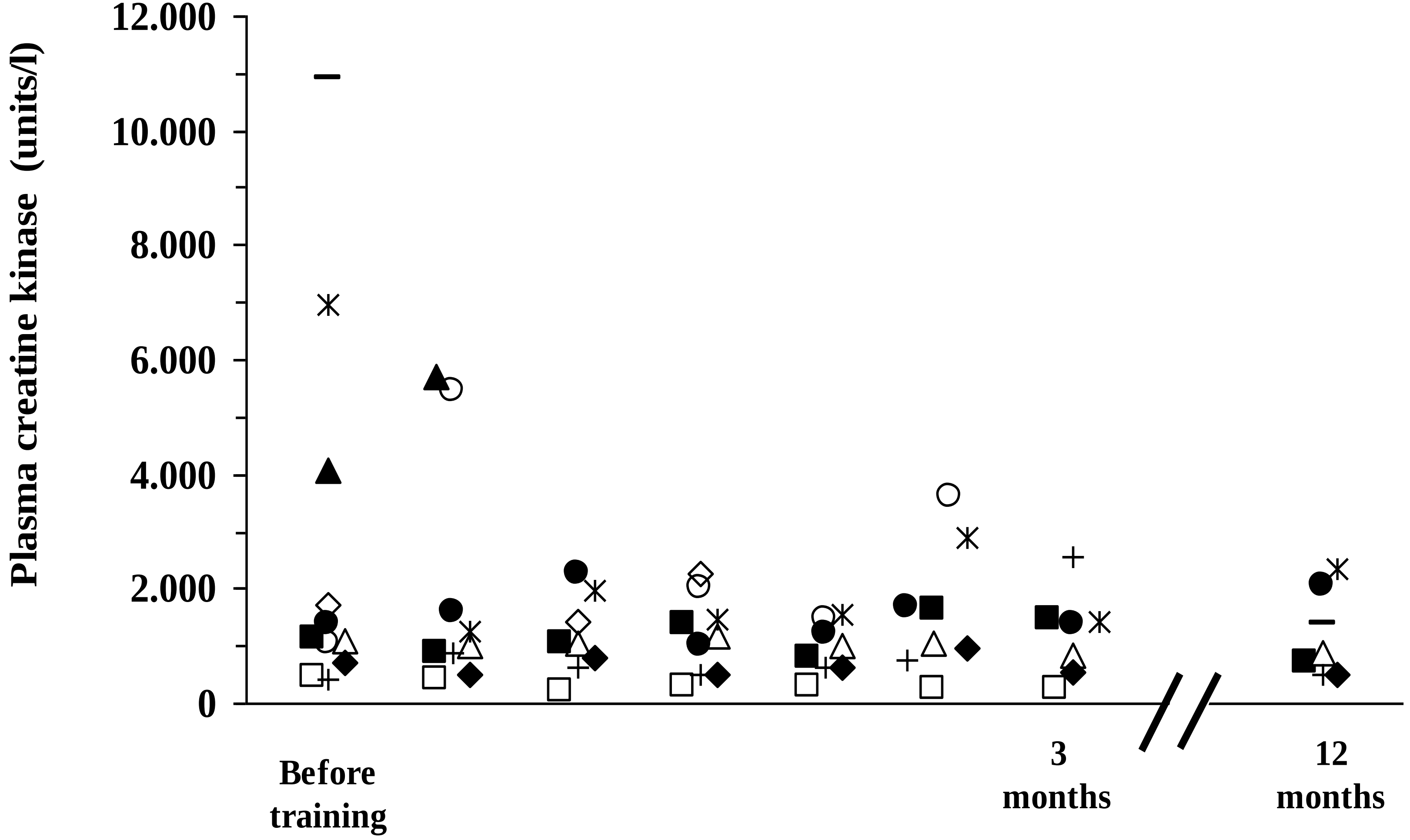
Reference: Sveen ML, et al. Endurance training improves fitness and strength in patients with Becker muscular dystrophy. *Brain*. 2008;131(Pt 11):2824-2831. doi:10.1093/brain/awn189.

Effect of aerobic training on strength in leg muscles of Becker patients

	3 mo. n=10	3 mo. n=6	12 mo. n=6
Hip Flexion	8 ± 4	7 ± 3	14 ± 8 *
Hip Extension	2 ± 4	3 ± 7	2 ± 7
Hip Adduction	-6 ± 27	14 ± 7	15 ± 8
Hip Abduction	22 ± 7 *	18 ± 6 *	13 ± 7 *
Knee Flexion	5 ± 11	16 ± 4 *	13 ± 8
Knee Extension	14 ± 12	31 ± 15 *	40 ± 15 *
Foot Dorsiflexion	13 ± 6 *	15 ± 4 *	25 ± 5 *
Foot Plantar flexion	20 ± 4 *	16 ± 4 *	21 ± 5 *

Significance is corrected for 5% intra-observer variance. * $p < 0.05$.

Plasma creatine kinase before and during training in 11 patients with Becker



Training Becker: Conclusions

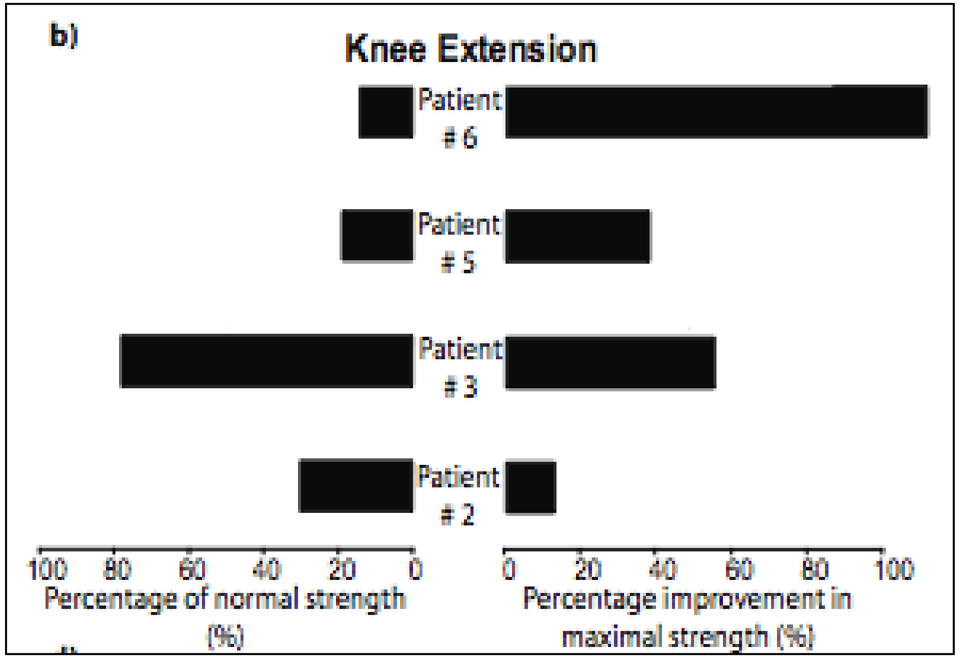
- Aerobic training is safe
- Aerobic training improves endurance and muscle strength
- The effect is long-lasting

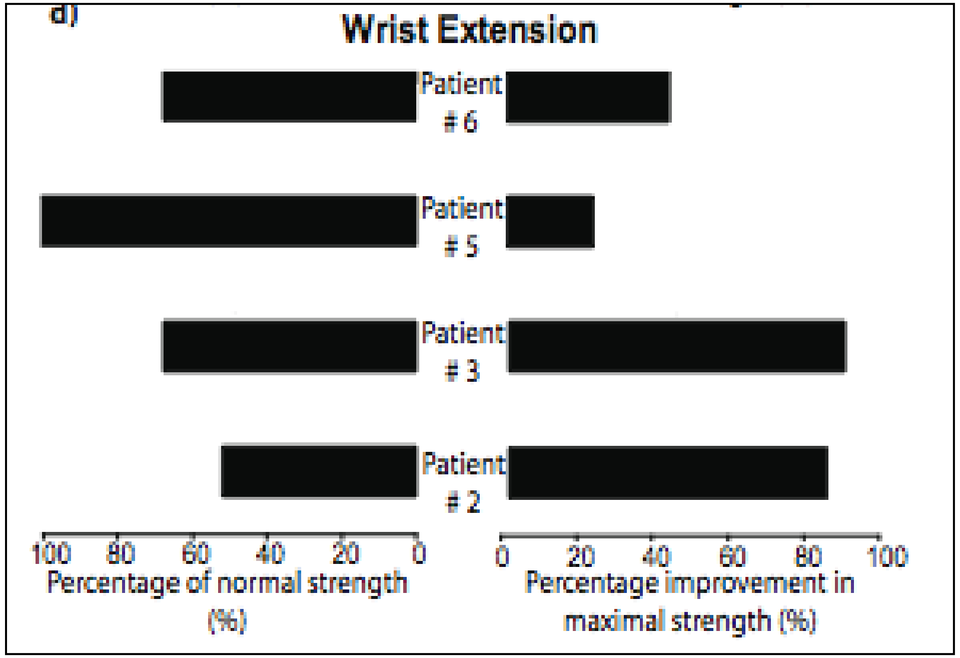
Reference: Sveen ML, et al. Endurance training improves fitness and strength in patients with Becker muscular dystrophy. *Brain*. 2008;131(Pt 11):2824-2831. doi:10.1093/brain/awn189.

Weak patients: can we train them?

- It is generally believed that muscles weaker than 10% of normal are not trainable

6 months of strength training in LGMD2I and Becker

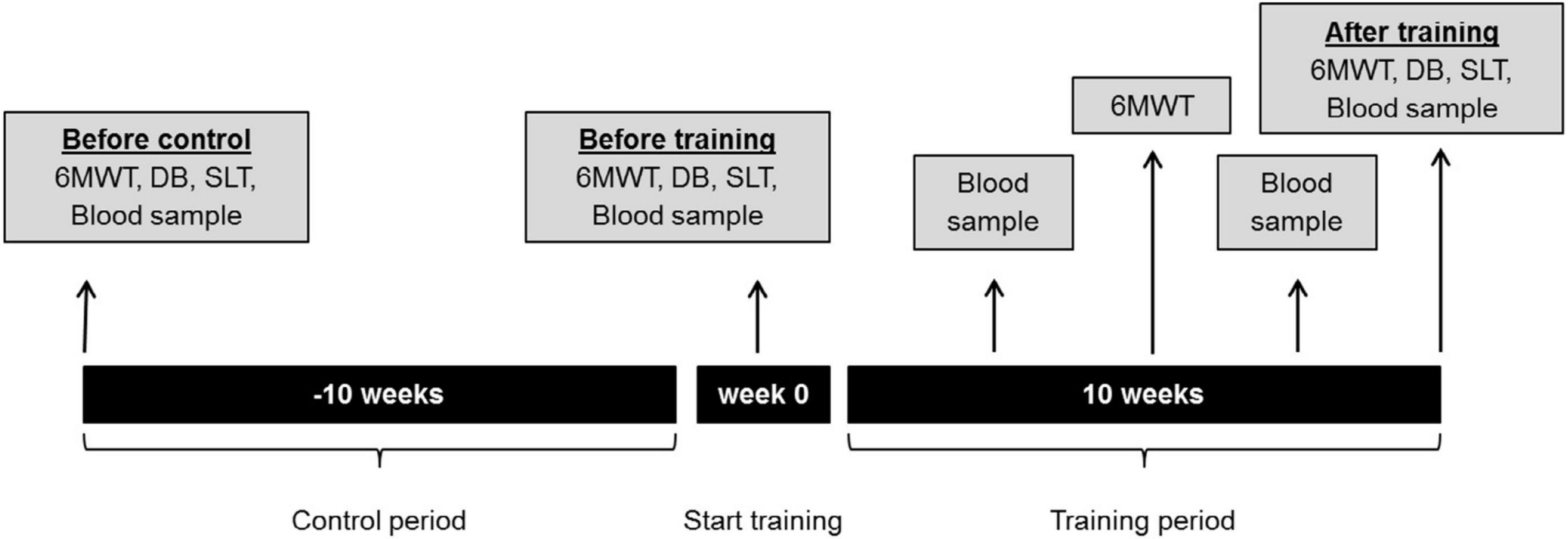




Reference: Resistance training in patients with Limb Girdle and Becker muscular dystrophies. Sveen ML, Andersen SP, Ingelsrud LH, Blichter S, Olsen NE, Jønck S, Krag TO, Vissing J. *Muscle Nerve*. 2013;47(2): 163-169. doi: 10.1002/mus.23491.

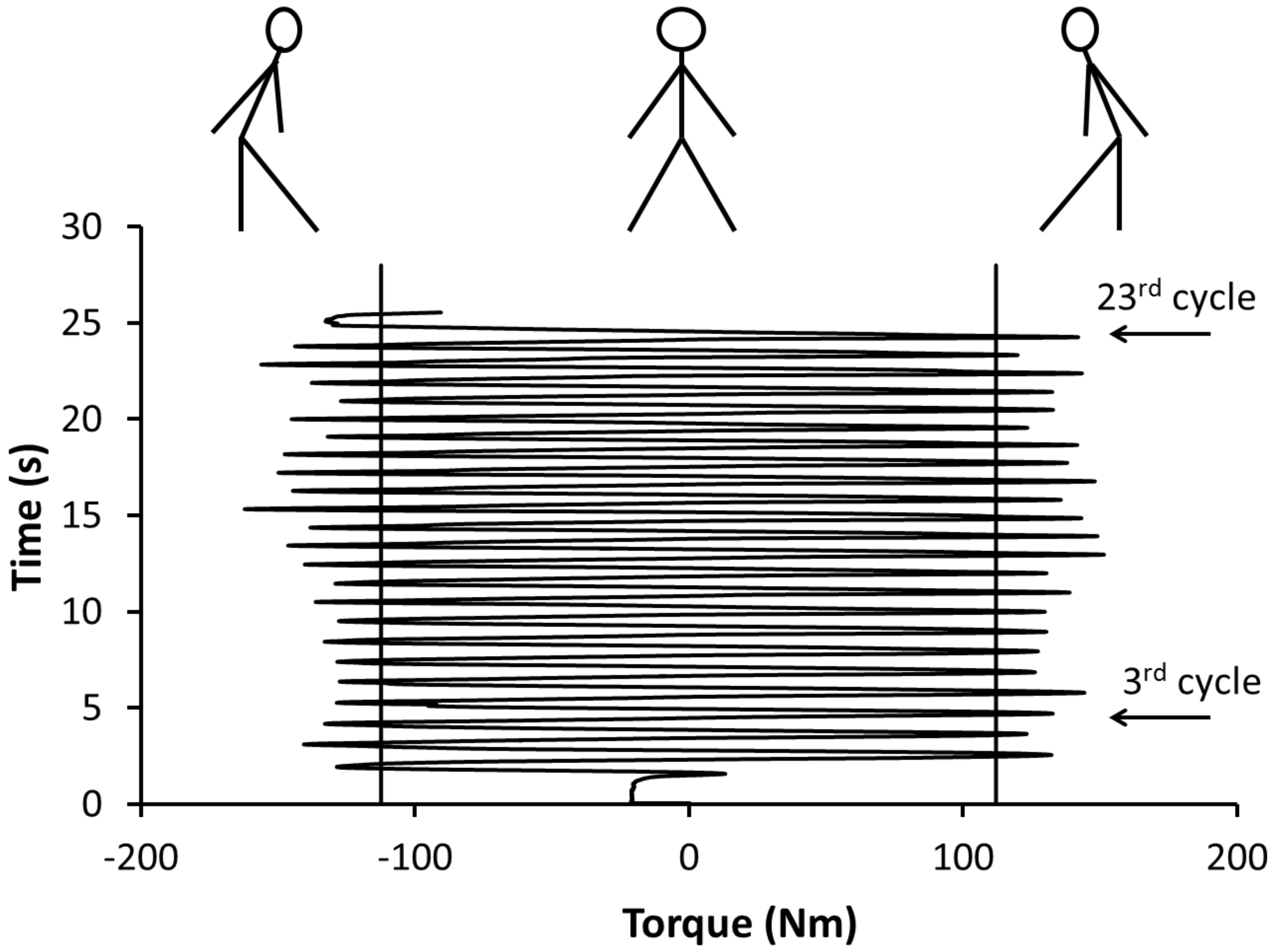
Patient Using an Antigravity Treadmill

Timetable for study design

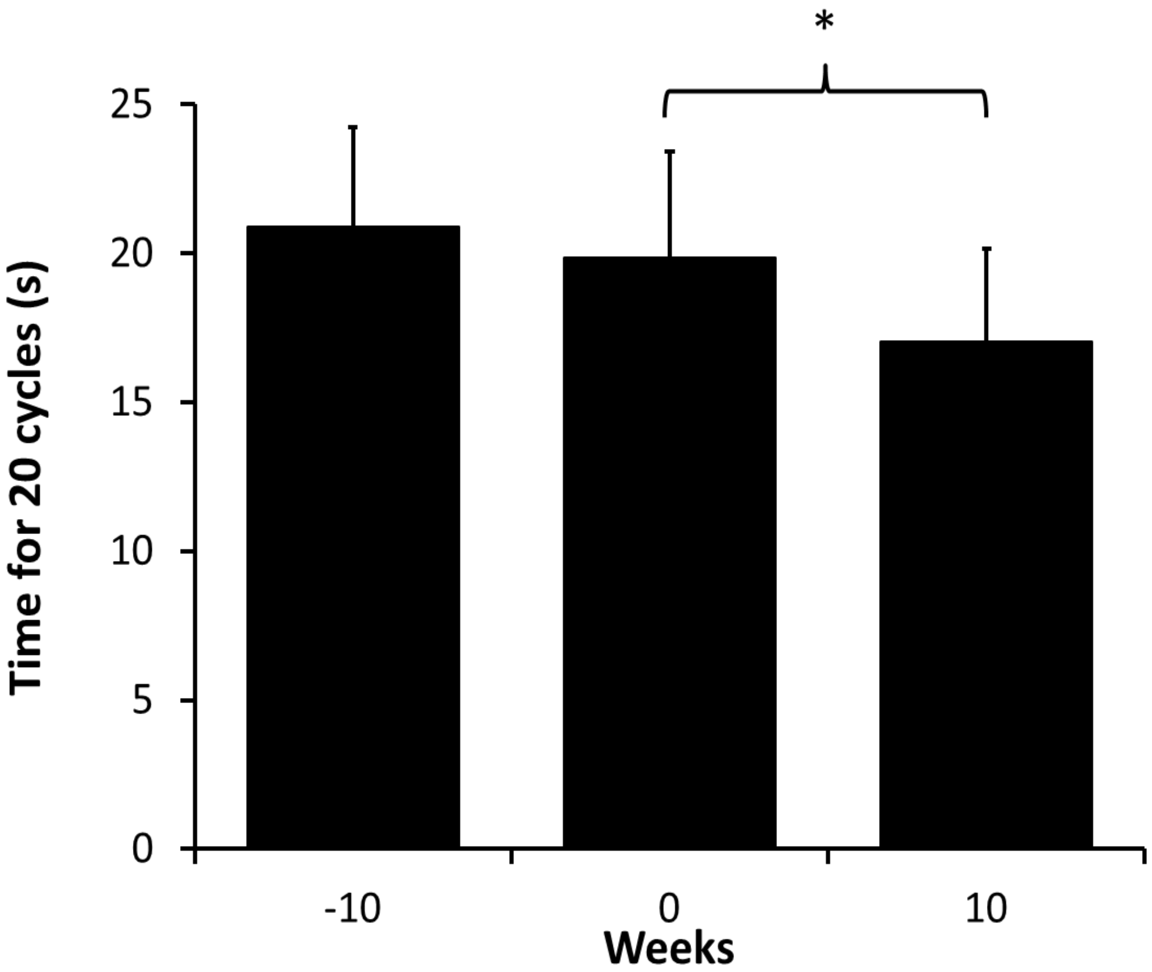


Reference: Berthelsen MP, Husu E, Chistensen SB, Prahm KP, Vissing J, Jensen BR. Anti-gravity training improves walking capacity and postural balance in patients with muscular dystrophy. *Neuromuscul Disord.* 2014; 24(6): 492-8. doi: 10.1016/j.nmd.2014.03.001.

