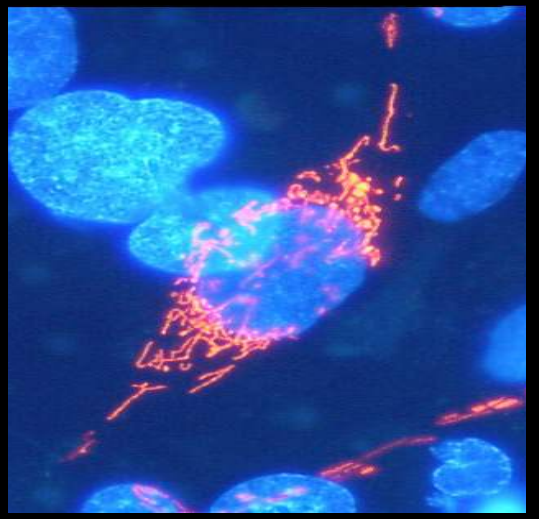
Exercise, Diet, Nutrition and Nutraceuticals for the and Mitochondrial Disease Patient.

MitoAction - 2022.

Mark Tarnopolsky, MD, PhD.
Professor of Pediatrics and Medicine ,
(Neuromuscular and
Neurometabolic Disorders),
McMaster University, Hamilton, CANADA.



Disclosure

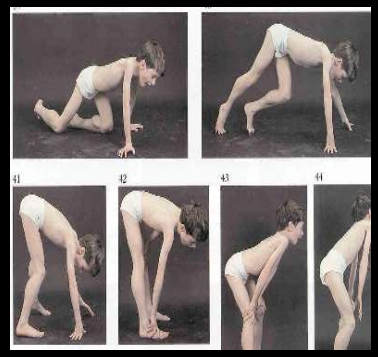
- Sanofi/Genzyme – speaker honorarium 2009, 2010-22, ad-board 2022.
- Ultragenyx – GNE study 2016-2018.
- Amicus Therapeutics – Pompe clinical trial site, 2020-22.
- Reneo Pharma – DSMB and eligibility expert, 2021-22.
- Stealth BioTherapeutics – clinical trial site – 2018-20.
- Founder and CEO of Exerkine Corporation/Stayabove Nutrition.

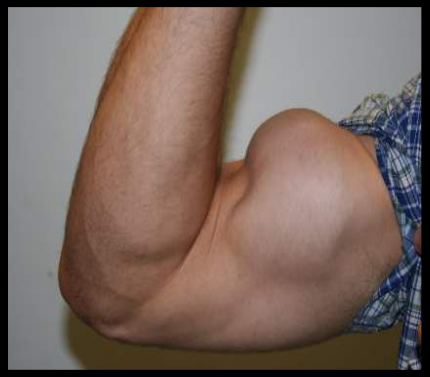
Pathological Disorders

Physiological Adaptation

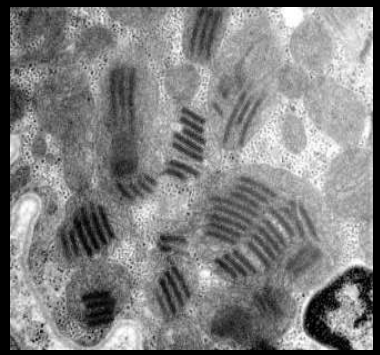
Atrophy

Hypertrophy





obesity, T2DM,
mitochondrial disease,
immobilization,
neuropathy
sarcopenia/aging,
cancer,
statin myopathy,
corticosteroids

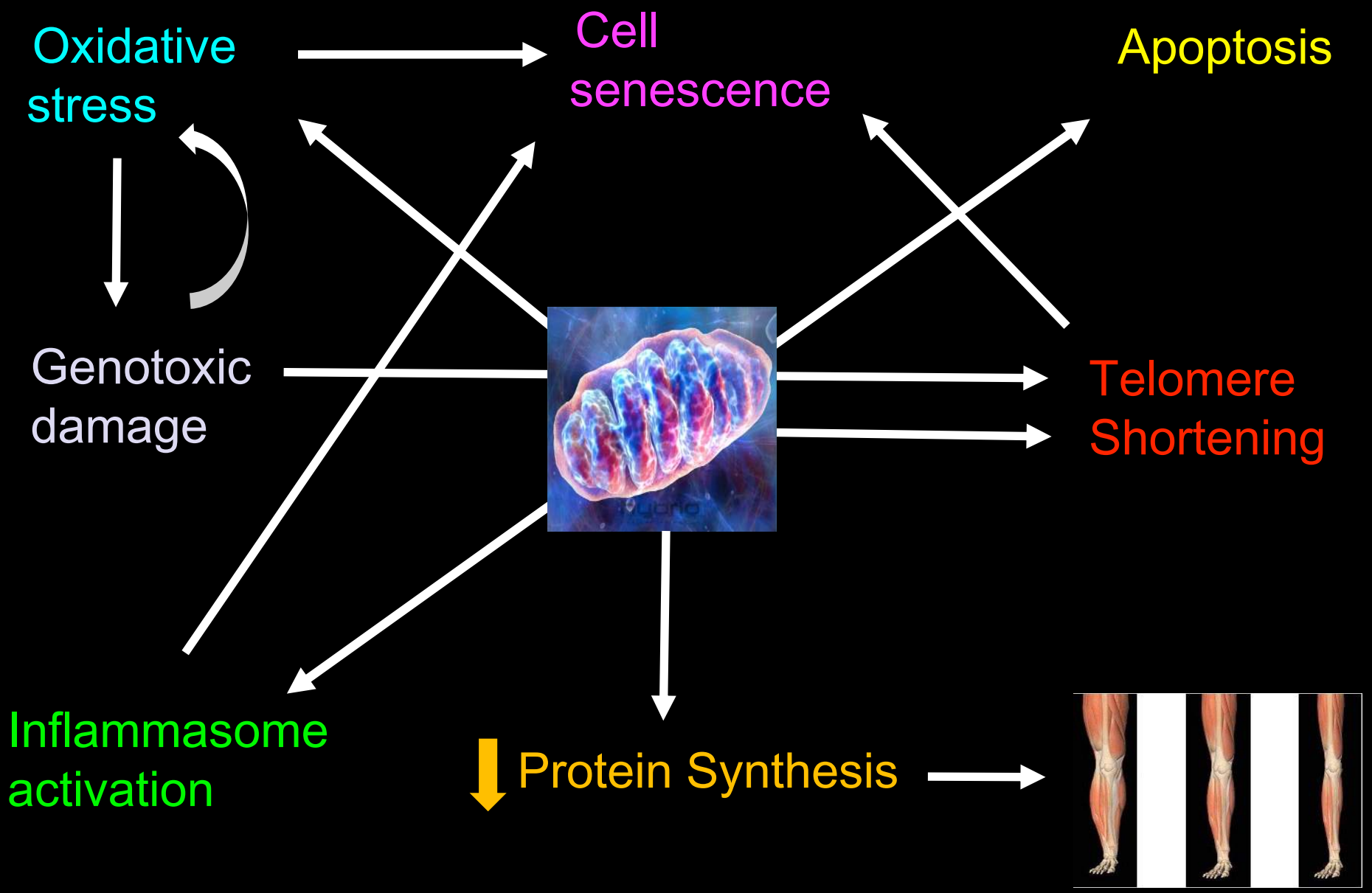


nutrition, drugs, exercise

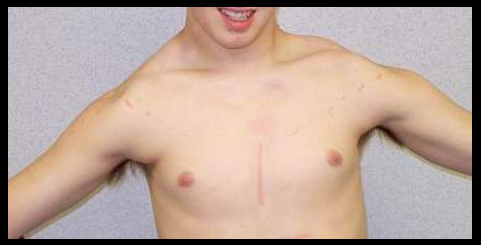
Mitochondrial Dysfunction

Mitochondrial Biogenesis

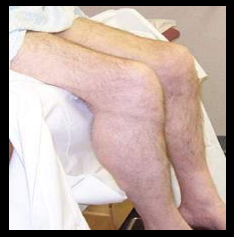
AGING/SARCOPENIA - Lopez-Otin, et al, *Cell*, 153:1194, 2013