Dynamic postural balance test



Training effects on dynamic postural balance



Reference: Berthelsen MP, Husu E, Chistensen SB, Prahm KP, Vissing J, Jensen BR. Anti-gravity training improves walking capacity and postural balance in patients with muscular dystrophy. *Neuromuscul Disord.* 2014; 24(6): 492-8. doi: 10.1016/j.nmd.2014.03.001.

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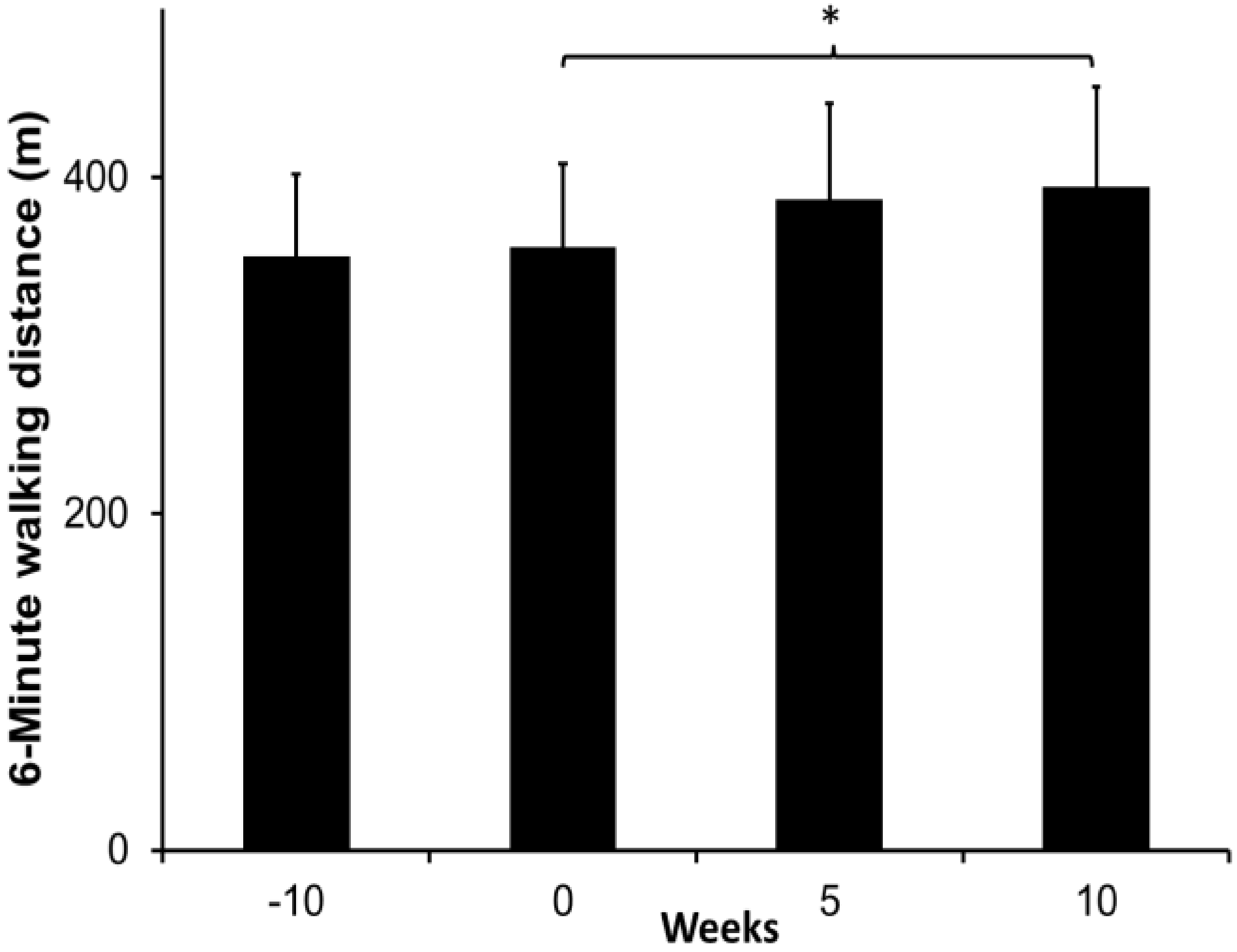
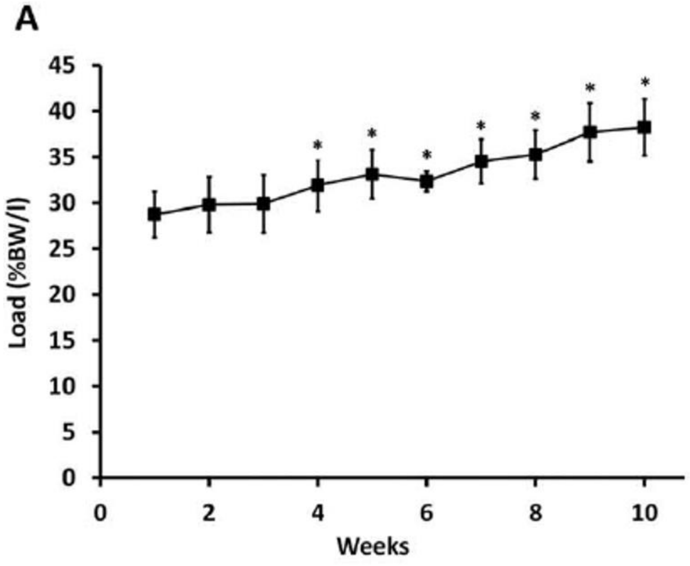
Training effects on 6-min walking distance



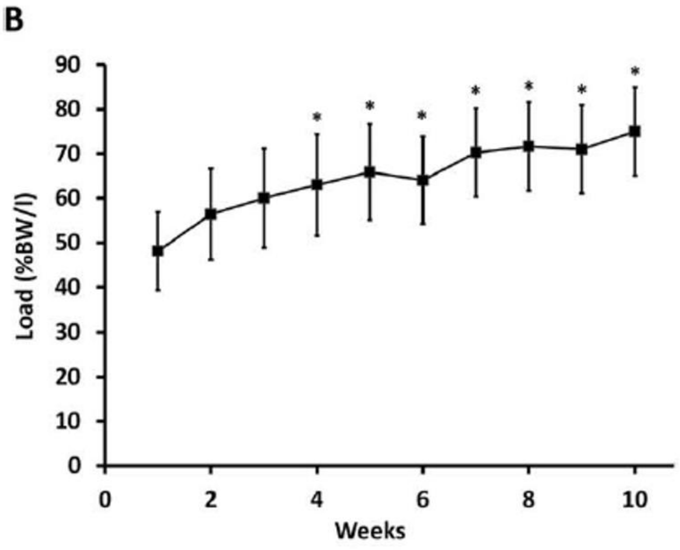
Reference: Berthelsen MP, Husu E, Chistensen SB, Prahm KP, Vissing J, Jensen BR. Anti-gravity training improves walking capacity and postural balance in patients with muscular dystrophy. *Neuromuscul Disord.* 2014; 24(6): 492-8. doi: 10.1016/j.nmd.2014.03.001.

Training effects on closed-kinetic chain leg muscle strength

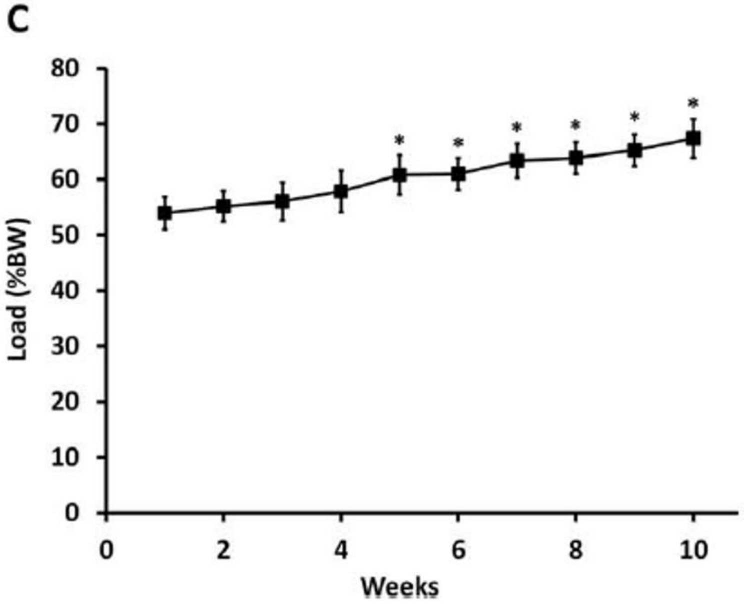
Squats



Calf raise



Lunges



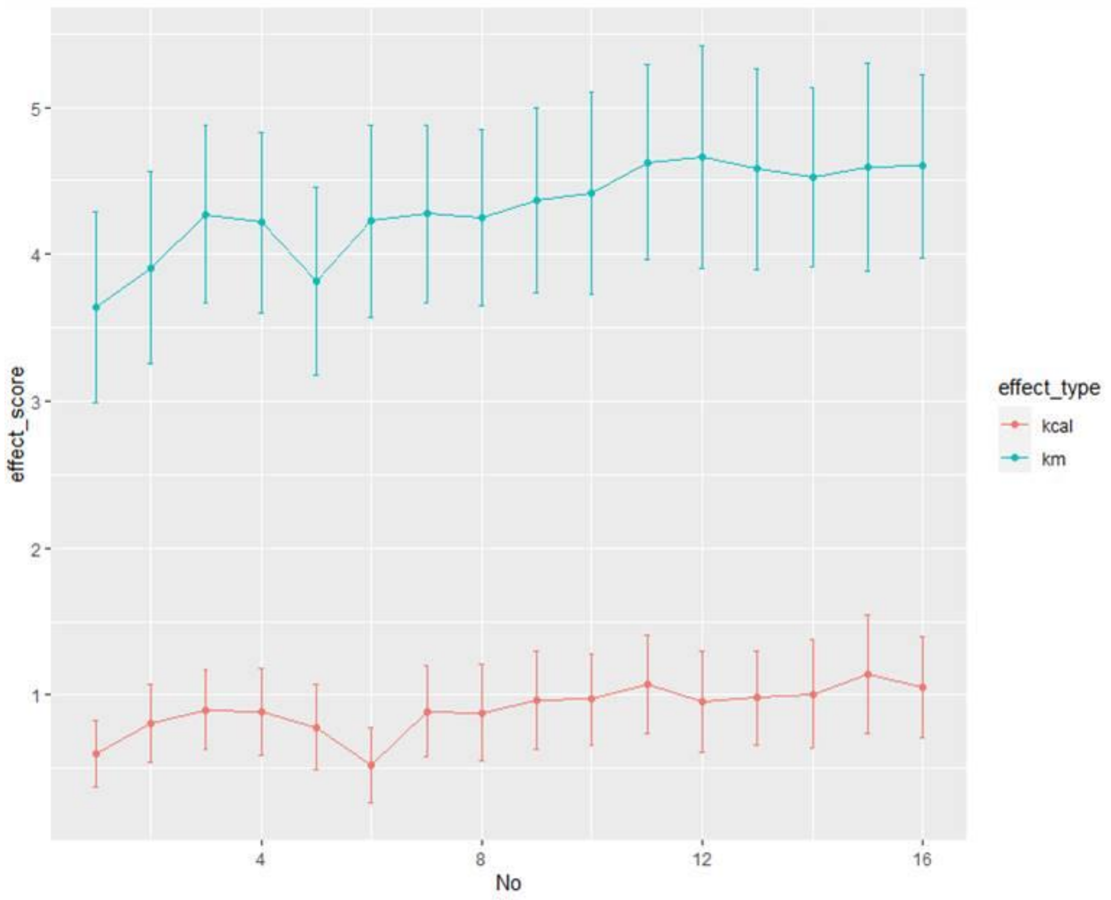
Reference: Jensen BR, Berthelsen MP, Husu E, Christensen SB, Prahm KP, Vissing J. Body weight-supported training in Becker and limb girdle 2I muscular dystrophy. *Muscle Nerve*. 2016;54(2):239-243. doi:10.1002/mus.25039.

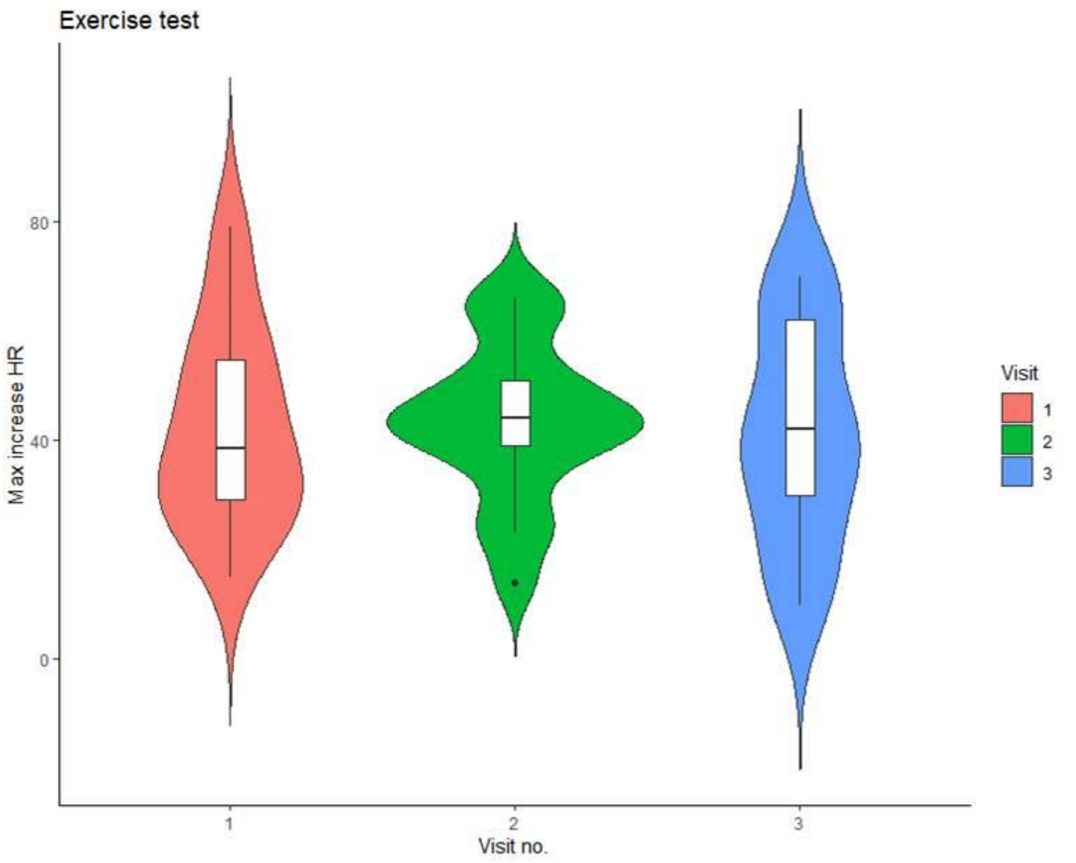
Assisted cycling for wheelchair users

PI: Nanna Scharff Poulsen

- 19 patients with different muscular dystrophies
- 2 with Becker and 3 with DMD

Aerobic training in wheelchair users with muscular dystrophies





Nanna Scharff Poulsen, MD
Unpublished data

Assisted training of wheelchair users: end-points

- Increase cardiovascular fitness
- Increase strength, but probably with minor functional importance
- Alleviate pain from sitting (butt and back)
- Alleviate GI symptoms related to immobilization

Conclusion

- **Do train your patients with BMD!**
- Stronger patients can be trained using similar exercise principles as for healthy
- Weak patients are trainable. Use assistive devices (motorized ergometers, using antigravity, etc)
- Both strength and endurance training are beneficial, but aerobic exercise is likely safer, has greater and quicker efficacy response
- Better endpoints. Endpoints differ according to phenotype. We need valid PROs. Long time follow-up/compliance in a real-world setting

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Overview of Physical Exercise in Boys with Duchenne Muscular Dystrophy