FSHD



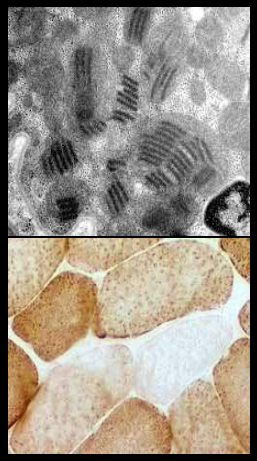
sIBM



DM1

HUMAN AGING

Mitochondrial Disease/ Dysfunction



Oxidative stress

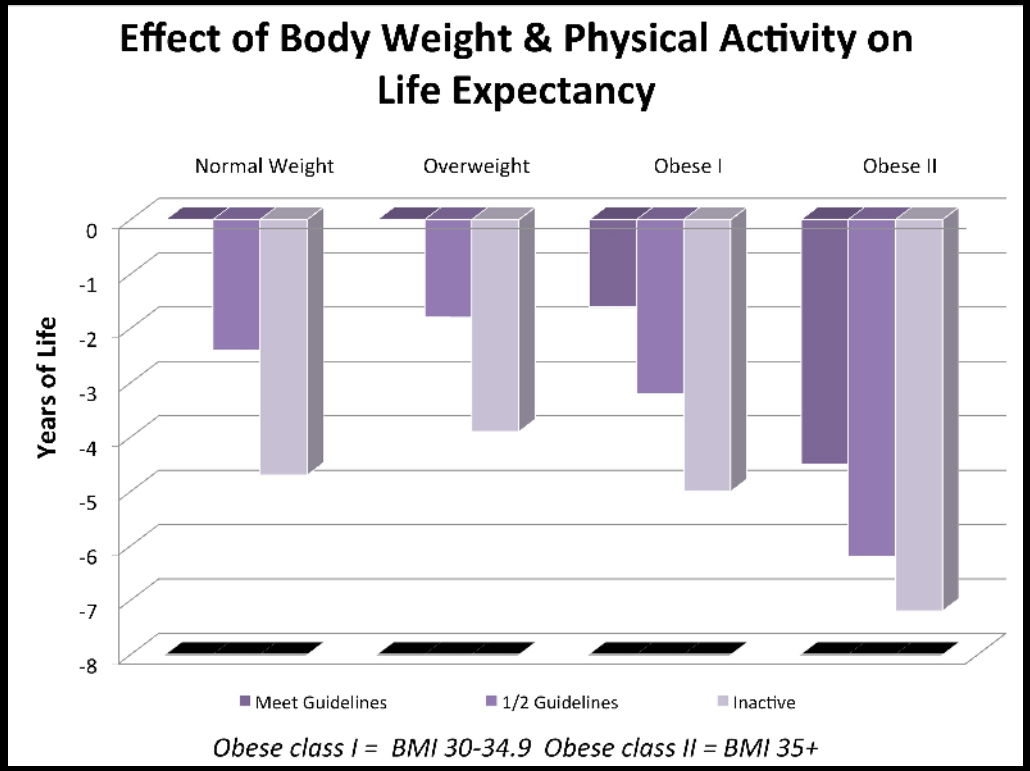
PRO SYN

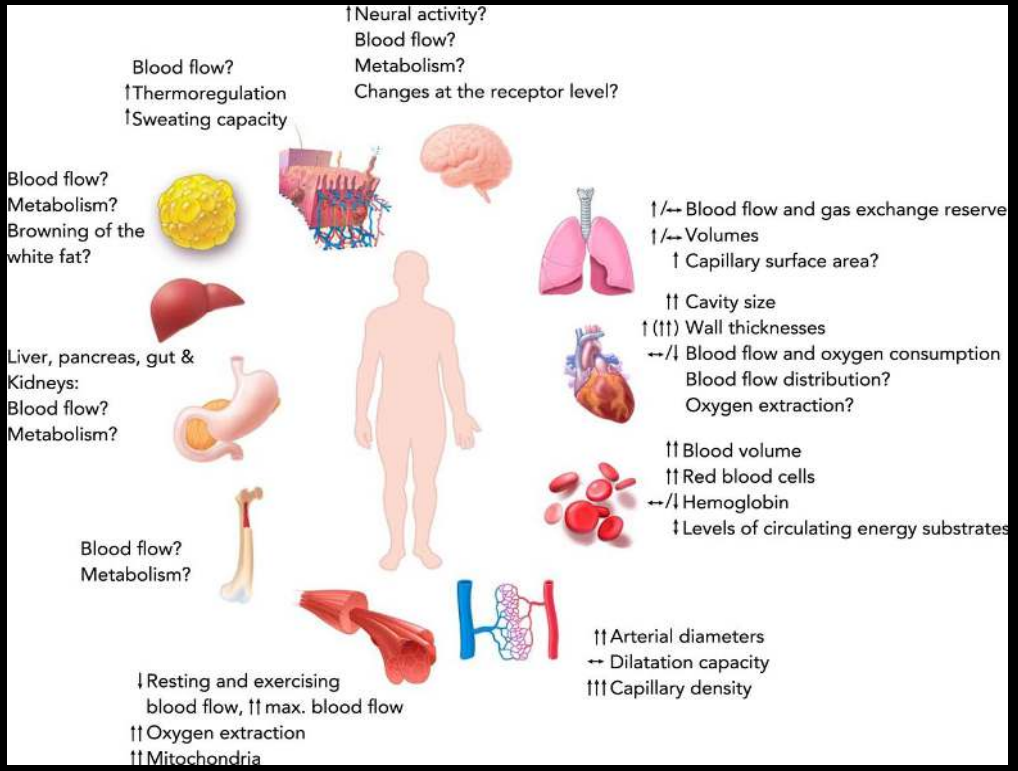
Inflammation

Stem (satellite) cell exhaustion/dysfunction

nutrition, drugs, exercise

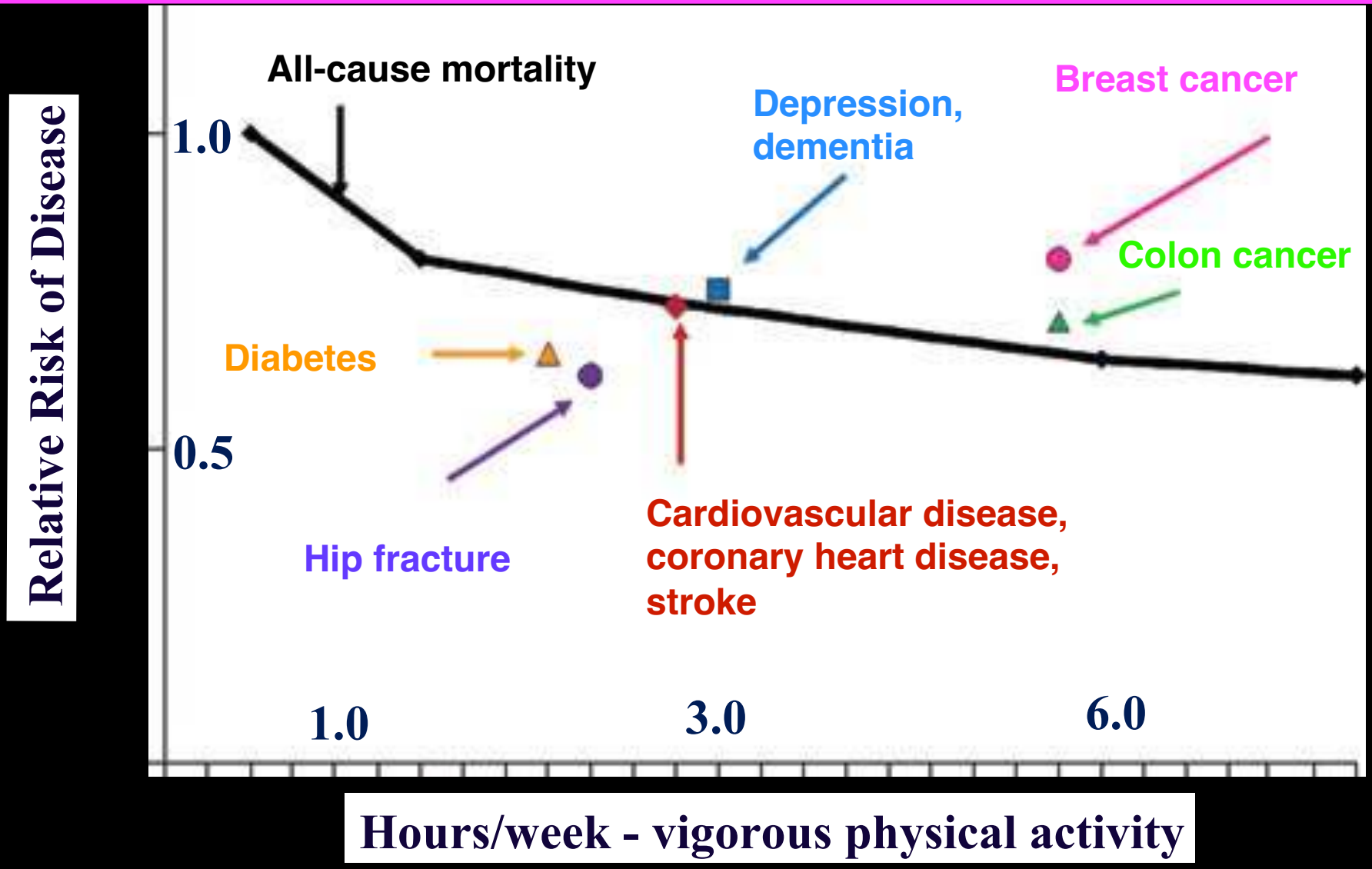
BENEFITS OF EXERCISE





Physical Activity for Health

Powell, Paluch, **Blair, SN**. *Ann Rev Public Health.* 32:349-, 2011.



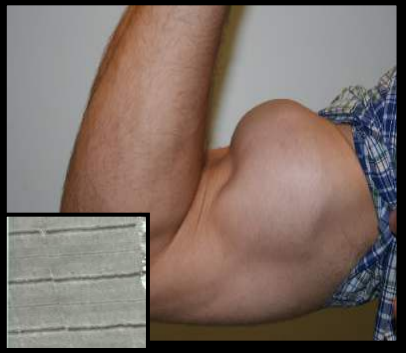
Endurance exercise in mito. disease

- A low VO_{2max} is a hallmark of mitochondrial disorders (+/- deconditioning).
- 14 d of immobilization of leg = coordinate down-regulation of over 50 mRNA species coding for mitochondrial components (Abadi, A., et al, *PLoS ONE*, 2009).
- Exercise can increase ETC enzyme activity and whole body VO_{2max} in healthy people.
- Even if O_2 extraction is not altered, an increase in DO_2 will increase VO_{2max}.

60 mins/day, 3/week, 4 months

ENDURANCE EXERCISE

RESISTANCE EXERCISE



10 reps x 3 sets, 3/week, 4 months

Endurance exercise training

- N = 20 MITO (14 point mutations in mtDNA; N = 16 healthy controls).
- 12 week cycle @ 70 % VO_{2peak}, 4 X/week.
- ⬆CS (67 %); ⬆VO_{2peak} (67 %); (same in controls).
- No increase in CK or muscle morphology.

Jeppesen T., et al., Brain 129:3402-, 2006

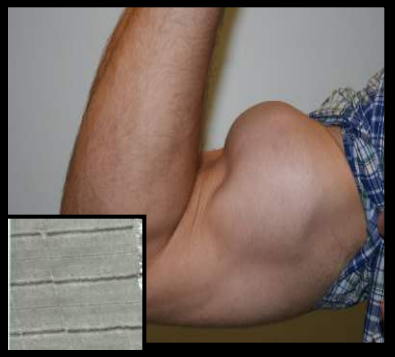
Endurance exercise training

- N = 8 MITO (single deletions).
- 14 weeks cycle training.
- 14 weeks of deconditioning.
- ⬆ sub-max work rate; O_2 extraction; SF-36 (QOL).
- Returned to baseline after 14 weeks.

Taivassalo, et al., *Brain* 129:3391-, 2006

60 mins/day, 3/week, 4 months

ENDURANCE EXERCISE



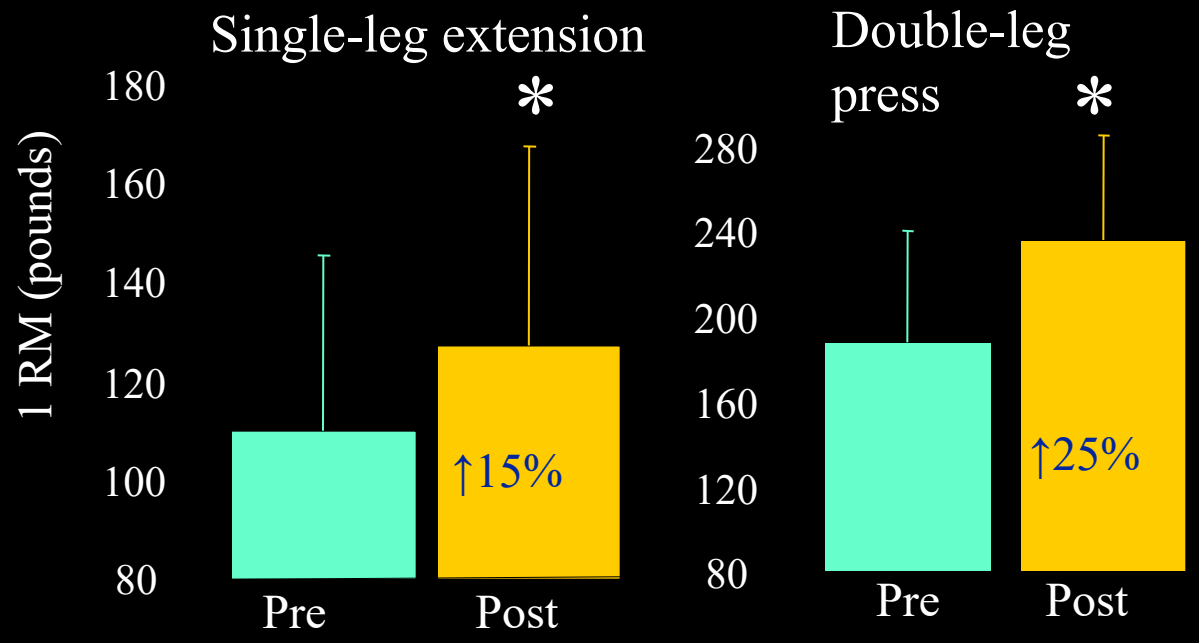
RESISTANCE EXERCISE

10 reps x 3 sets, 3/week, 4 months

Resistance training in Mitochondrial myopathy

- Group of 8 patients: (39±9 y) with single large-scale deletions.