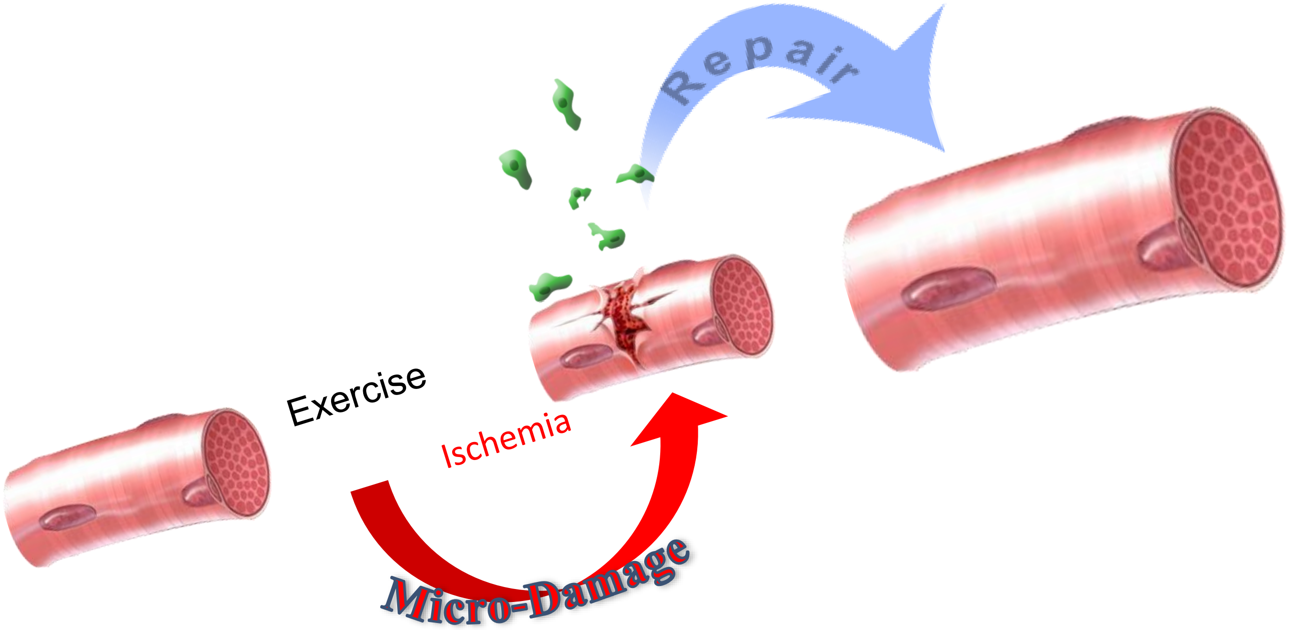
Tanja Taivassalo, PhD

Associate Professor, Department of Physiology and Aging
University of Florida

Disclosures

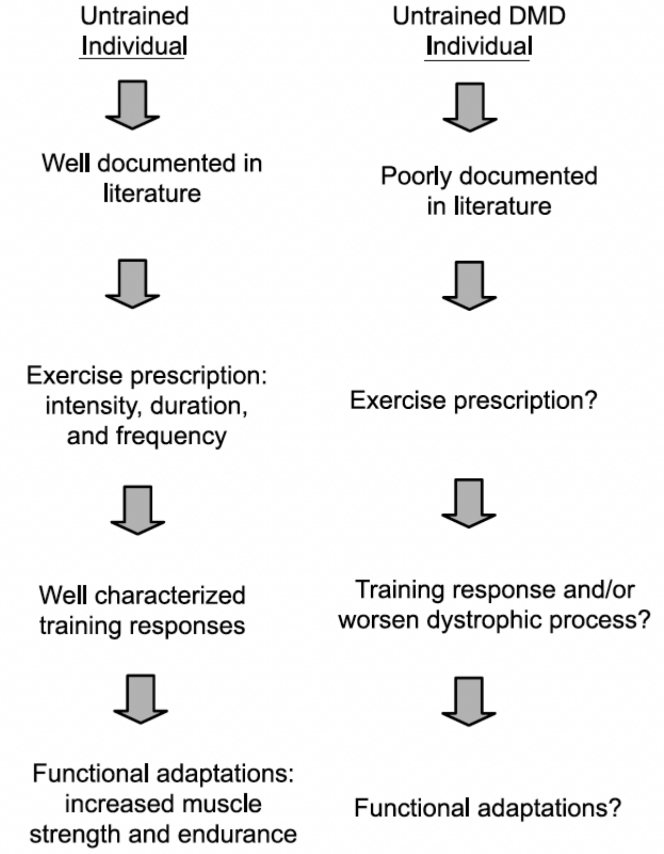
- Travel support, and/or speaker honoraria from Edgewise Therapeutics
- Consultant for CFD Research Corporation

Does exercise exacerbate or protect muscle in DMD?



Recommendations to Define Exercise Prescription for Duchenne Muscular Dystrophy

Robert W. Grange and Jarrod A. Call *Exercise and Sciences Reviews, 2007*



References: Grange RW, Call JA. Exercise and Sciences Reviews, 2007.

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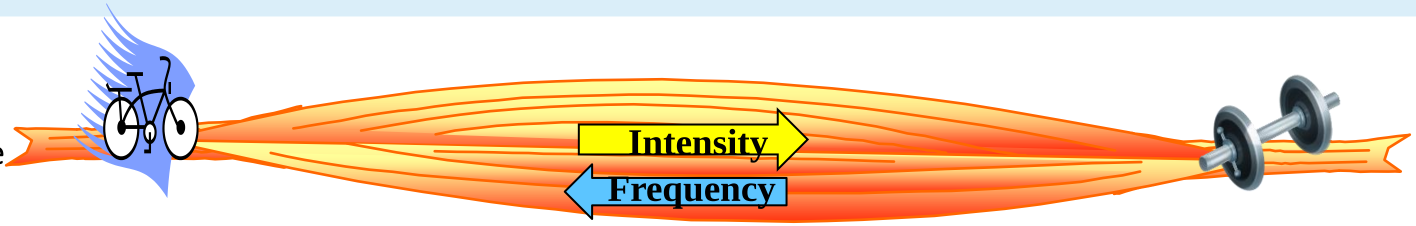
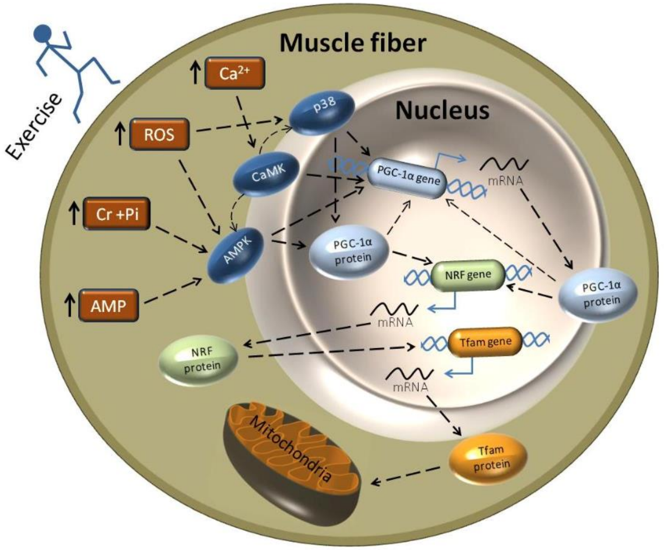
Exercise intensity and frequency induce varying signaling pathways to remodel muscle and increase resiliency

Fatigue resistance

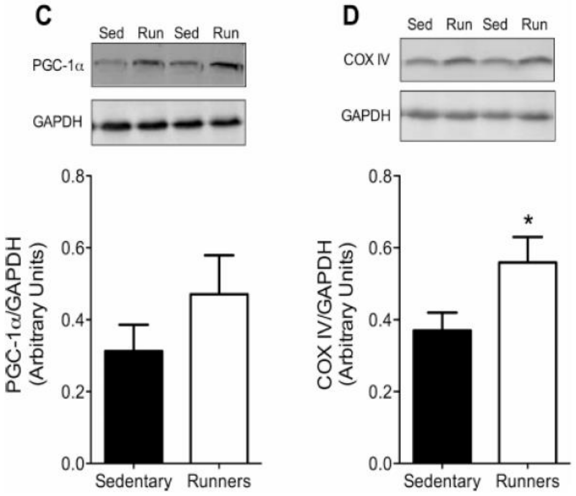


Hypertrophy and improved strength

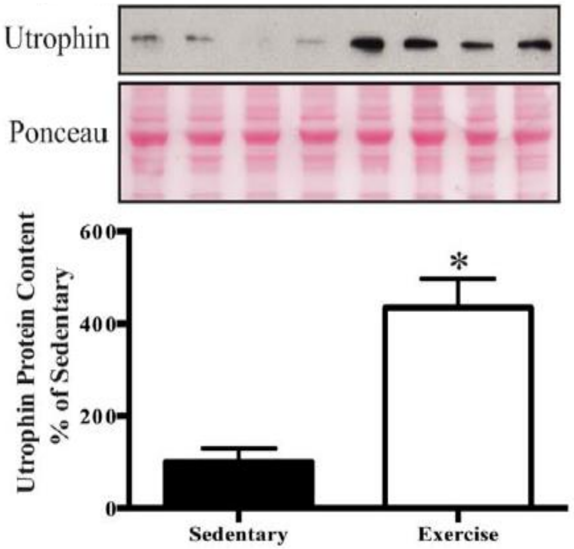


Slow oxidative phenotype

- ↑mitochondria
- ↑antioxidants and reduce ROS
- ↑Ca^{2+} handling
- ↑blood vessel formation
- ↑ Utrophin expression along sarcolemma



Baltgalvis K, et al, MSSE, 2012



Gordon B, Muscle & Nerve 2014

12-weeks voluntary wheel running induces slow oxidative phenotype in *mdx* mice

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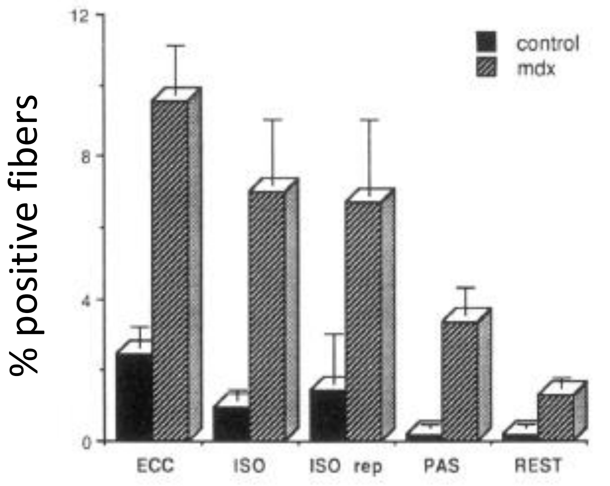
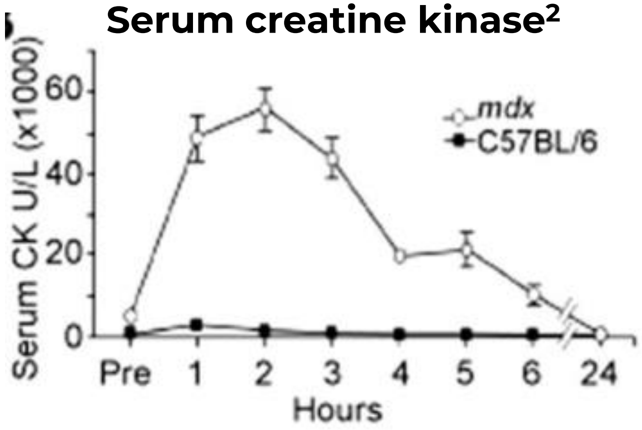
In *mdx* mice, contraction-induced injury is dependent on the type of exercise

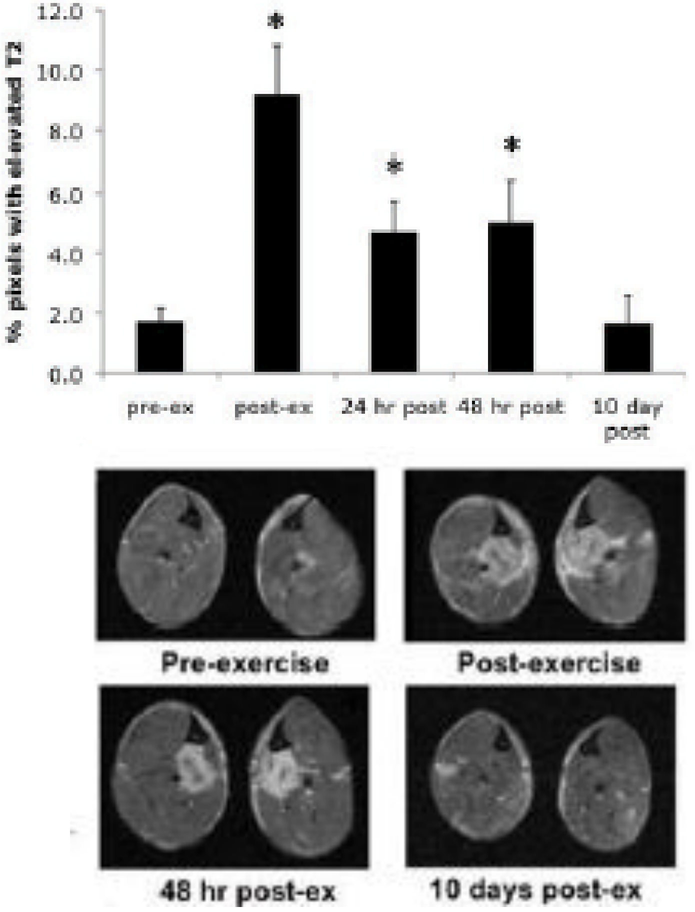
Dye-positive fibers in diaphragm[1]

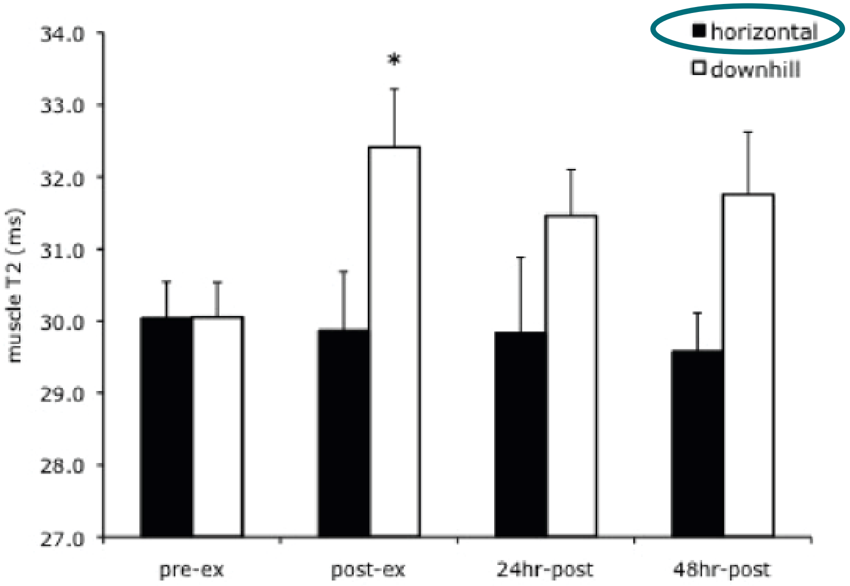


Serum creatine kinase[2]



MRI-T2 in lower hindlimbs[3]





References: 1. Petrof et al, 1993. 2. Kobayashi et al. 2012. 3. Mathur et al, 2011.

Early studies suggested link between physical activity and muscle degeneration in boys with DMD

Pseudohypertrophic muscular dystrophy

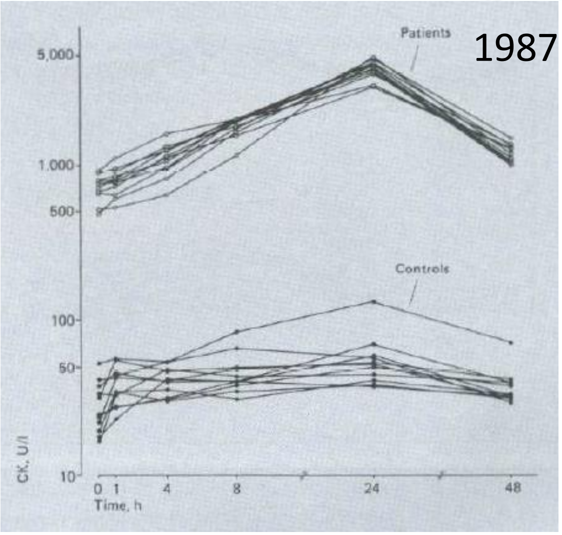
Distribution of degenerative features as revealed by an anatomical study

Charles A. Bonsett, M.D. 1963

intimately related to, or affected by, physical activity which hastens the muscle's demise.

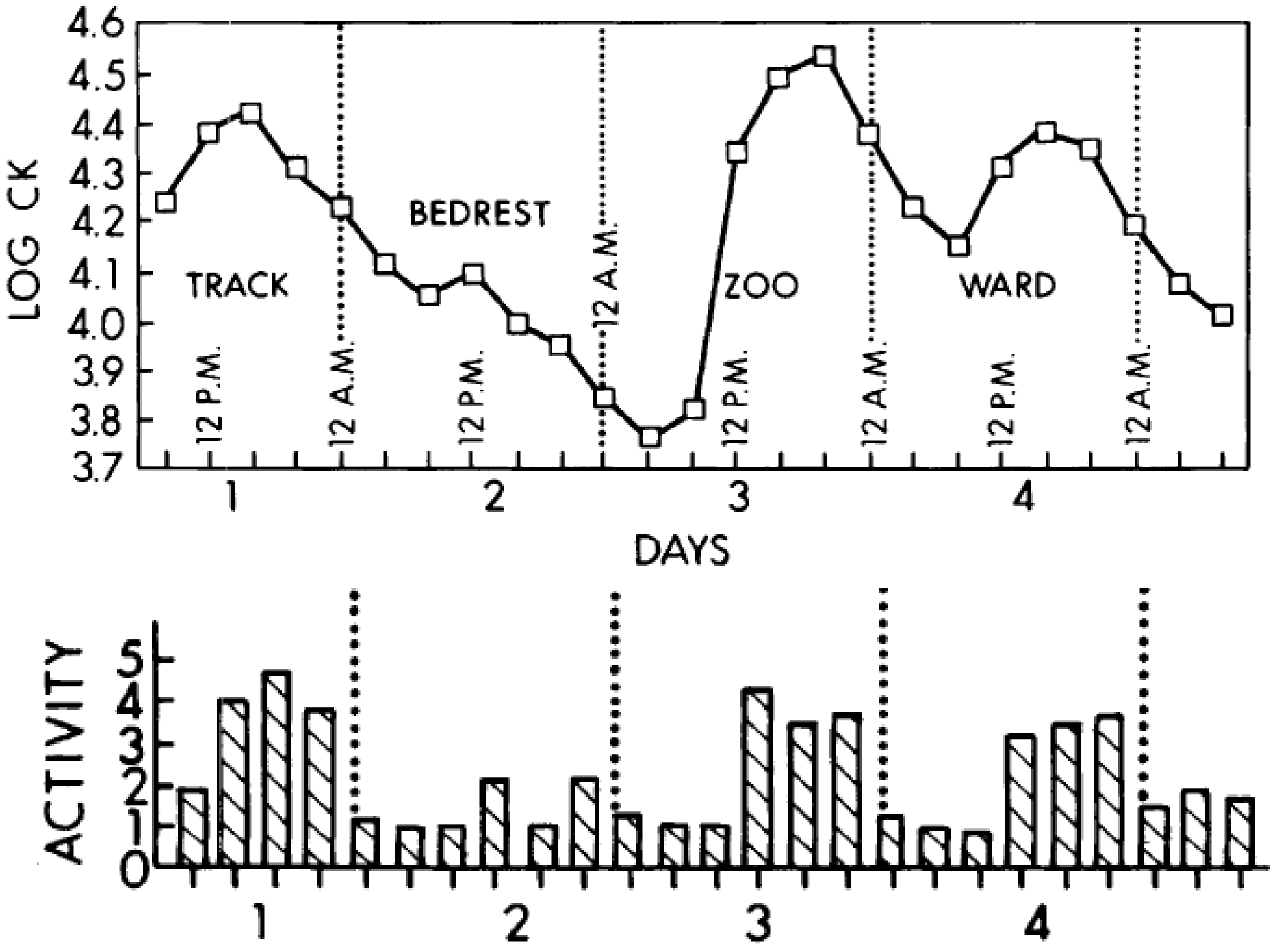
Effect of Exercise on Patients with Duchenne Muscular Dystrophy

Hubert Pöche[a], Werner Hopfenmüller[b], Manfred Hoffmann[b]



1987

Serum CK tracks physical activity



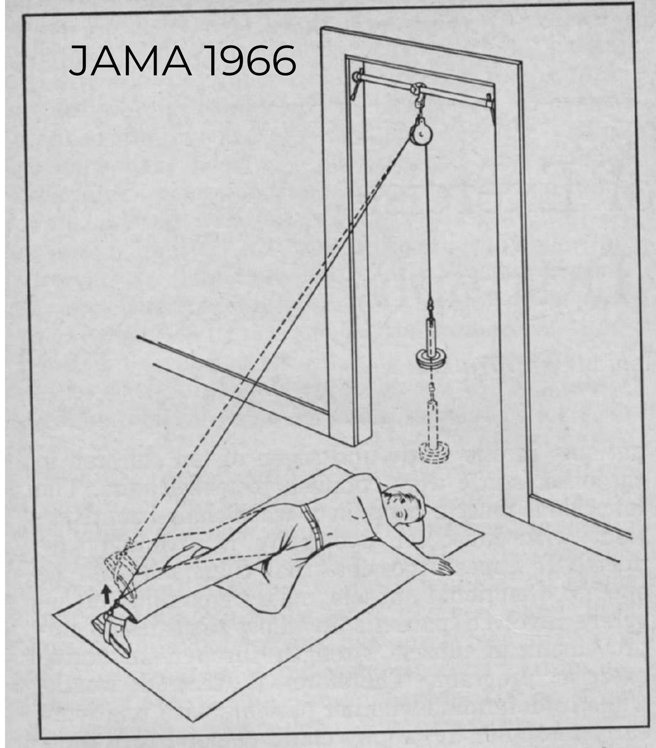
Edgewise THERAPEUTICS

First study of strength training in DMD did not support negative effects of exercise

The Effect of Exercise in Muscular Dystrophy

Paul J. Vignos, Jr., MD, and Mary P. Watkins

JAMA 1966



1. Performance of hip-abduction exercise with weight for assistance.

- n=12 boys (5-10 yrs)
- 10 reps of each (hip abduction, hip extension, knee extension, arm flexion, sit ups
- daily for first 6 months/ 3-5 times per week for following 6 months
- no 'ill' effects
- Increase in weight lifted at 4 months

provement. The opinion that active forms of exercise are deleterious in muscular dystrophy is not supported by our results. The suggestion that exercise programs should consist of only a small number of repetitions because of rapid, easy fatigue which might contribute to further deterioration of muscle strength is, also, not supported.[4] The pa-

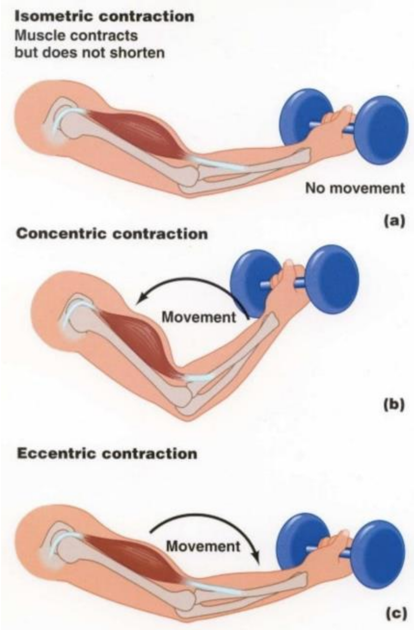
Table 2.—Changes in Muscle Strength in Exercised and Unexercised Patients With Duchenne Muscular Dystrophy

	Age at Beginning of Program (Yr)	Functional Class,* Beginning of Program	% Muscle Strength at Beginning of Program	Change in % Muscle Strength During Year Before Program	Change in % Muscle Strength During Year of Program
Unexercised patients (14)					
Mean	7.7	2.1	61	−3.36	−7.71
SD				6.82	2.61
Exercised patients (14)					
Mean	7.4	2.0	59	−8.0	+1.07
SD				3.04	3.76
P				>0.5	<0.01

*Functional class ranges from class 1 denoting normal functional ability to class 9 denoting wheelchair confinement.[5]

Edgewise THERAPEUTICS

No evidence of muscle damage after acute isometric strength exercise in boys with DMD



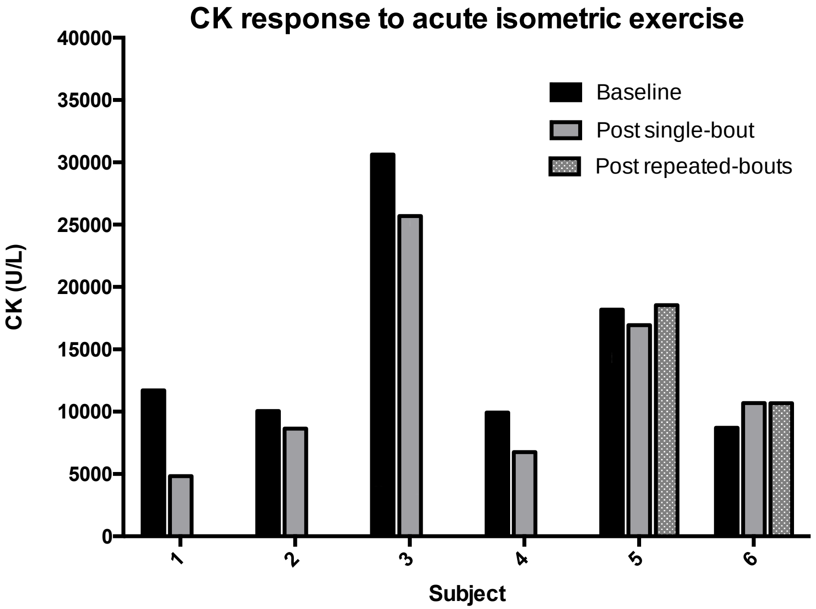
Received: 4 June 2020 | Revised: 2 December 2020 | Accepted: 6 December 2020
DOI: 10.1002/mus.27137

CLINICAL RESEARCH ARTICLE

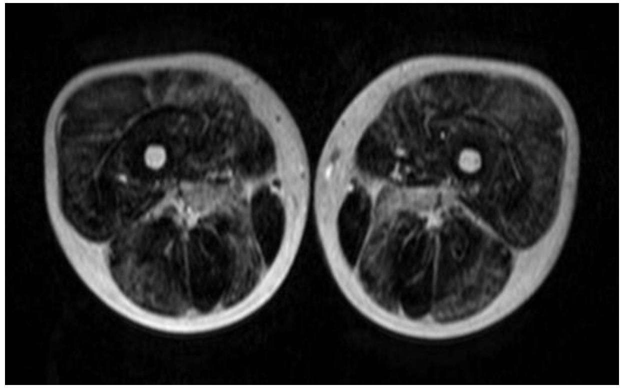
MUSCLE&NERVE

Safety, feasibility, and efficacy of strengthening exercise in Duchenne muscular dystrophy

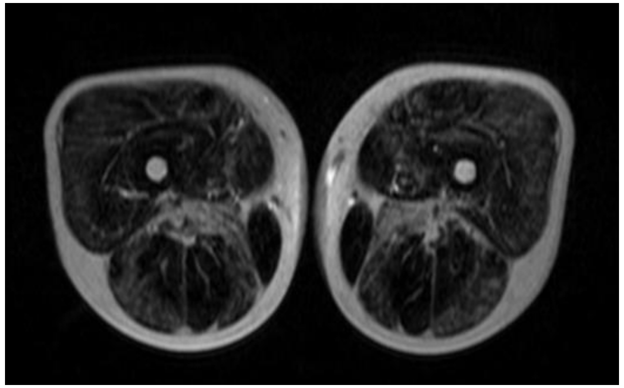
Donovan J. Lott PT, PhD[1] | Tanja Taivassalo PhD[2] | Korey D. Cooke DPT[1] | Hyunjun Park BS[1] | Zahra Moslemi OT, MS[3] | Abhinandan Batra PT, PhD[1] | Sean C. Forbes PhD[1] | Barry J. Byrne MD, PhD[4] | Glenn A. Walter PhD[2] | Krista Vandenborne PT, PhD[1]



T2 weighted MRI
Baseline



+ 48 hours (-0.3% change in T2)

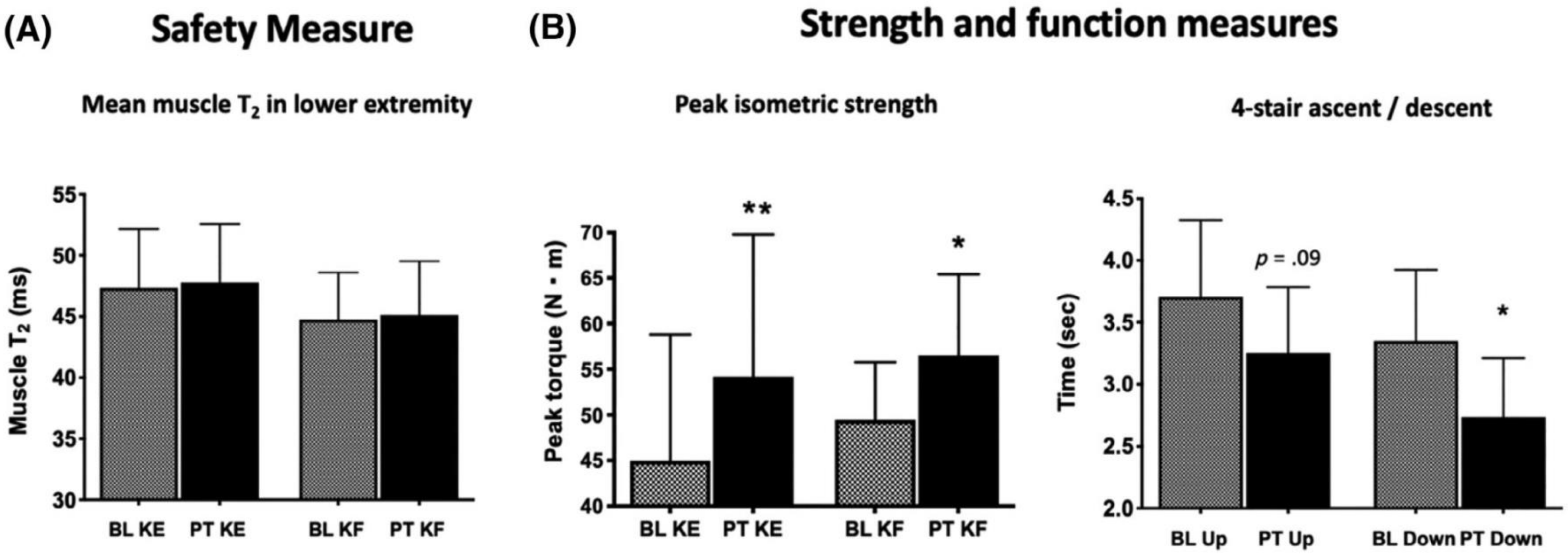


Edgewise THERAPEUTICS

Isometric strength training is safe and effective in boys with DMD

Exercise parameters:

- 12 weeks (3x/week)
- Isometric strengthening at 50% MVC
- At home, remotely supervised
- High (>85%) compliance to intervention



Reference: Lott D, et al. 2020

Edgewise THERAPEUTICS

Motor-assisted cycle exercise training is safe and has potential to delay functional deterioration in DMD

Assisted Bicycle Training Delays Functional Deterioration in Boys With Duchenne Muscular Dystrophy: The Randomized Controlled Trial "No Use Is Disuse"

Neurorehabilitation and Neural Repair
27(9) 816–827

DOI: 10.1177/1545968313496326
nnr.sagepub.com
SAGE

Jensen M, et al

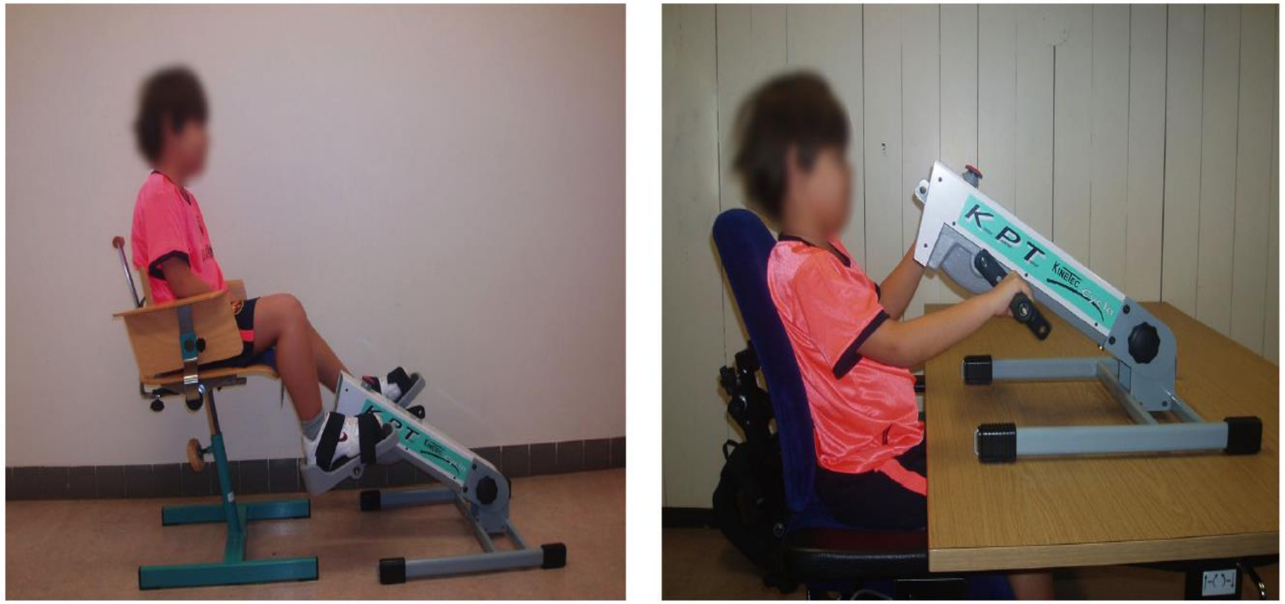


Figure 3 Posture during dynamic leg and arm training

Exercise parameters:

- 6 months (5 x per week, 15 min)
- Assisted ergometry (motor support using KPT)
- Intensity = OMNI $\leq$ 6

Results:

- 6% decline in motor function in control group
- Motor function measure stable in exercise group

Considerations:

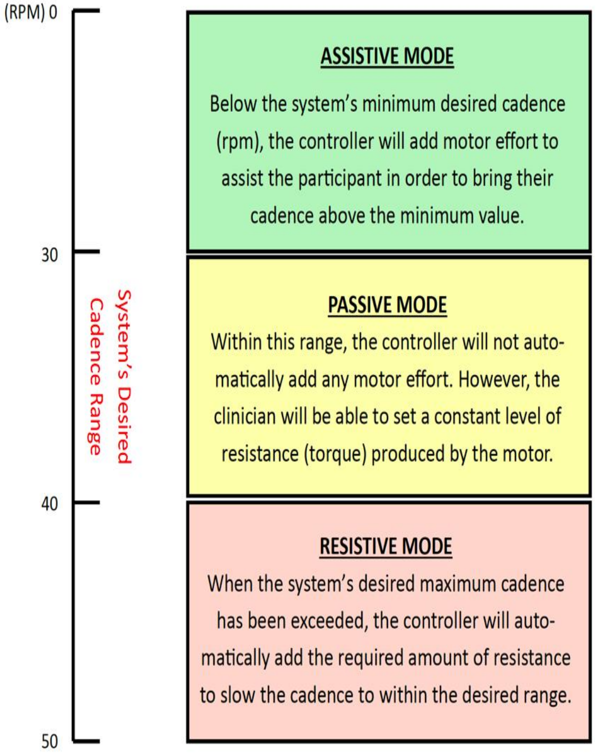
- *No measures of muscle damage obtained*
- *No information on how much work was performed*

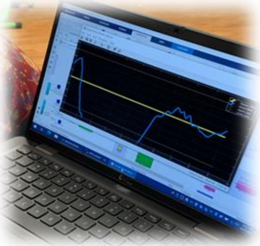
Reference: Jensen M, et al. Neurorehabil Neural Repair. 2013.