- Training Protocol
  - Bilateral leg extension/flexion, leg press
  - 12 weeks, 3 x per week at 80-85% 1RM 6 sets, 6-8 reps)



CK pre: 187 ± 115 U/L
CK post: 166 ± 159 U/L

Taivassalo, Gardner, Haller and Turnbull, Brain, 2009.

The Journal of Clinical Investigation CLINICAL MEDICINE

Aerobic exercise elicits clinical adaptations in myotonic dystrophy type 1 patients independently of pathophysiological changes

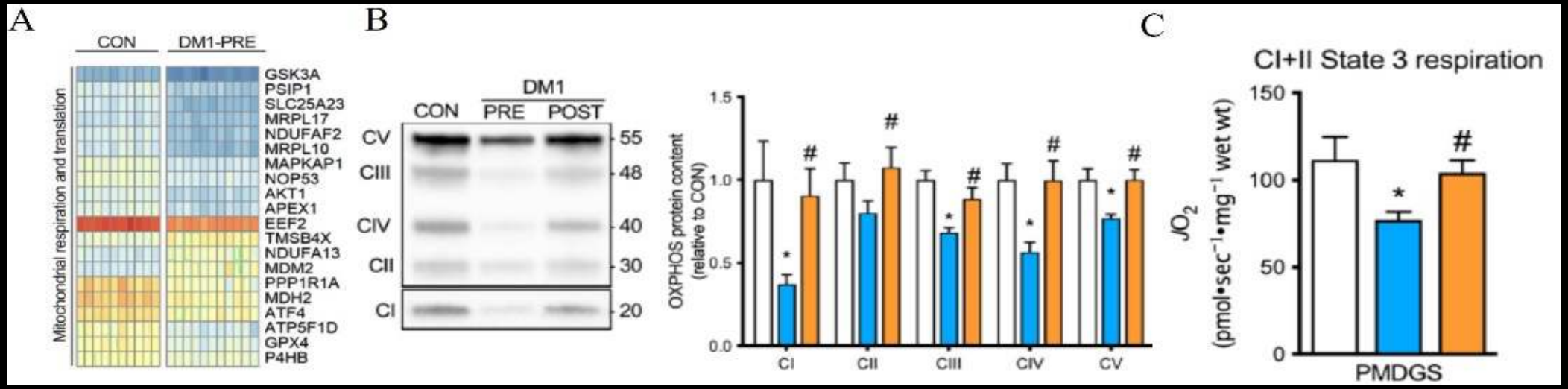
Andrew I. Mikhail,[1] Peter L. Nagy,[2] Katherine Manta,[3] Nicholas Rouse,[2] Alexander Manta,[1] Sean Y. Ng,[1] Michael F. Nagy,[2] Paul Smith,[2] Jian-Qiang Lu,[4] Joshua P. Nederveen,[3] Vladimir Ljubicic,[1] and Mark A. Tarnopolsky[3,5]

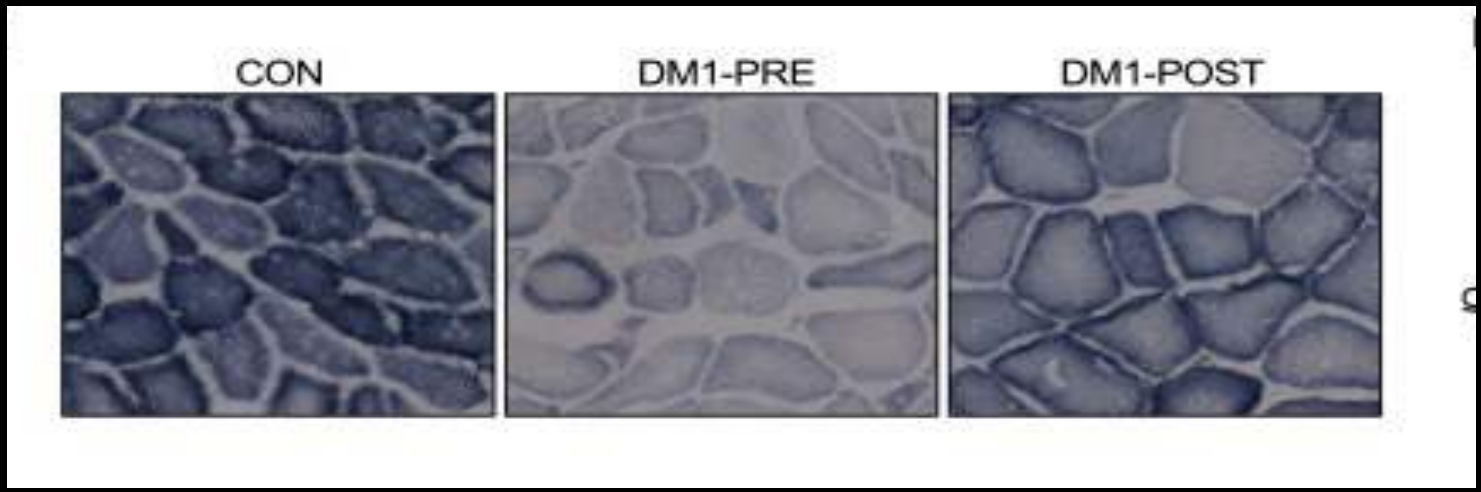
[1]Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada. [2]Praxis Genomics LLC, Atlanta, Georgia, USA. [3]Department of Pediatrics, McMaster University Children's Hospital, Hamilton, Ontario, Canada. [4]Department of Pathology and Molecular Medicine/Neuropathology, McMaster University, Hamilton, Ontario, Canada. [5]Exerkine Corp., McMaster University Medical Center, Hamilton, Ontario, Canada.

- DM1 is a CTG trinucleotide spliceopathy that affects most tissues and leads to muscle weakness disability and death – therapy is supportive.
- N – 11 DM1 vs age and sex matched controls.
- 3 months cycling, 3 times a week at 65 % VO2 peak for 35 min.

Mikhail, et al., *J.Clin.Invest.*, 132 (10), 2022.

Exercise can reverse mitochondrial dysfunction in Myotonic MD Type 1.





Mikhail, et al., *J.Clin.Invest.*, 132 (10), 2022.

Exercise can improve function in Myotonic MD Type 1.

Mikhail, et al., *J.Clin.Invest.*, 132 (10), 2022.

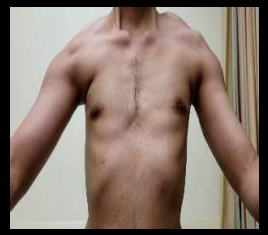
- Safe – histopathology, CK, cardiac, joint.
- Increase function (6MWT – 47 m, TUG, 5XSTS).
- ~ 30 % $VO_{2peak.}$
- 1.6 kg (4.3 %) LBM.

Impact of Habitual Exercise on the Strength of Individuals with Myotonic Dystrophy Type 1

ABSTRACT

Brady LI, MacNeil LG, Tarnopolsky MA: Impact of habitual exercise on the strength of individuals with myotonic dystrophy type 1. Am J Phys Med Rehabil 2014;93:739–750.

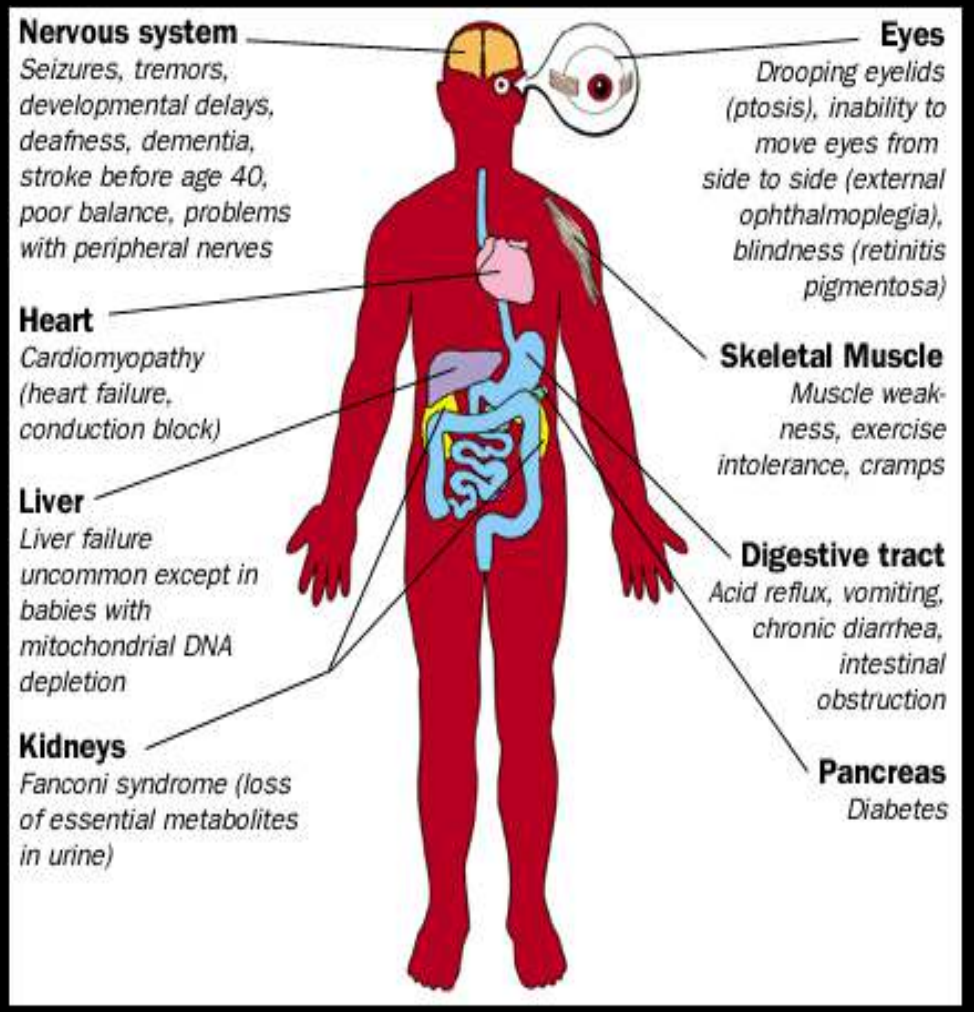
Exercise is Medicine!



FSHD – demethylation of DUX4 = oxidative stress and MITOCHONDRIAL DYSFUNCITON

Mitochondrial Disorders

- Habitual diet.
- Specific Nutrients and the Mitochondrial cocktail.
- Novel mitochondrial cocktails.



Nutritional Inadequacy in Patients with Muscular Dystrophy.

- N = 51 MD patients (DM1, LGMD, FSHD).
- N = 14 DMD patients (< 16y).
- Prospective dietary analysis for 3 days separated by 5 months.
- Mean values reported.
- Compare to Canadian DRI.

Motglah, et al, *Muscle and Nerve*, 2005

Current Research-Nutrition % NOT meeting the DRI.

- Energy = 68/64
- Vit A = 45/14
- Vit C = 40/14
- Vit D = 78/71
- Vit E = 98/78
- Vit K = 86/85
- Thiamine = 26/14
- Riboflavin = 33/7
- Niacin = 15/7
- PRO = 16/0
- Vit B6 = 31/7
- Folate = 82/42
- Vit B12 = 23/0
- Pantothenate = 80/35
- Biotin = 90/17
- Calcium = 72/64
- Iron = 29/21
- Zn = 54/14

ADULT/PEDIATRIC

MD vs Mitochondrial disease.

Motagleh, and Tarnopolsky, *Muscle Nerve*, 2005, Tarnopolsky, et al, *Muscle Nerve*, 1997.

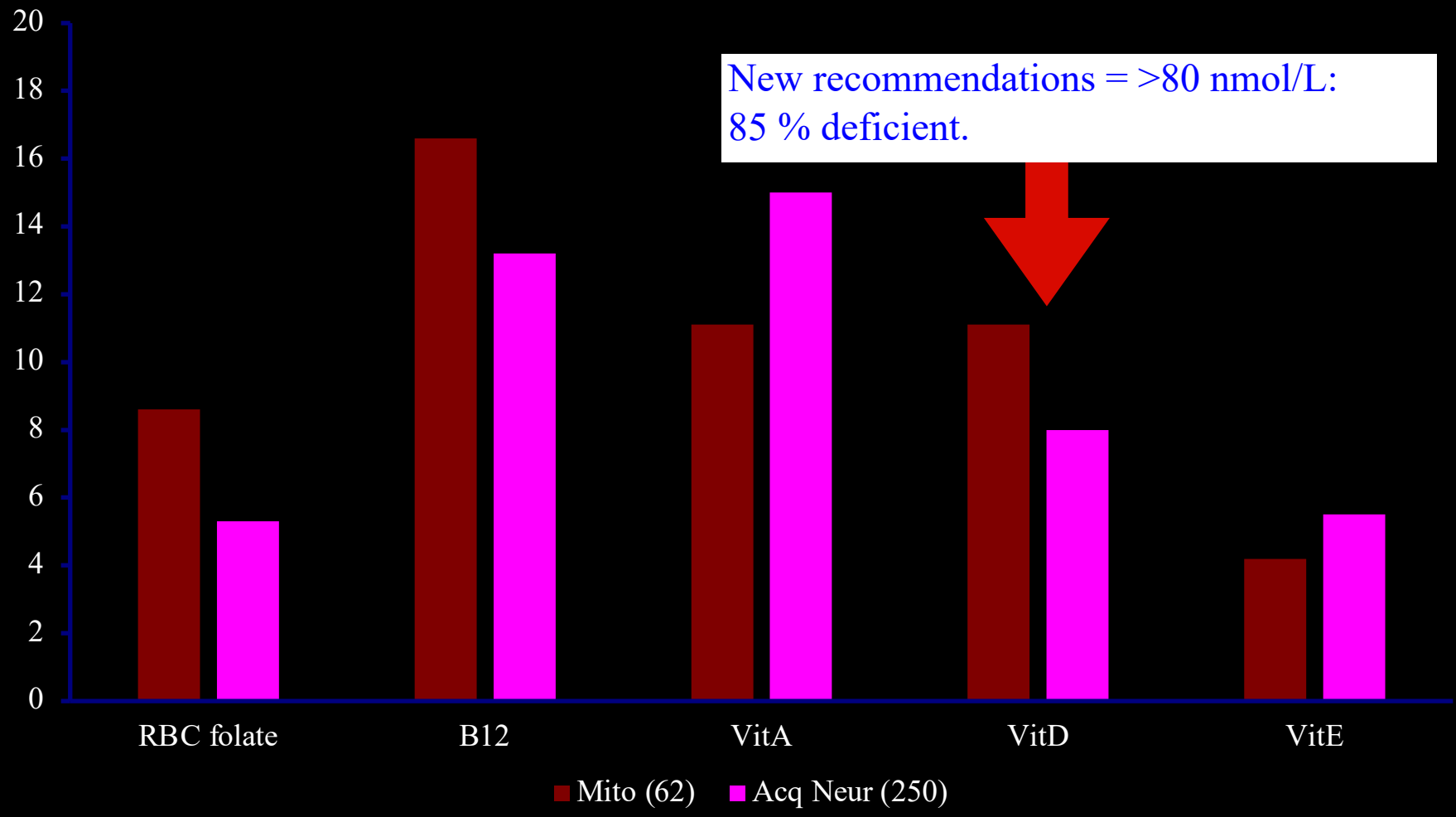
	DM1 (29)	MD (21)	MITO (9)
BMI (> 30)	10 %	18 %	14 %
BMI (< 18.5)	13 %	9 %	14 %
Energy (< RNI)	62 %	82 %	43 %
PRO (< RDI)	10 %	5 %	14 %
FAT (> 30 %)	55 %	86 %	57 %
Vit. E (< ADMR)	90 %	86 %	44 %
Vit C (< ADMR)	31 %	18 %	14 %
Vit. B2 (< ADMR)	45 %	14 %	N/A
Vit. B12 (< ADMR)	17 %	5 %	N/A
Folate (< ADMR)	68 %	48 %	N/A