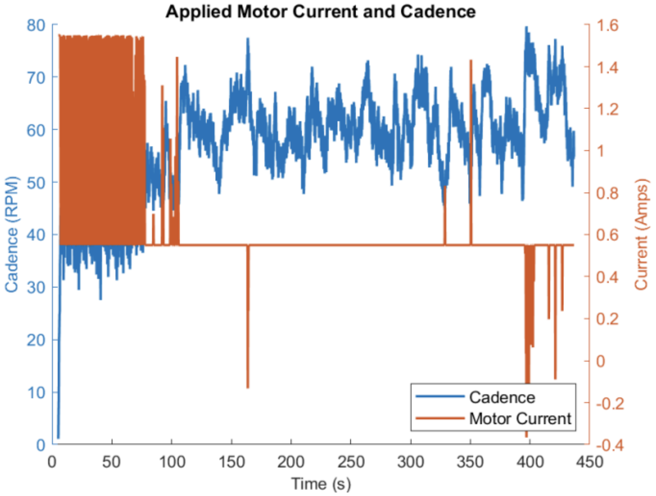
Edgewise THERAPEUTICS

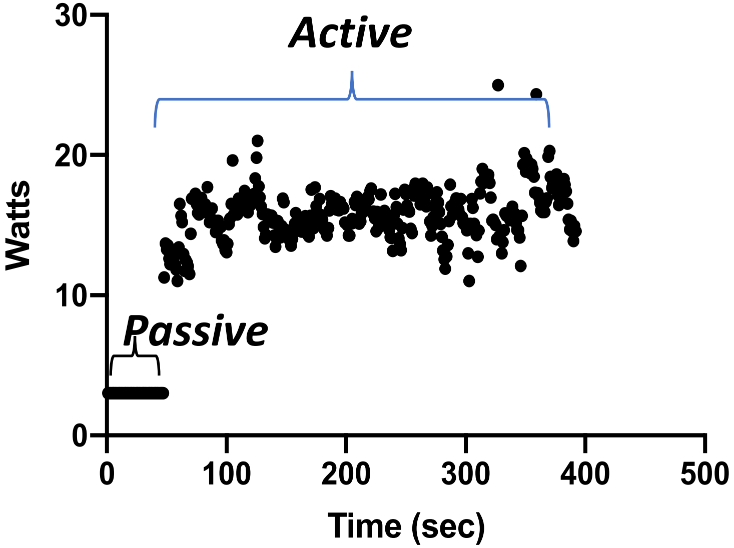
Development of an active cycling paradigm to induce adaptation in dystrophic muscle

Feedback controllers track cadence and adjust level of motor-assistance in real-time









Edgewise THERAPEUTICS

6-month home-based cycle exercise training intervention

Training week **0** **12** **24**

Rx

+

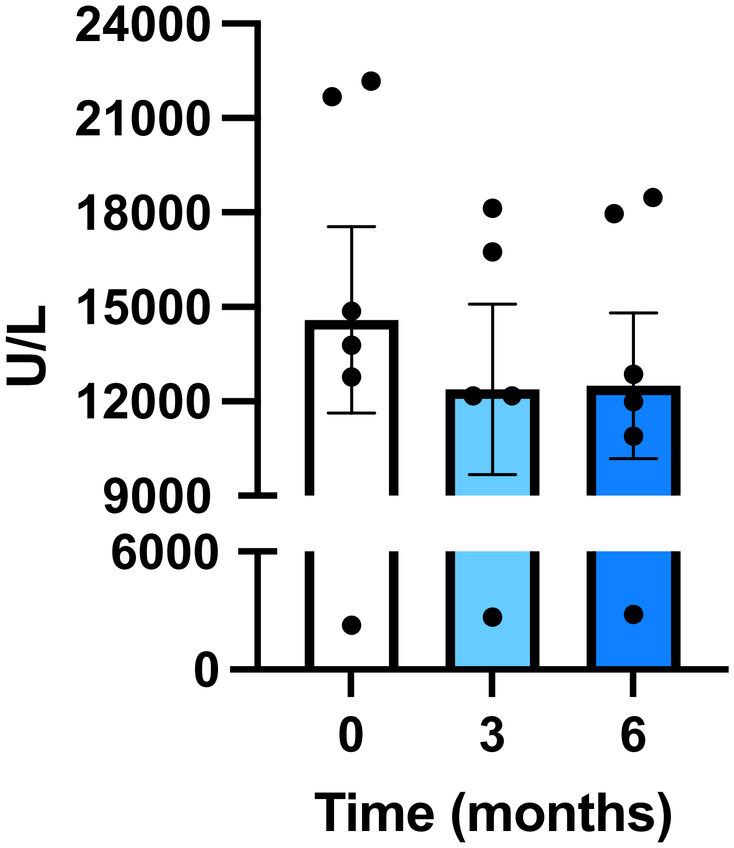
- 3 x/wk
- 15-30 min per session
- 50-60% peak heart rate reserve

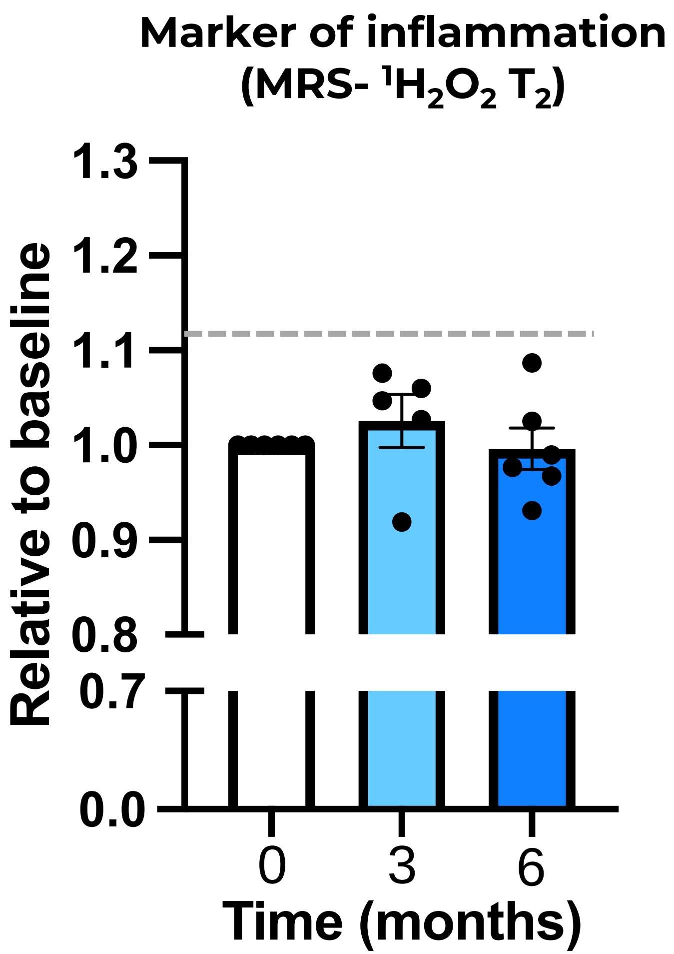
- 2 to 3x /wk; 4 sets of 6 reps
- Intensity 50% MVC
- Cycle exercise 1 x/wk

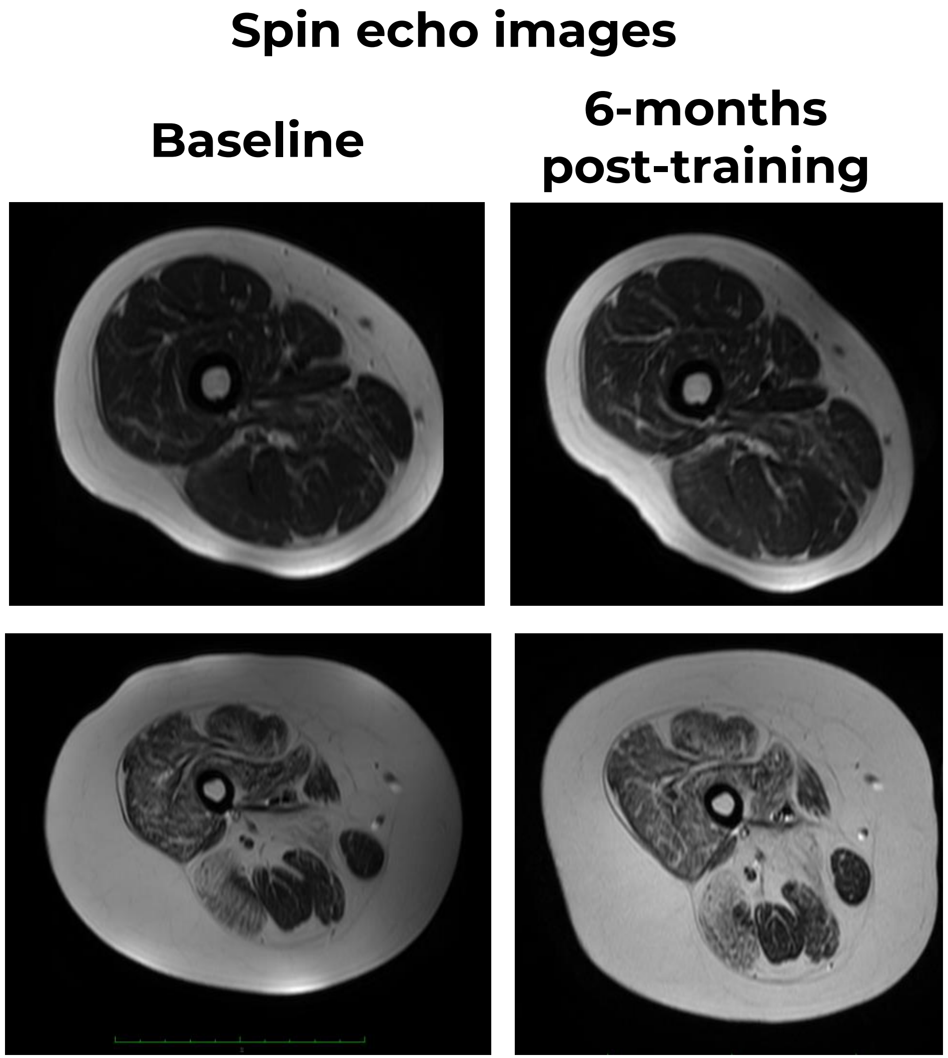
ID	Age (yrs)	Mutation	EF (%)	6MWD (m)	Compliance	HR zone (bpm)
01	7.5	c.5082delA	68	387	93%	120-140
02	7.0	Del 46-50	69	426	78%	150-170
03	8.5	Del 4-8	70	509	87%	145-170
04	6.5	Del 31-43	67	343	87%	140-160
05	8.0	c.7075C>T	50	300	85%	120-150
06	9.0	Del 49-52	66	177	95%	140-160

Outcome	Safety	Efficacy
Primary	MRS T_2 (inflammation)	• Time to fatigue • Submaximal exercise tolerance
Secondary	Serum Creatine Kinase	• Caregiver impression questionnaire • Muscle cross-sectional area and fat
Exploratory	Echo	• ^{31}P MRS recovery kinetics • Bone density (Dexa) • Circulating metabolic biomarkers

No evidence of muscle damage after 6-months cycling exercise





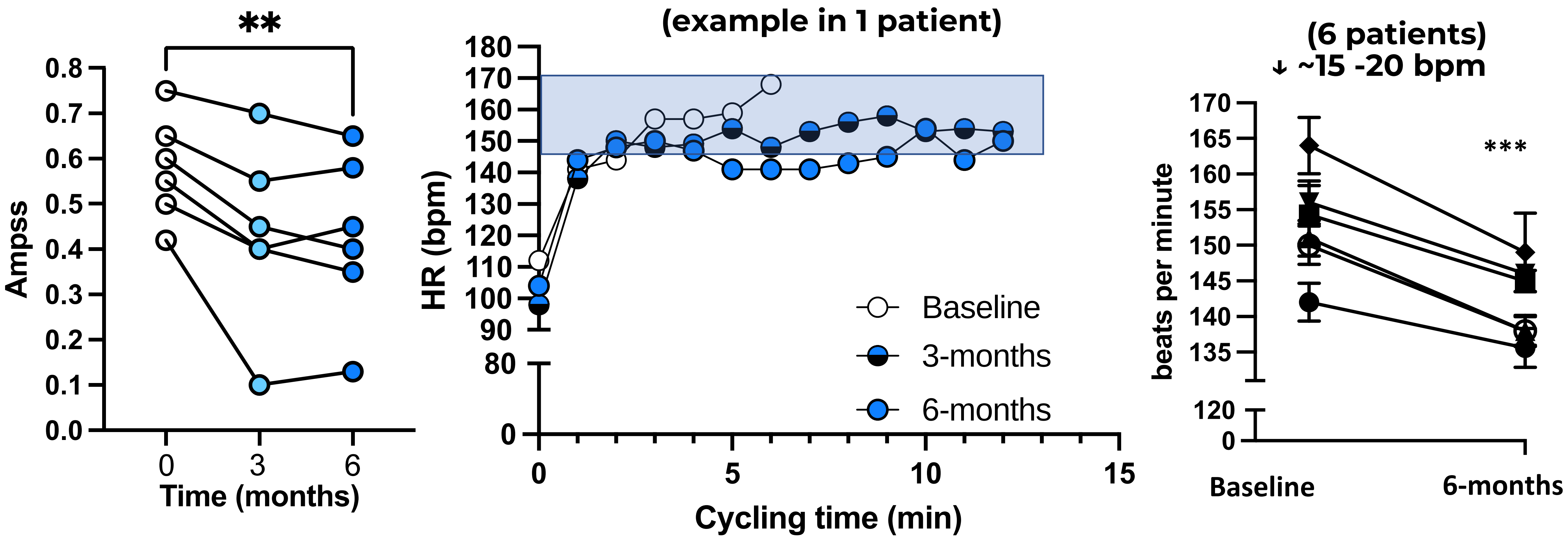


Edgewise THERAPEUTICS

Cycle exercise training induces physiological adaptations

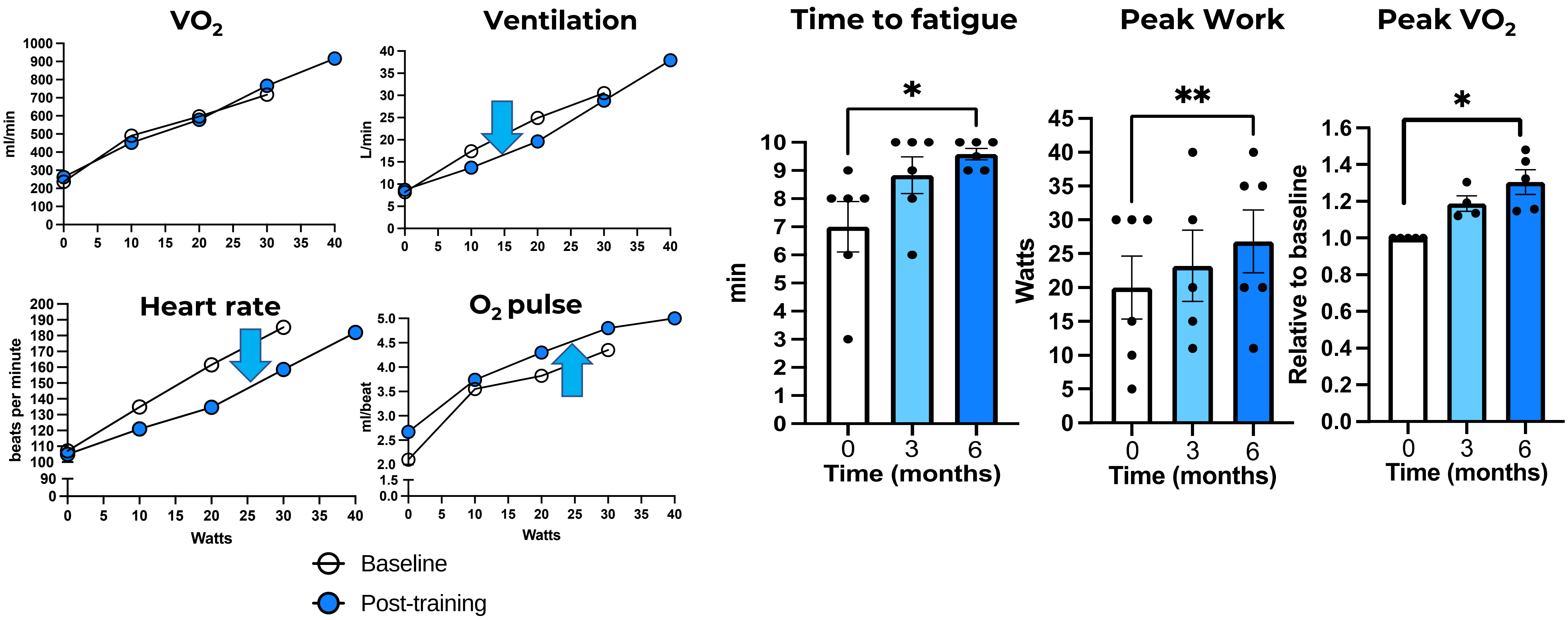
Reduction in motor-assistance

Reduction in heart rate during submaximal exercise



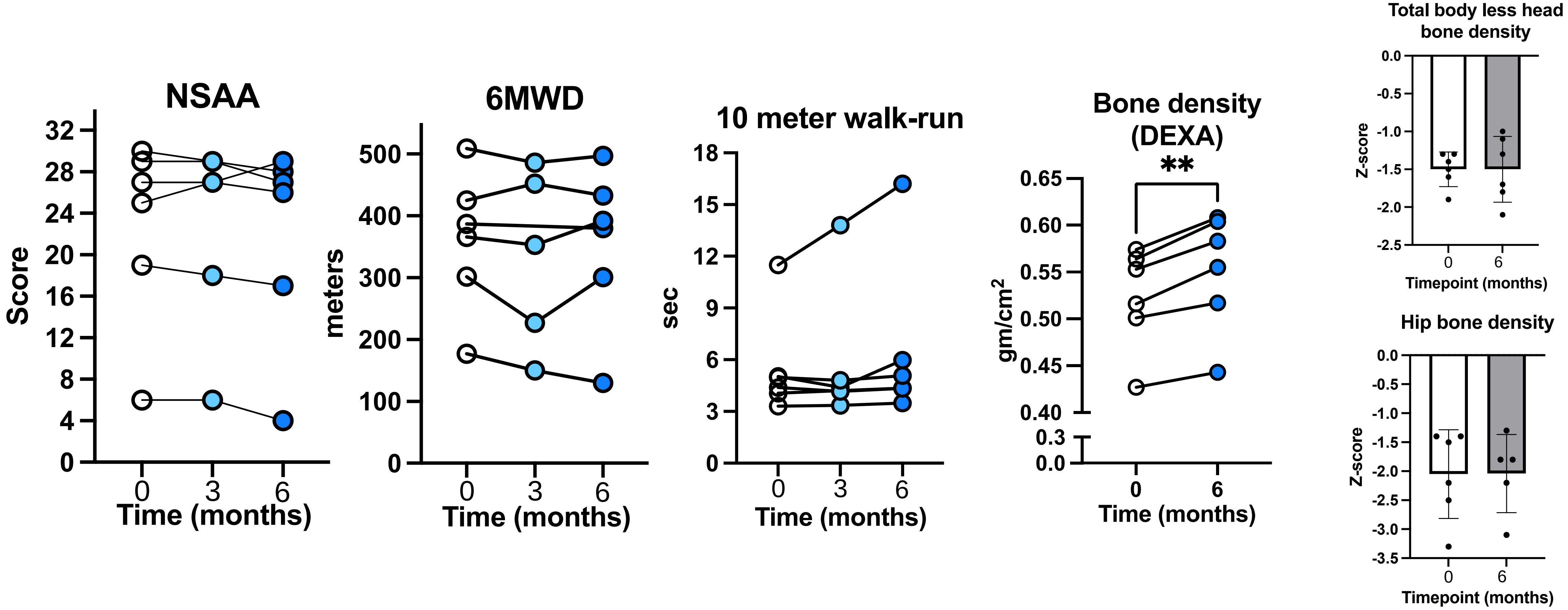
Reference: Data on File

Cycle training normalizes physiological responses to submaximal exercise and improves peak exercise capacity



Reference: Data on File

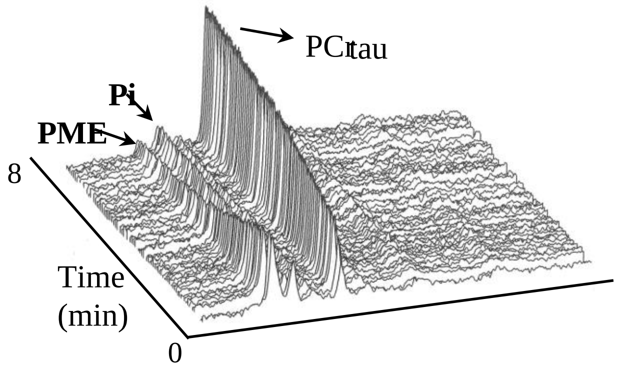
Impact of cycle training on functional performance is variable; bone density is maintained