Serum Vitamin Levels

- July 1, 1996 ➡ June 15, 2001.
- McMaster University Neuromuscular Clinic
- N = 1852 (♂ = 905; ♀ = 947) blood tests with at least one vitamin level sent:
  - RBC folate
  - B12
  - Vitamin A
  - Vitamin D (25-OH)(Old recommendation).
  - Vitamin E

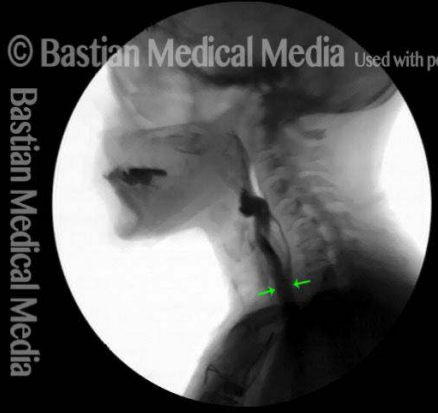
Dodig, D. and Tarnopolsky M., MS in preparation, 2022

Serum Vitamin Levels



Dodig, D. and Tarnopolsky M., MS in preparation, 2022

Habitual Diet – General conclusions/suggestions:

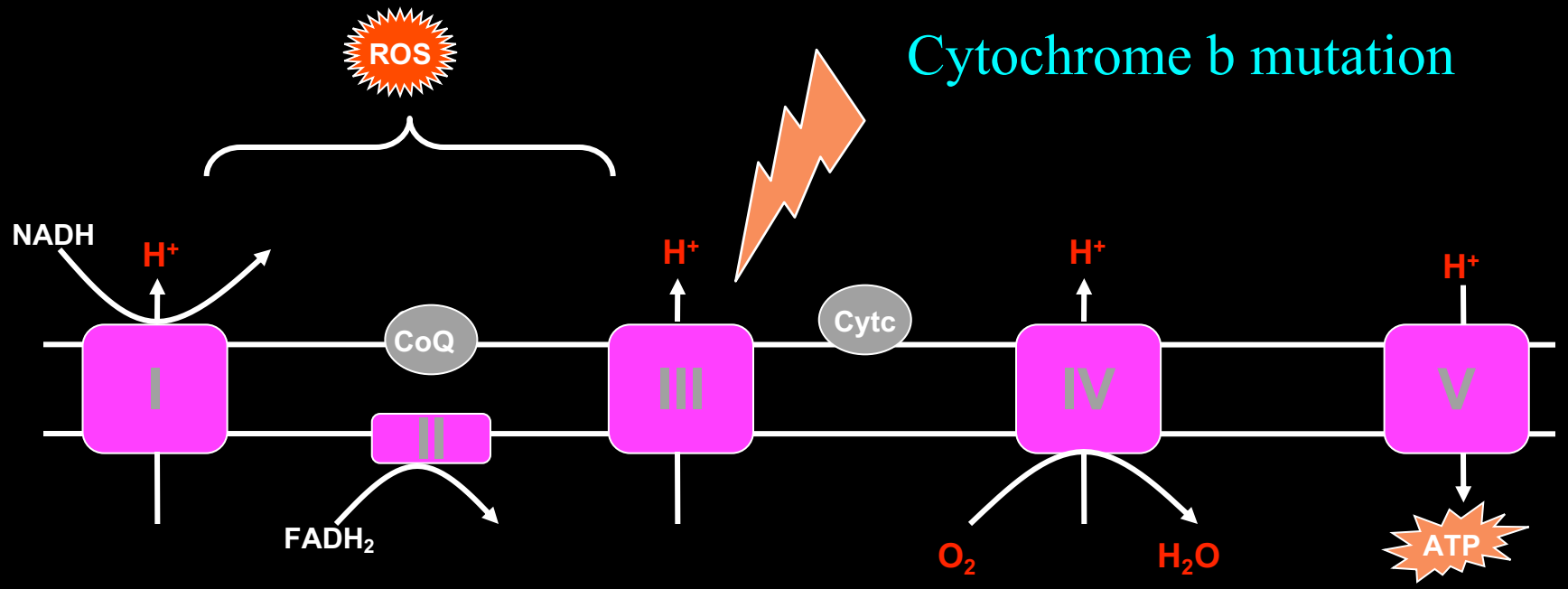


- Energy intake is low.
- Low expenditure; ? Low RMR.
- Food preparation/eating may be difficult.
- Fear of swallowing.
- Suggestions:
  - Swallowing study if any suggestion of dysphagia (CPEO).
  - Take a balanced multivitamin.
  - Check for deficiencies in patients – Rx as appropriate.
  - A deterioration in function in mitochondrial disease could be a vitamin deficiency.
  - G-tube early in kids falling off growth curve.

Habitual Diet – General suggestions – Continued.

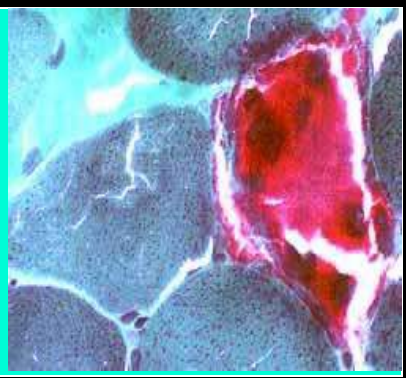
- Avoid fasting for prolonged periods (> 10 h).
- More frequent meals.
- Consider high fat in complex I with seizures or PDH deficiency.
- Treat iron and copper deficiency (ferritin > 50).
- Avoid alcohol > 2 drinks/day maximum.
- Avoid MSG and other migraine triggers (red wine, aged cheese, etc.) in MELAS patients with migraines.

Mitochondrial Dysfunction



- ATP
- Alt. E. Source
- ROS (free radicals)
- Lactate

- Mito proliferation
- Apoptosis
- Anti-oxidant enzyme



Mitochondrial Disease R_x Strategies

- **Bypass Defect** (**CoQ_{10}, succinate, riboflavin**).
- **Reduce Lactate** (**Dichloroacetate, thiamine**)
- **Anti-Oxidants** (**Vit E, lipoic acid**)
- **Alternative Energy** (**Creatine monohydrate**)
- **Exercise training** (**Aerobic vs strength**)
- **Vasodilatation** (**L-arginine**)
- **Folate deficiency** (**folate, folinic acid**)
- **Nucleotide precursors** (**triacetyluridine**)

Clinical Trials in Mito Disease.

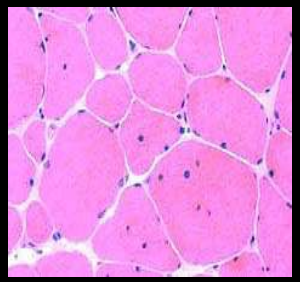
- Small numbers/OPEN studies.
- Outcome variables (ie. Anti-oxidant not likely to alter strength, exercise capacity in short-term).
- Often redundant "cocktails" (i.e., multiple anti-oxidants).
- Often single agents.
- Suggest: target the 3 "final common pathways"

(↑ ROS; ↓ Alt. E source; ↓ ETC flux)

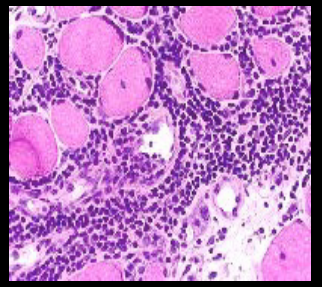
Low muscle TCr/PCr stores.