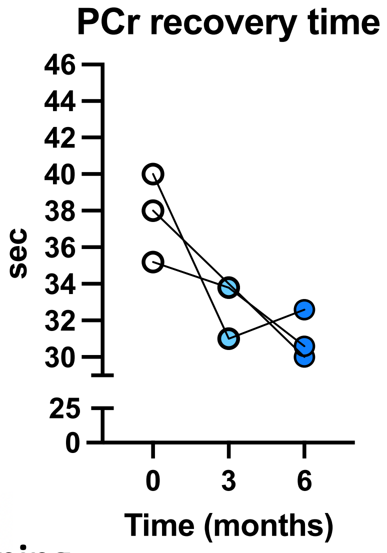


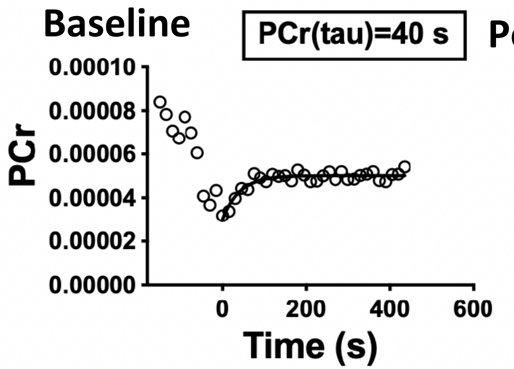
Reference: Data on File

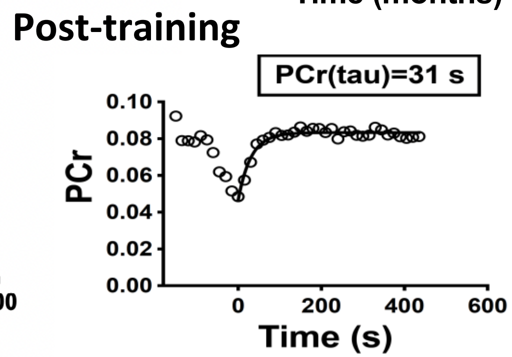
Edgewise THERAPEUTICS

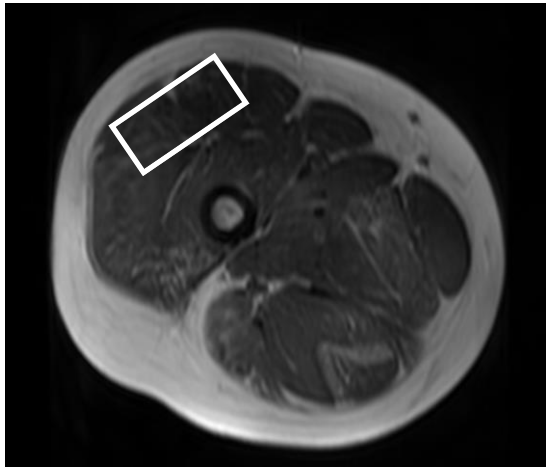
Cycle exercise training improves muscle oxidative capacity and fat fraction

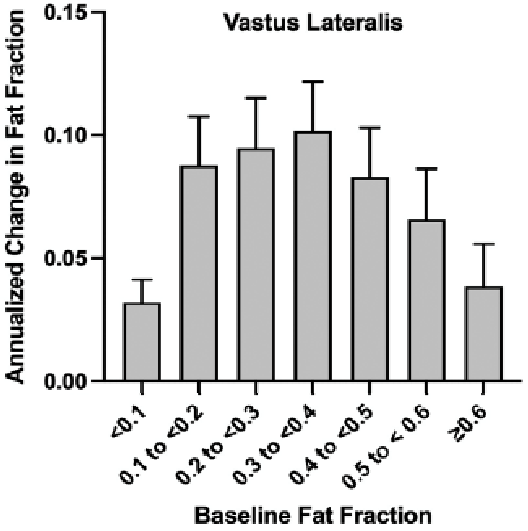




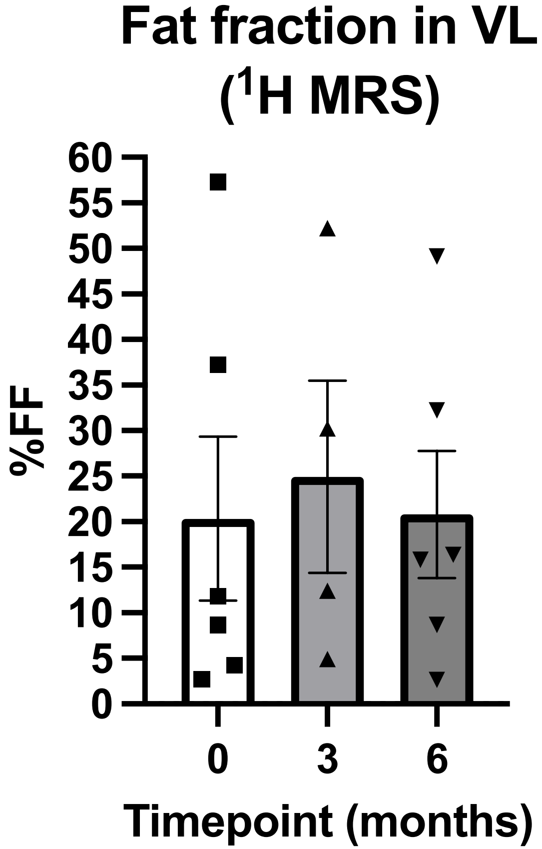








Willcocks, R. 2023



Reference: Work from Dr. S. Forbes

Exercise training improves quality of life in boys with DMD

1. Since your child began the exercise training, how would you describe your child's overall physical wellbeing?

1	2	3	4	5	6	7
Very much worse	Much worse	Somewhat worse	No change	Somewhat improved	Much improved	Very much improved

Briefly explain your response or provide an example in your own words:

[redacted] WILLING TO RUN DOWN TO THE NEIGHBORS HOUSE (1/4 MILE) & BACK HOME.
[redacted] GYM TEACHER SAYS HE ISNT TAKING BREAKS IN CLASS ANYMORE & HE IS PARTICIPATING A LOT MORE.

9. Since your child began exercise training, how would you describe your child's overall quality of life?

1	2	3	4	5	6	7
Very much worse	Much worse	Somewhat worse	No change	Somewhat improved	Much improved	Very much improved

Briefly explain your response or provide an example in your own words:

[redacted] OVERALL QUALITY IS BETTER FOR ALL OF THE REASONS STATED ABOVE. HE ISNT SITTING OUT OF AS MANY ACTIVITIES AS HE ONCE DID AND IS STRONGER IN HIS BELIEFS THAT HE CAN DO IT.

1. Since your child began the exercise training, how would you describe your child's overall physical wellbeing?

1	2	3	4	5	6	7
Very much worse	Much worse	Somewhat worse	No change	Somewhat improved	Much improved	Very much improved

Briefly explain your response or provide an example in your own words:

He himself feels stronger which makes him want to help himself more (get out of a chair ~~independently~~ independently, dress himself. I also feel the muscles in his legs are more noticeable. He also says "mom watch I can run faster".

2. Since your child began exercise training, how would you describe your child's energy levels?

1	2	3	4	5	6	7
Very much worse	Much worse	Somewhat worse	No change	Somewhat improved	Much improved	Very much improved

Briefly explain your response or provide an example in your own words:

He now is wanting to be more active and asks to go swimming and also wants to play more and will do activities longer.

…and boys don't want to stop exercising

Month 1:
5 x 2 min

Month 6:
2 x 15 min

Rifton X330 adapt tricycle with resistance levels

Month 12:
30 min consecutive

Take home messages about exercise in DMD

- Frequency and dose of exercise play an important role in therapeutic outcomes
- **Appropriate** exercise is safe and feasible for boys with DMD
  - Moderate intensity (~50% MVC) isometric strength exercise
  - Moderate intensity (50-60% HRR) active cycling
- Appropriate exercise is effective, reversing deconditioning and promoting adaptations similar to healthy muscle
- Preliminary evidence that cycle (aerobic) exercise training may protect muscle from excessive contraction-induced injury, leading to better outcomes
- Further work needed (serum biomarkers, systemic benefits)
- Exercise needs to be considered as an **adjuvant** to other developing therapeutics for DMD

Edgewise THERAPEUTICS

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- **Dr. S. Forbes**
- **Dr. D. Lott**
- **M. Bomma, Bsc**
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- Dr.Vandenborne
- Dr. R. Willcocks
- Dr. A. Bernier
- Dr. J. Sladky
- Dr. C. Zingariello

- J. Berthy, RN
- J. Lammers, PT
- T. Cousins, DNP
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- C. Powers
- V. Bordeaux

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- Dr. K. Stubbs
- H. Sweatland.
- E. Griffins

Congressionally Directed Medical Research Programs CDMRP Department of Defense

Supported by Department of Defense (Grant number: W81XWH191033)
Clinical Trials.gov: NCT04322357

rifton

MDA Muscular Dystrophy Association

The Patients and Families!

Edgewise THERAPEUTICS

Targeting protection against contraction-induced injury in Becker: an overview of the sevasemten (EDG-5506) clinical program

Joanne Donovan, MD, PhD

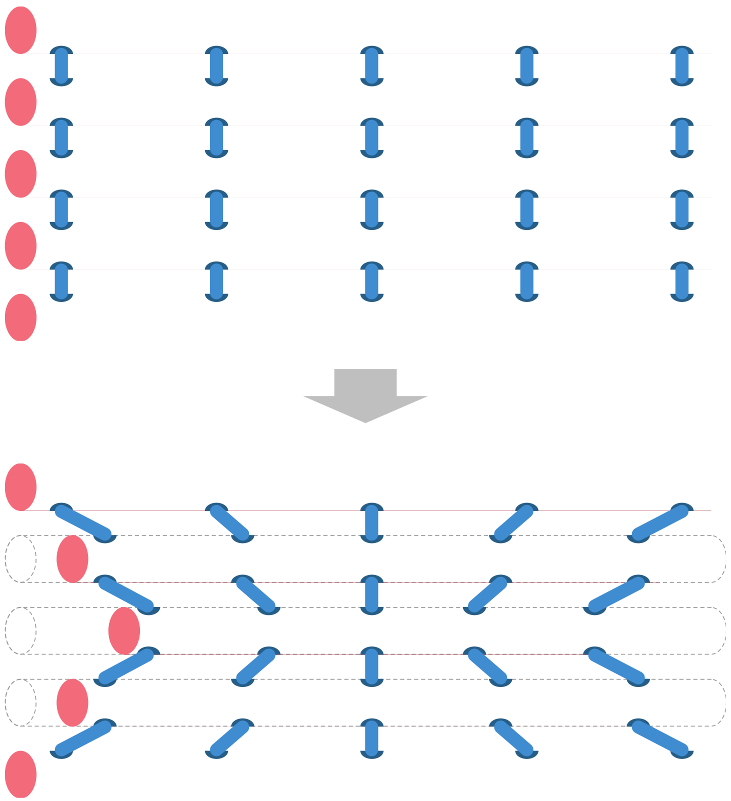
Chief Medical Officer
Edgewise Therapeutics

Edgewise THERAPEUTICS

Contraction-induced muscle damage & sevasemten (EDG-5506)

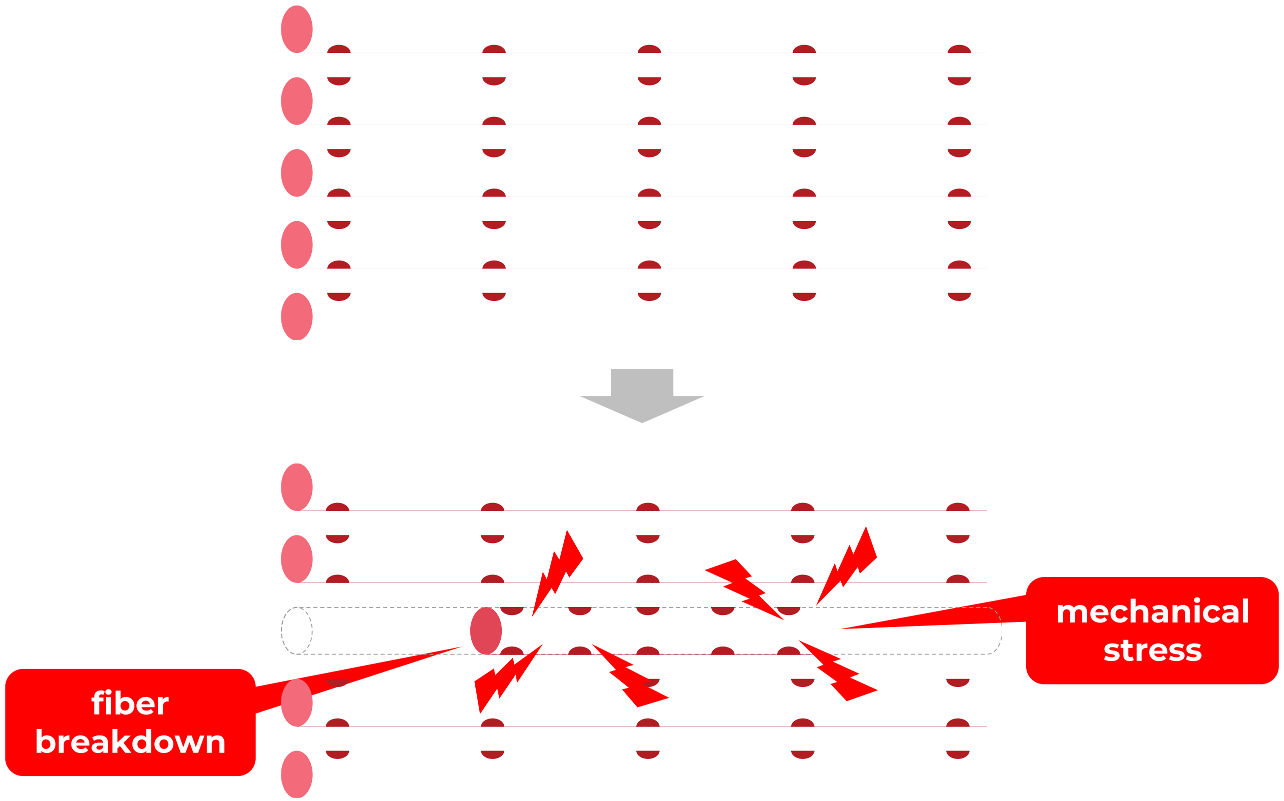
In dystrophinopathy, **fast muscle fibers** are disproportionately injured by contraction

Healthy muscle contraction



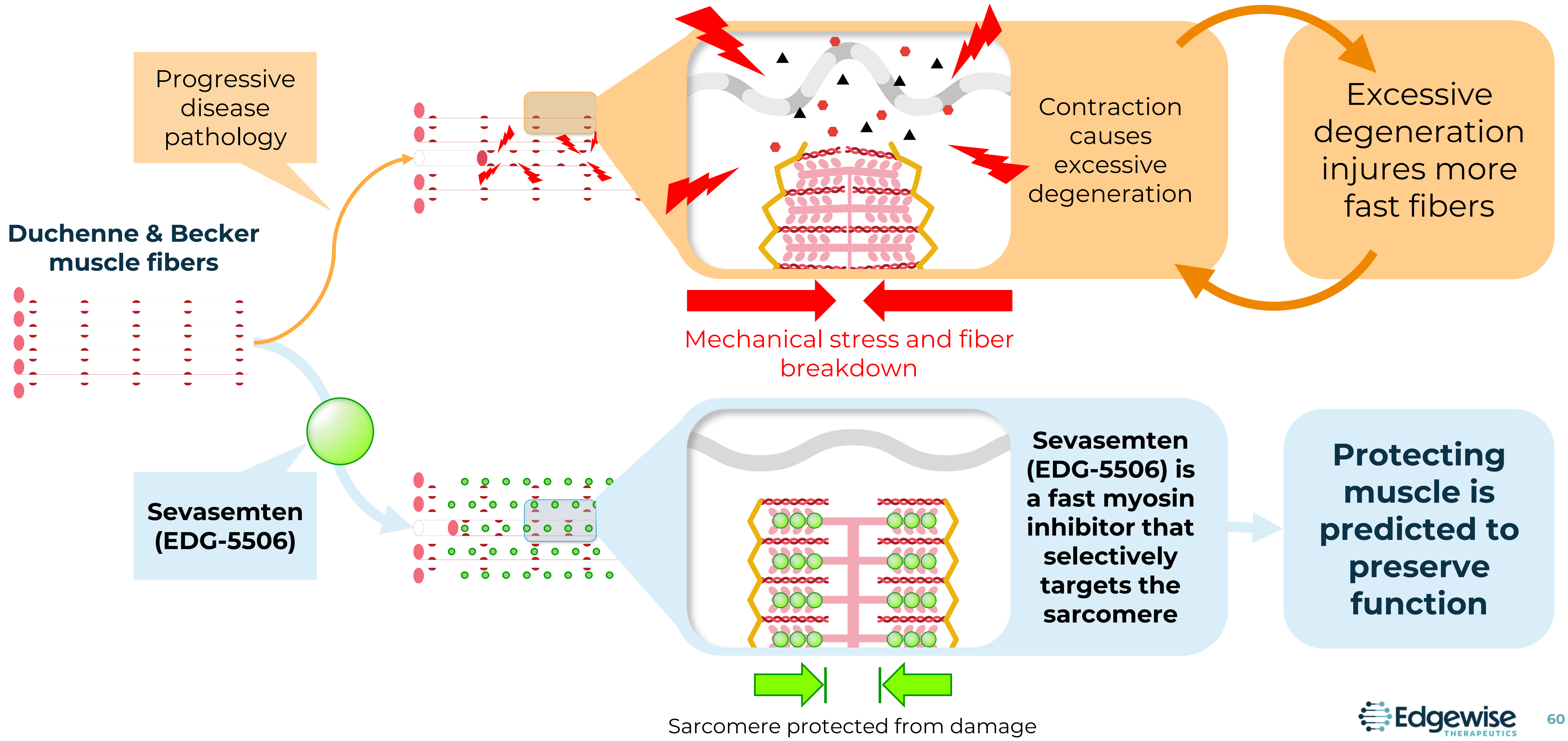
Dystrophin connects contractile proteins to the membrane and surrounding matrix to protect against contraction-induced injury.

Dystrophic muscle contraction



Contraction-induced muscle injuries occur in the absence of full-length dystrophin.

A new strategy to rebalance dystrophic muscle:
sevasemten (EDG-5506) designed to address the root cause of muscular dystrophy

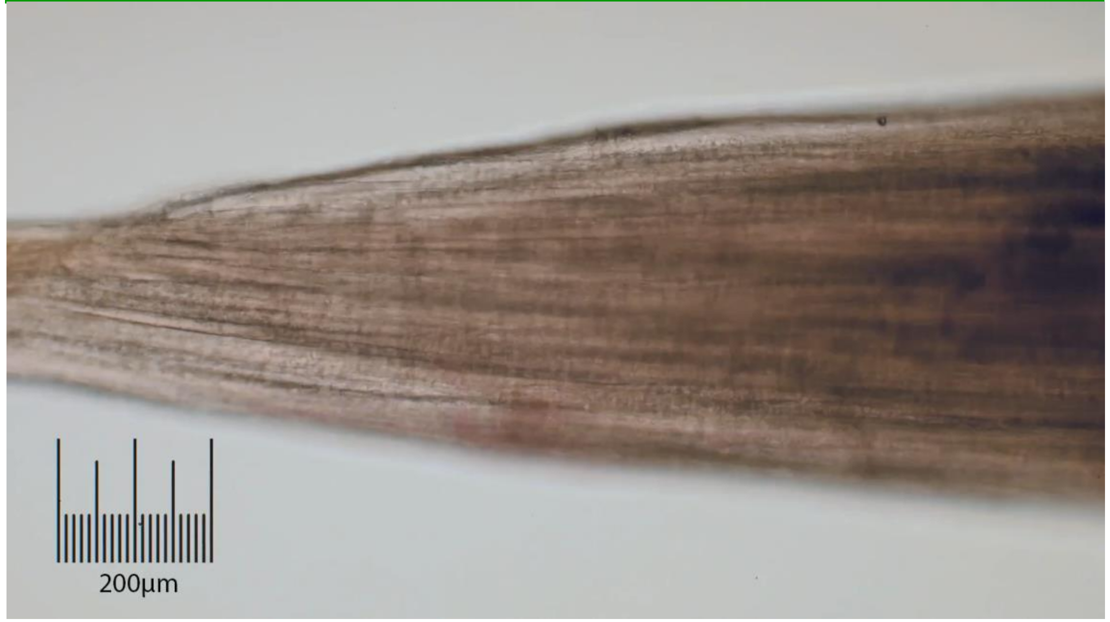


Sevasemten (EDG-5506) targets fast myosin to protect dystrophic muscle against contraction-induced injury in mouse models

Contracting at 100% without sevasemten (EDG-5506)

In *mdx* mouse muscle, even a few contractions cause visible injury

Contracting at 85% following sevasemten (EDG-5506) administration



By minimally decreasing contraction, while preserving function, contraction-induced injury is prevented

Both videos have been sped up 3x

Reference: Russell AJ, et al. J Clin Invest. 2023;133(10):e153837. doi:10.1172/JCI153837

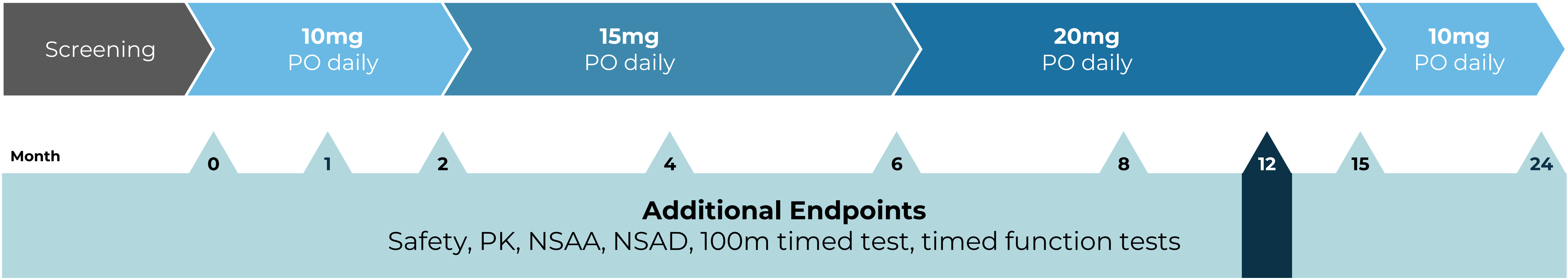
ARCH study overview

ARCH

An open-label, single-center study to assess sevasemten (EDG-5506) safety and pharmacokinetics in adults with Becker

- **Primary objective:** Safety and tolerability over 24 months
- **Key inclusion criteria:** Ambulatory males aged 18 to 55 years with a dystrophin mutation and a BMD phenotype, not on corticosteroids, who could complete 100-m timed test
- **Patients enrolled:** 12

Study design - 24 months



Reference: NCT05160415

ARCH

Significant functional impairment & decreased muscle mass at baseline

CHARACTERISTIC	BECKER PARTICIPANTS (n=12)	AGE NORMATIVE VALUES
Age (SD)	33 (8) years	–
Functional Measures (median)		
10-meter walk/run	8.4 sec	< 4 sec
Rise from floor	6/12 could perform	< 3 sec
NSAA	15.5 (range 4-31)	–
Serum Creatinine (mean, mg/dL)	0.44	0.92 - 1.16
Serum CK (mean, U/L)	1,390	<210
DXA % Lean Mass	55%	>75%

Unlike most Duchenne patients in clinical trials, all Becker patients in ARCH were in **functional decline**

Abbreviations: DXA, dual energy x-ray absorptiometry
Reference: Data on file

ARCH

Sevasemten (EDG-5506) was **well-tolerated at all doses**

	NUMBER OF PATIENTS REPORTING >1 AE
	AFTER 12 MONTHS OF DOSING
Dizziness	4 (33%)
COVID-19	4 (33%)
Arthralgia	4 (33%)
Somnolence	3 (25%)
Headache	3 (25%)
Nasopharyngitis	3 (25%)
Fall*	3 (25%)
Viral URI	3 (25%)
Influenza	2 (17%)
Sinusitis	2 (17%)
GERD	2 (17%)
Procedural pain	2 (17%)

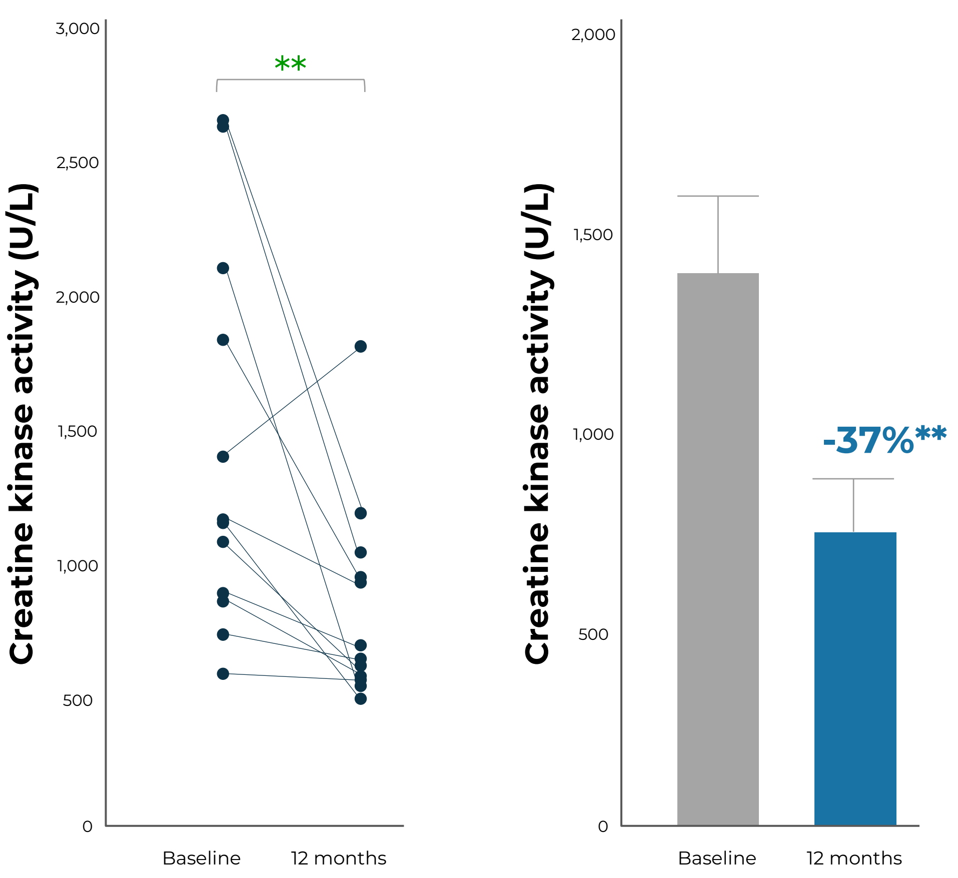
No dose reductions/ adjustments, treatment discontinuations, or SAEs

* Unassociated with other AEs and typical of falls observed in Becker patients
Reference: Data on file

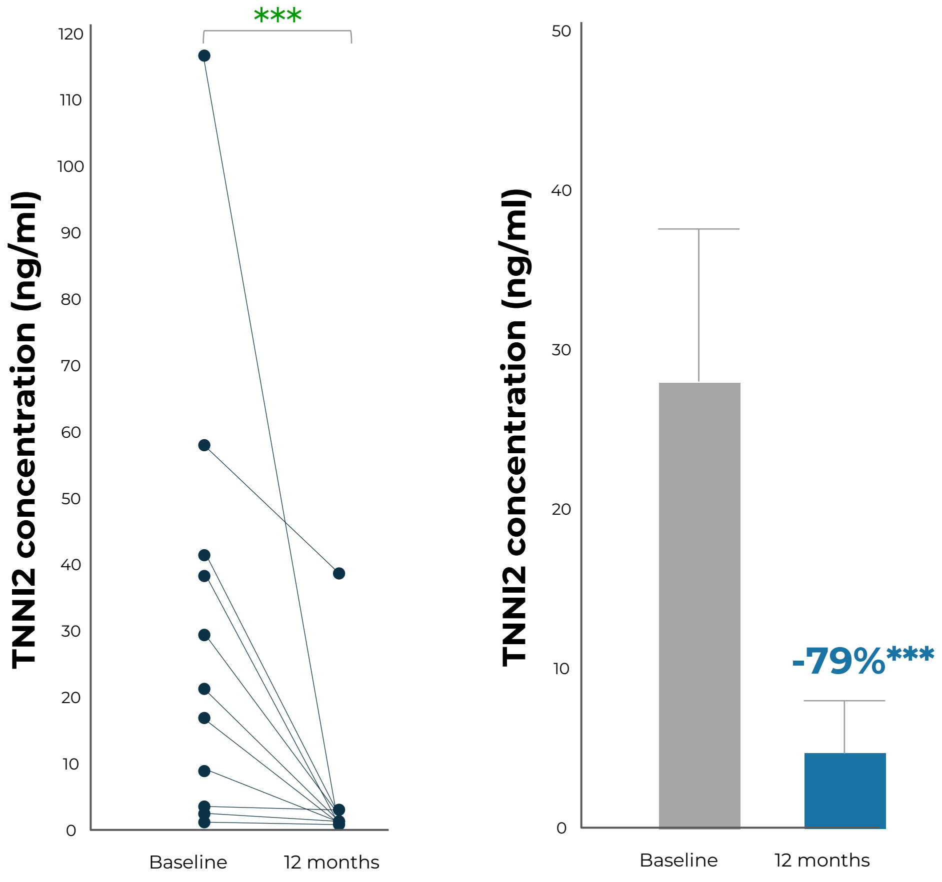
ARCH

Sevasemten (EDG-5506) led to a **sustained decrease in biomarkers of muscle damage** after 12 months of dosing

Creatine kinase (CK)



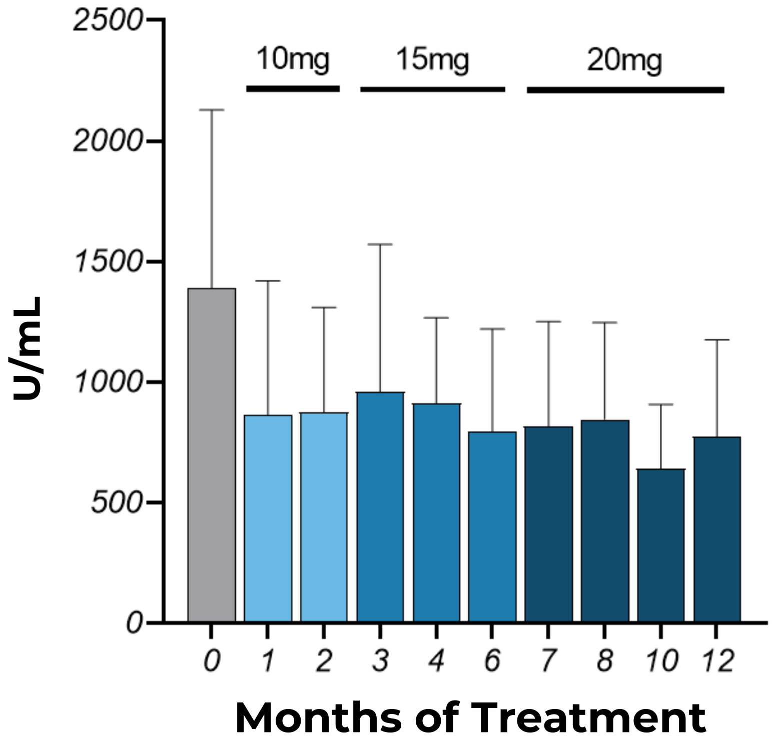
Fast skeletal muscle troponin I (TNNI2)



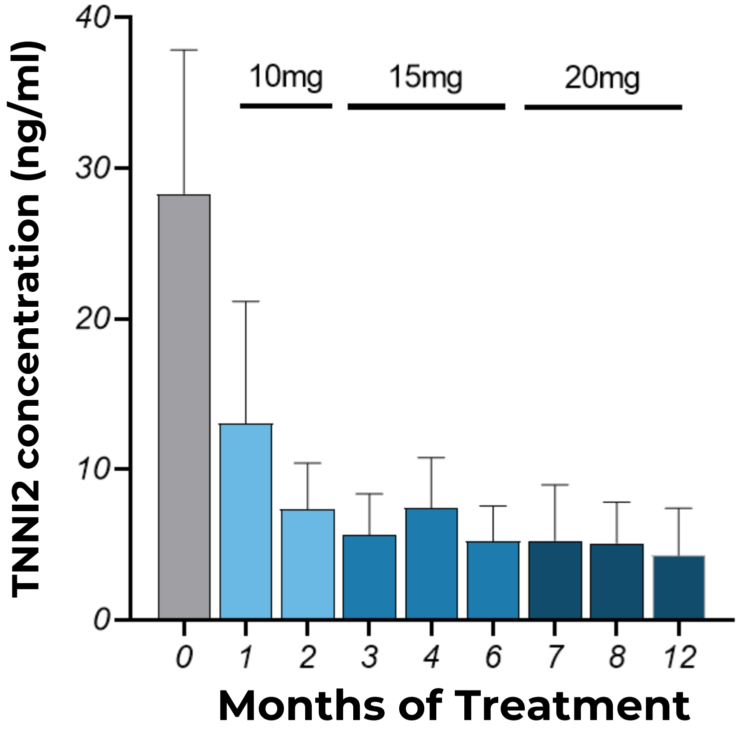
TNNI2 data projected from SOMAscan; % difference from baseline shown; Means ± SEM (**p=0.001 and ***p<0.0001)
Reference: Data on file

Biomarkers of muscle damage show **near maximal decrease at 2 months** of 10 mg daily dosing

Creatine kinase (CK)



Fast skeletal muscle troponin I (TNNI2)

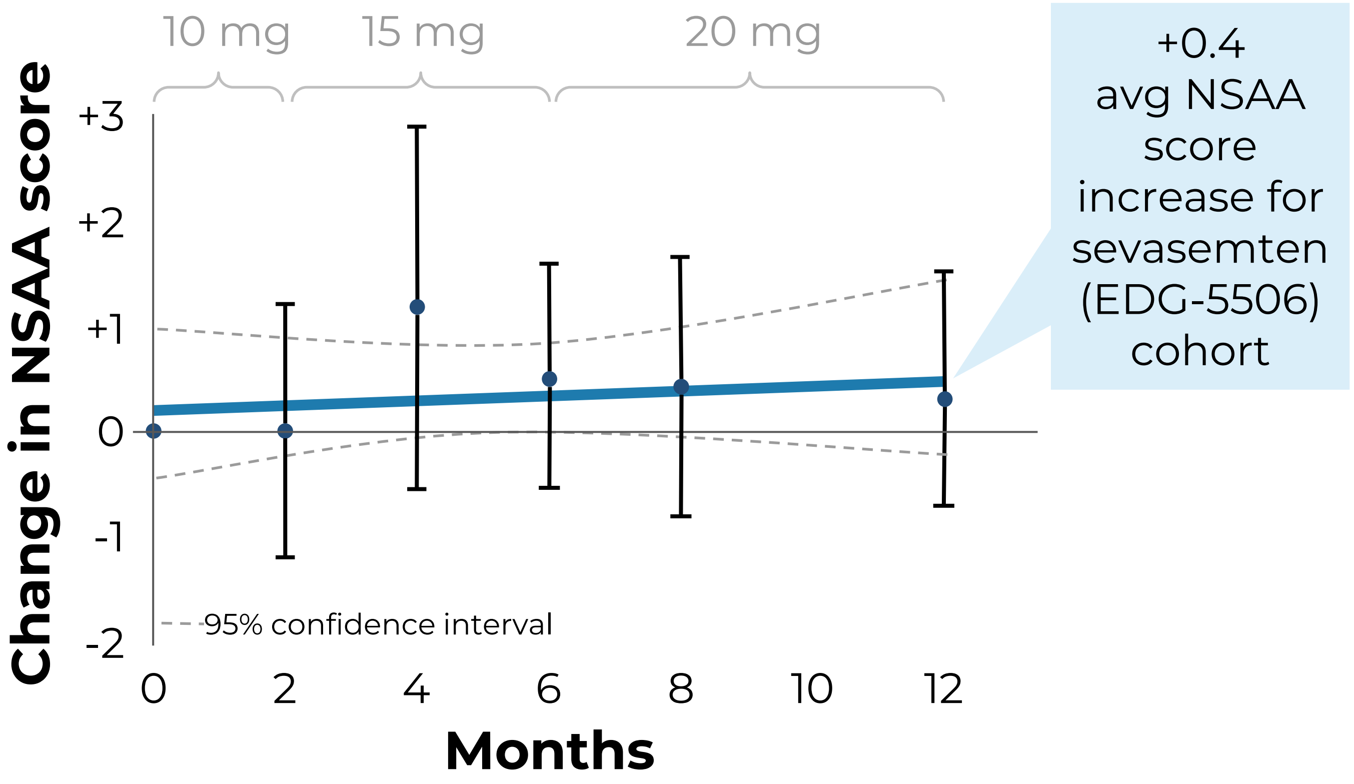


Rapid, significant and sustained decreases in biomarkers of muscle damage

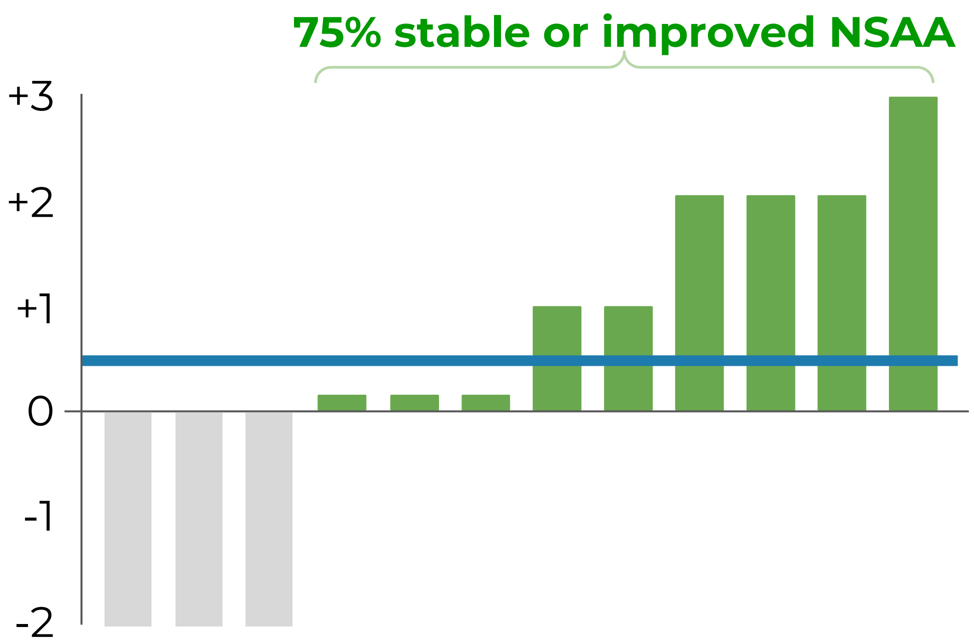
Means ± SEM; * Fast skeletal muscle troponin I assessed by SOMAscan
Reference: Data on file