Mitochondrial DNA disorders. →

Muscle dystrophy. →

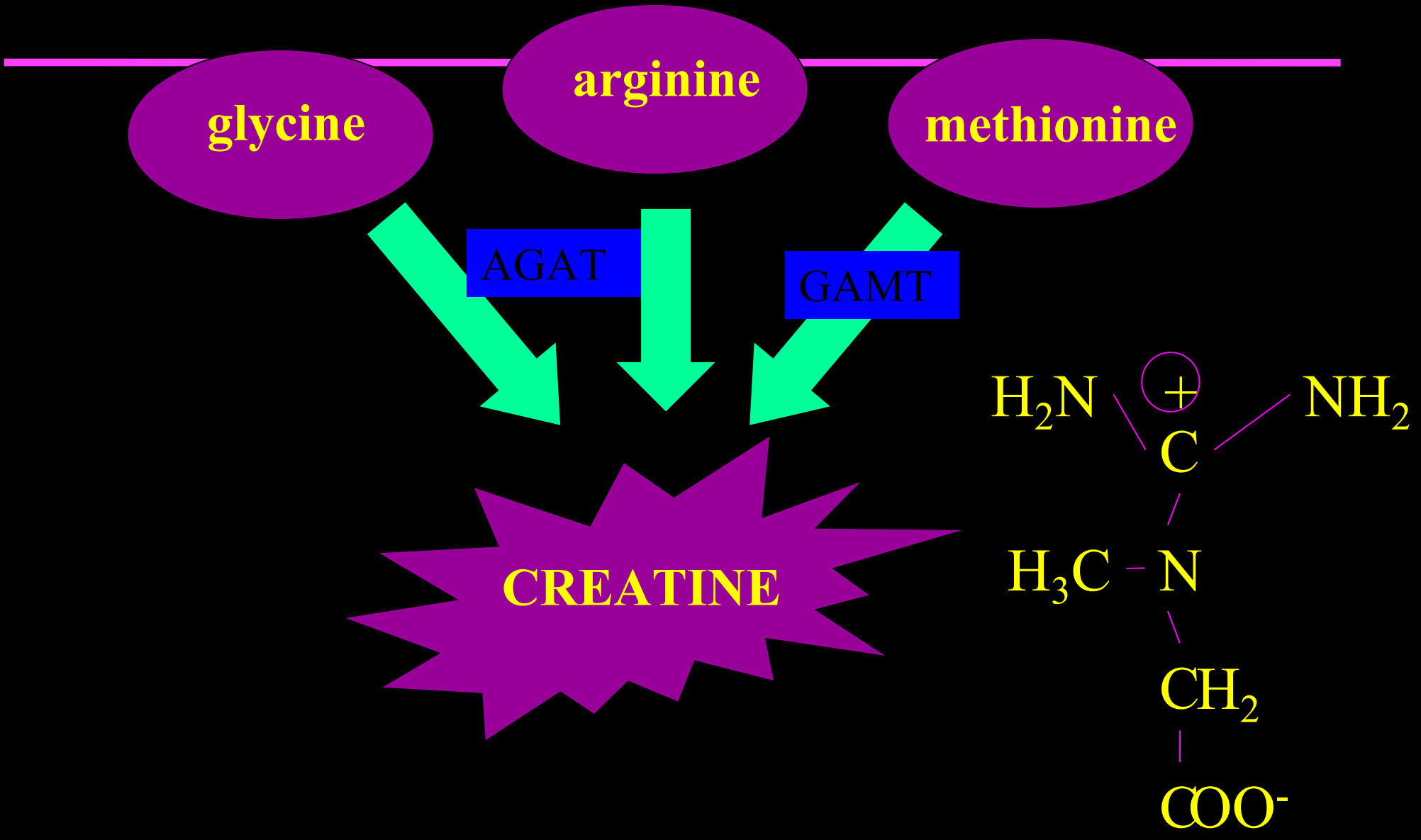


Inflammatory muscle disease. →

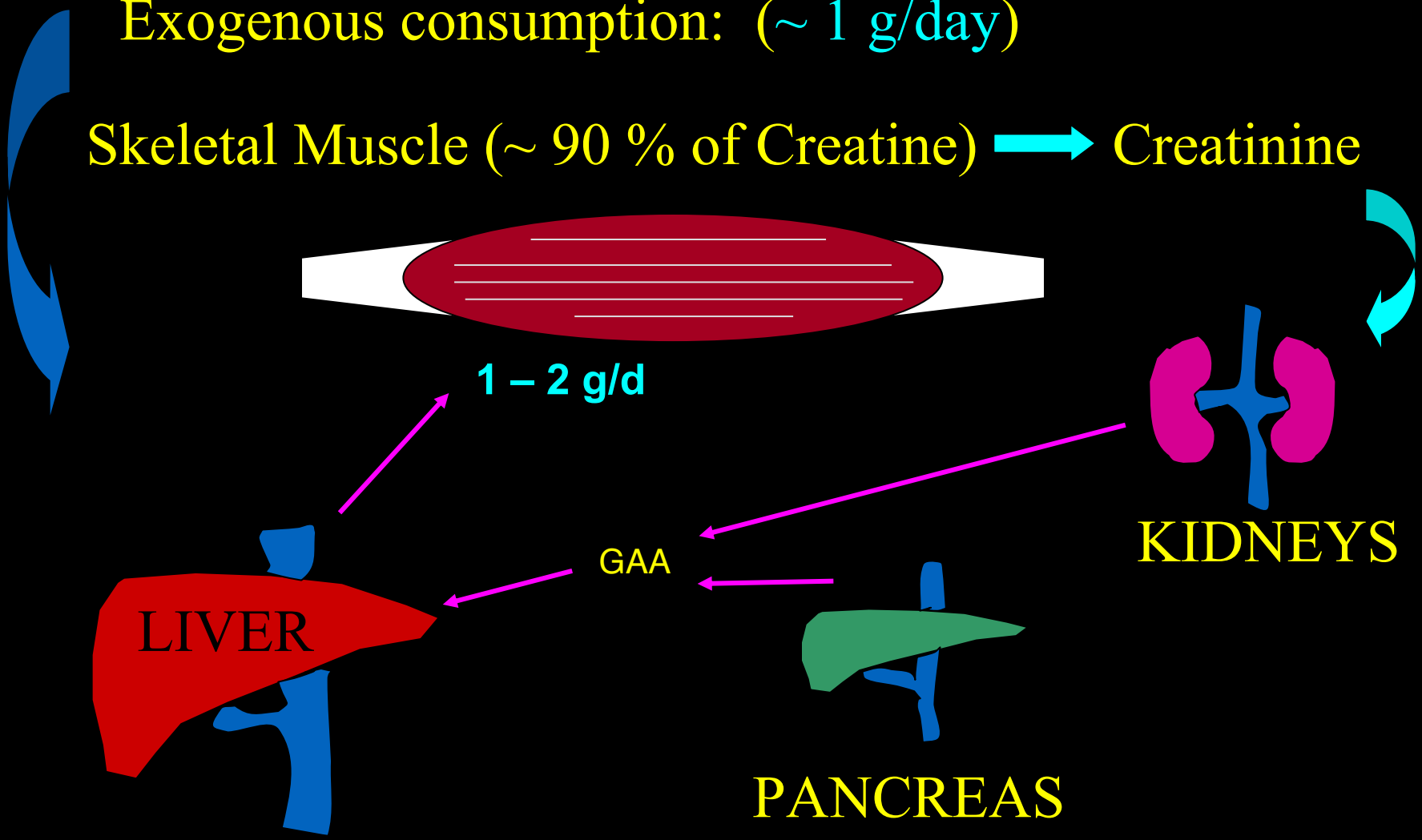


(Tarnopolsky and Parise, *Muscle + Nerve*, 1999).