NSAA mean +0.4 improvement relative to -1.2 point predicted by natural history

NSAA change over 12 months



Individual ARCH participant NSAA responses at 12 months

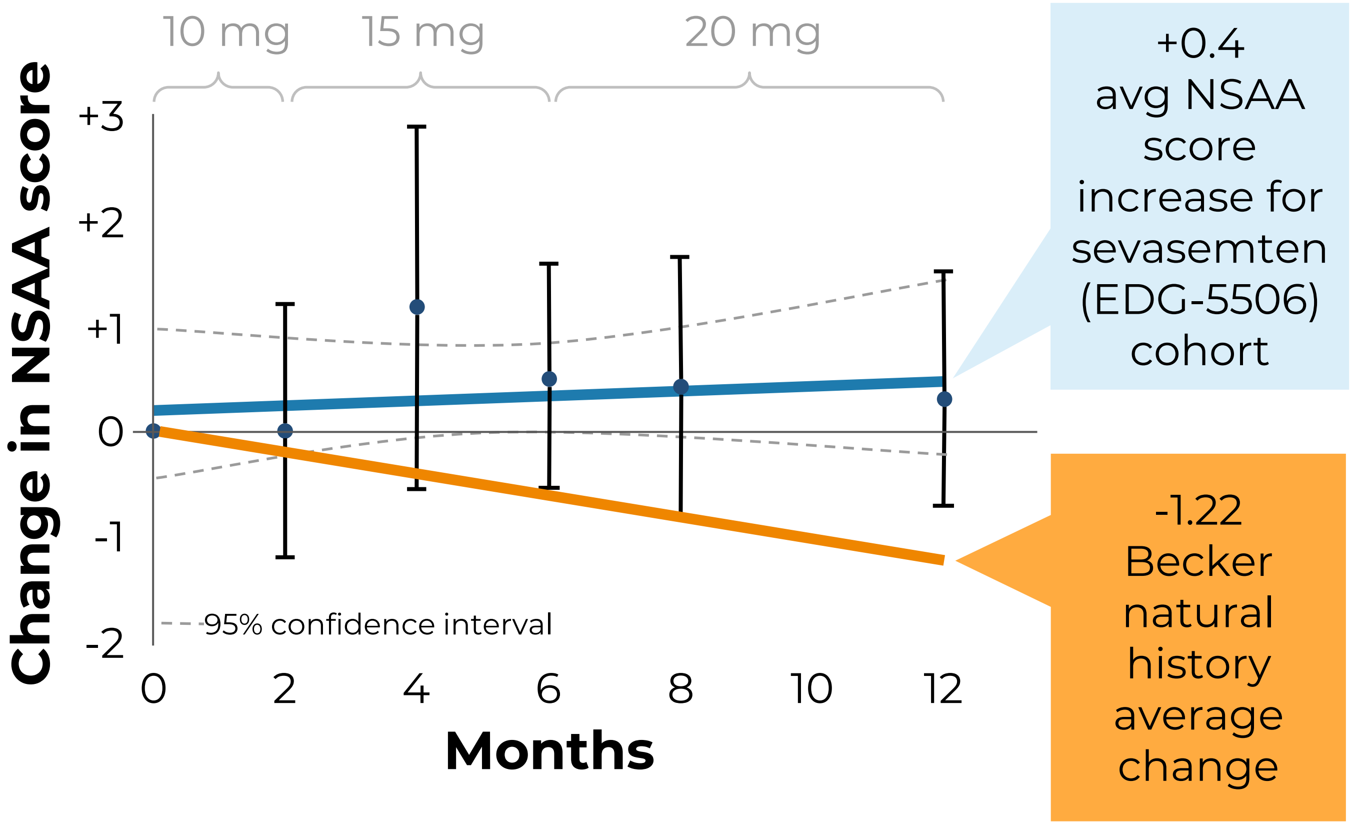


Means ± 95% CI; Natural history based on data presented by Luca Bello at MDA (2022) and van de Velde NM et. al., Neurology, 2021
Abbreviations: NSAA, North Star Ambulatory Assessment
Reference: Data on file

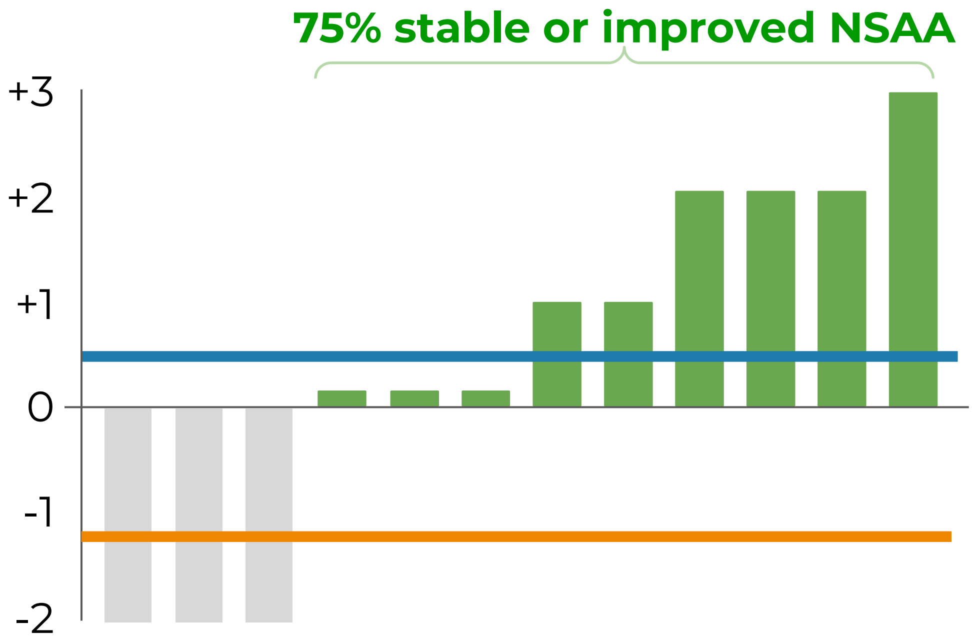
NSAA mean +0.4 improvement relative to -1.2 point predicted by natural history

ARCH

NSAA change over 12 months



Individual ARCH participant NSAA responses at 12 months

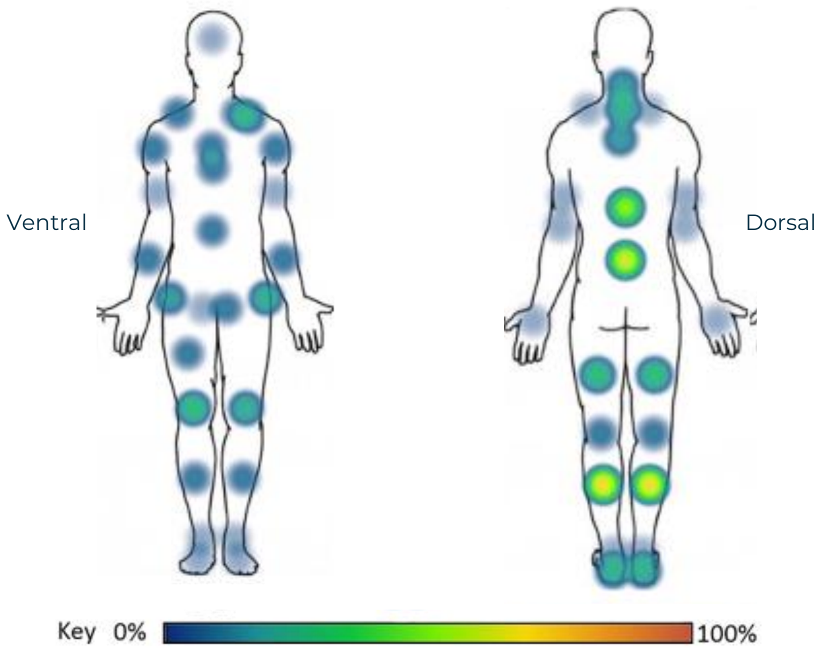


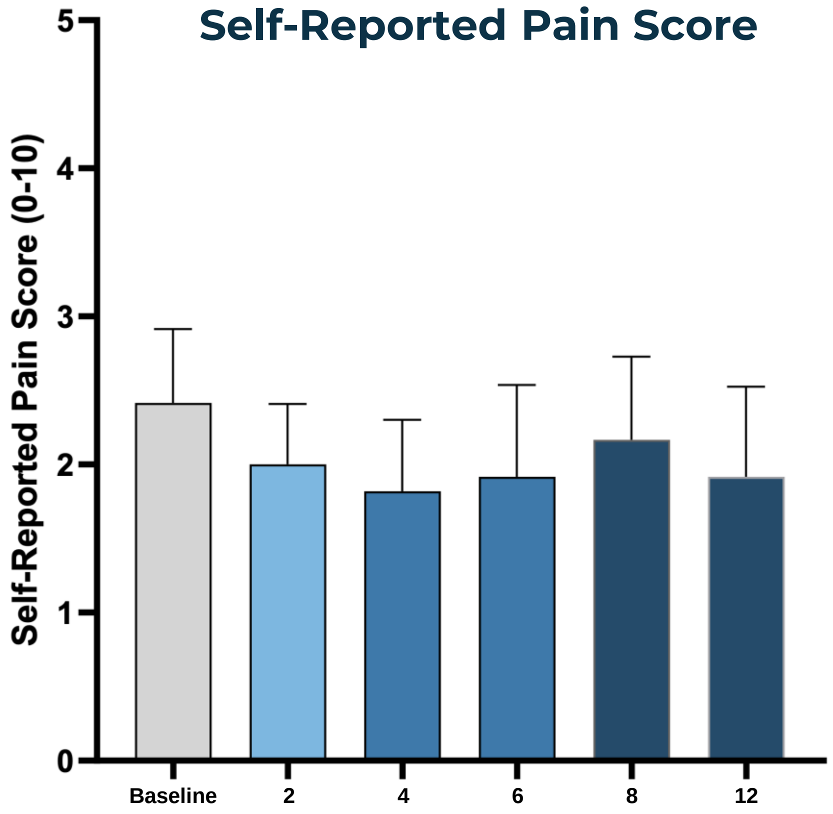
Means ± 95% CI; Natural history based on data presented by Luca Bello at MDA (2022) and van de Velde NM et. al., Neurology, 2021
Abbreviations: NSAA, North Star Ambulatory Assessment
Reference: Data on file

Self-reported pain scores trended better after 12 months with sevasemten (EDG-5506)

ARCH

Becker individuals report diffuse pain, particularly in back and calves





While the ARCH study is not placebo controlled, a positive trend in self-reported pain scores was observed after 12 months of sevasemten (EDG-5506) dosing

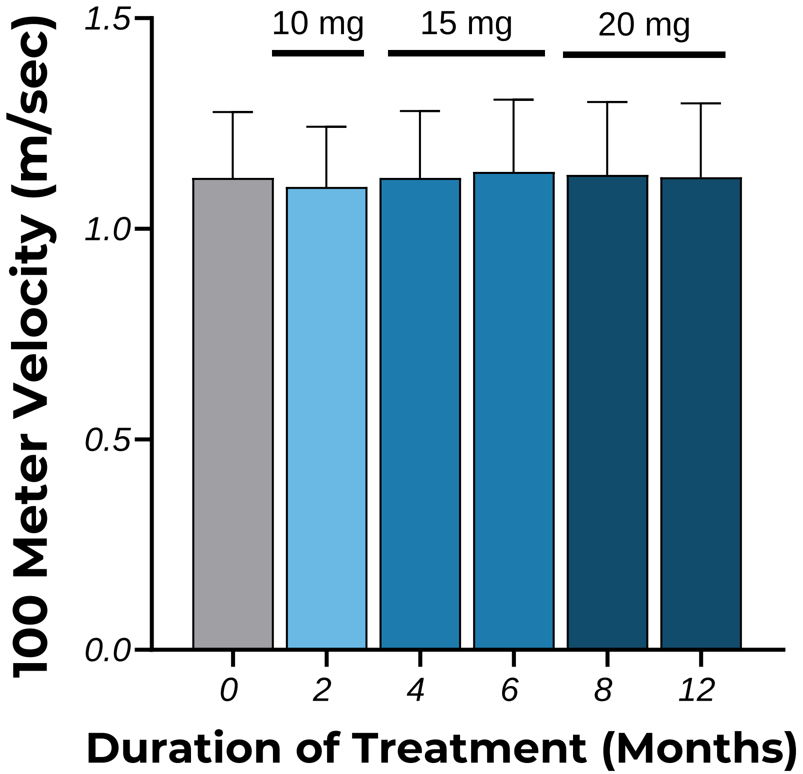
Means ± SEM;

References: 1. Data on file; 2. Jacques MF, et. al., 2019, PLOS ONE

ARCH

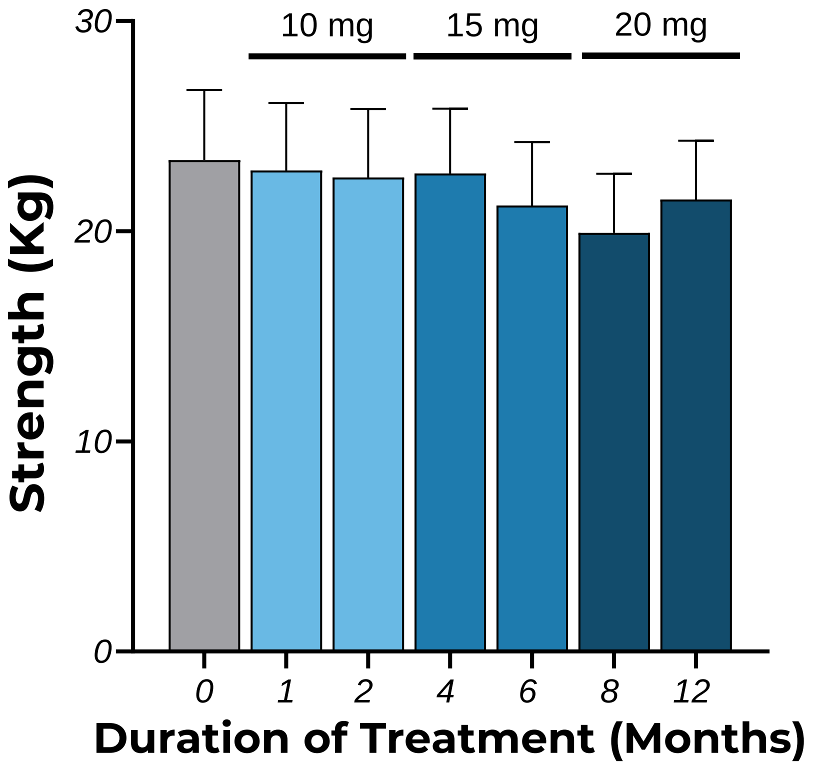
No decline from baseline at 12 months on other functional endpoints

100-Meter Timed Test Velocity



No statistically significant change at 12 months

Maximum Grip Strength



No statistically significant change at 12 months

All N=12, except for 2 missing values, month 4 and 8 for which last observation was carried forward
Mean ± SEM
Reference: Data on file

ARCH Outcomes of the ARCH study

Safety	Biomarkers	Function	Pivotal dose identified
Well-tolerated at all doses	Demonstration of **rapid, sustained and significant decreases** in multiple biomarkers of muscle damage	**Stabilization of functional assessments** with trends toward improvement	Maximal biomarker response at 10 mg dose PK/PD supportive of **10 mg dose for pivotal cohort** (NCT05291091)

Overall, the ARCH trial identified key factors for the design of a potentially registrational trial

GRAND CANYON Pivotal study in Becker

An 18-month long trial to evaluate the effect of sevasemten (EDG-5506) on efficacy and safety in individuals living with Becker

Key inclusion criteria:

- ✓ Male, ages 18-50
- ✓ Mutation in Duchenne gene with Becker phenotype
- ✓ Ambulatory with NSAA between 5 and 32

Anticipated to enroll 120 adult males diagnosed with Becker muscular dystrophy in the US and Europe

*NCT05291091

Sevasemten (EDG-5506) ongoing trials in muscular dystrophy

ARCH
Phase 1 Open Label
Becker
Fully Enrolled

DUNE
Phase 2
LGMD2I, Becker, McArdle
Fully Enrolled

MESA
Open Label Extension Study
Becker
Enrolling

GRASP-01-002
Natural History Study
Becker
Enrolling

CANYON
Phase 2
Becker
Fully Enrolled

Grand CANYON
Pivotal Cohort
Becker
Enrolling

LYNX
Phase 2
Duchenne
Enrolling

FOX
Phase 2
Duchenne (on Gene Therapy)
Enrolling

Legend: Becker; Duchenne

Abbreviations: LGMD2I, limb-girdle muscular dystrophy

Thank you

- We wish to thank the patients, investigators, study site personnel, and all those helping facilitate clinical trials and improving care!
- To inquire about clinical trial participation, email: studies@edgewisetx.com
- To learn more about us and our commitment to rare muscular dystrophies, visit us at Booth #501