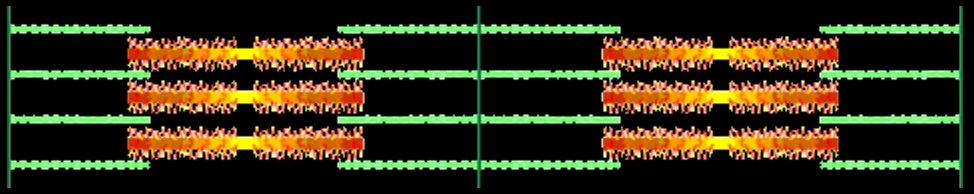
Creatine synthesis

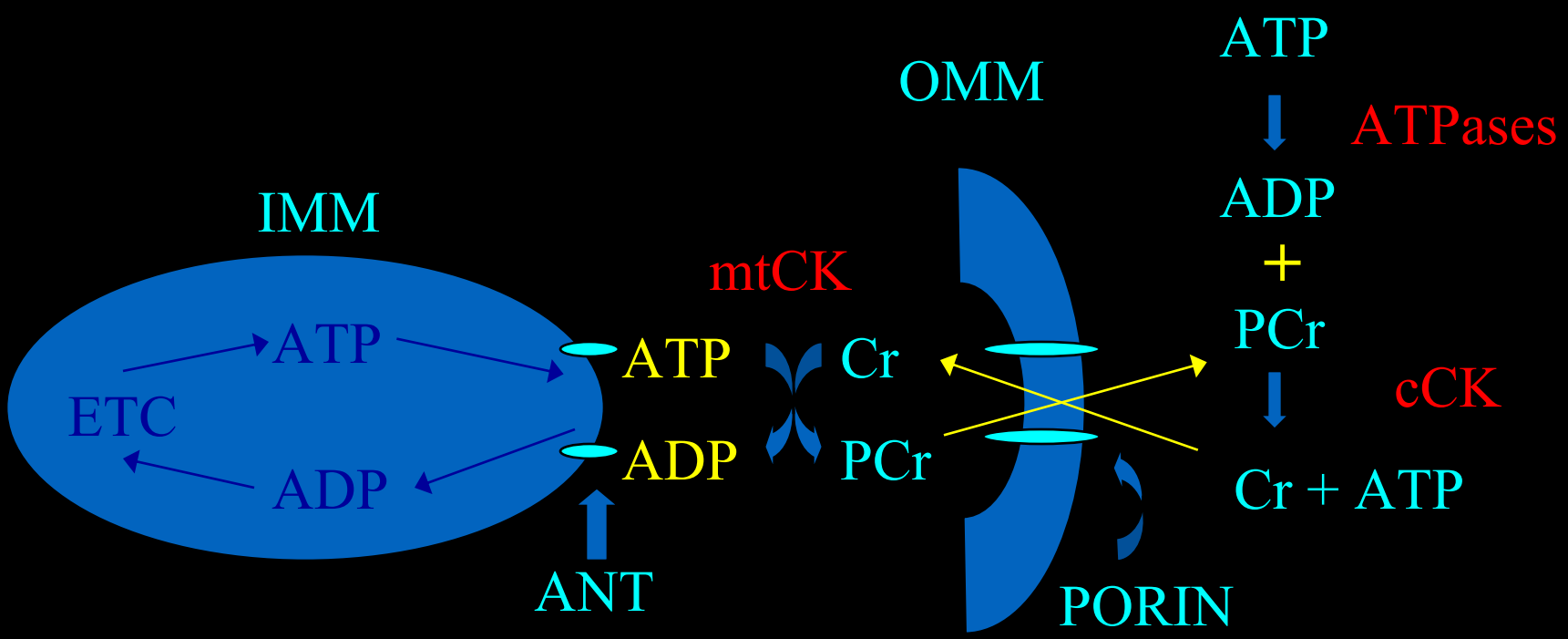


Creatine in the body:

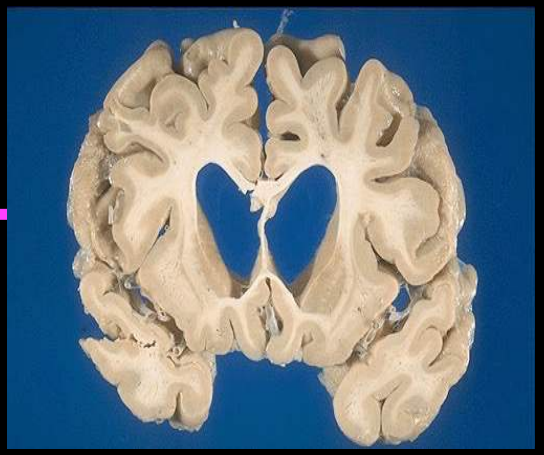


Cr-PCr Metabolism





Potential Benefit in Neurological Disorders.



- ↑ Fat-free mass
- ↑ Strength/Power
- ↓ Neuro-toxicity (ALS, HD, PD)
- ✚ Anti-oxidant (direct and indirect)
- ✚ Anoxia protection
- ↑ Mitochondrial function (*mdx, ?* humans)

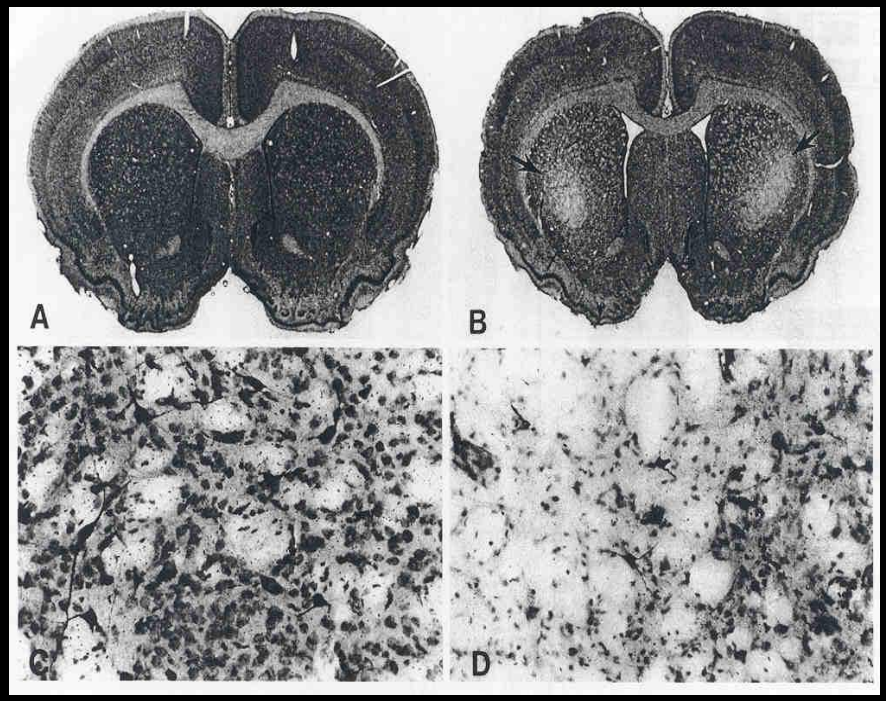
Potential Benefit in Neurology – Huntington Disease.

Matthews, et al, *J Neurosci*, 18:156-163, 1998.

Malonate and 3-NP toxicity (complex II inhibitors) - striatal lesions similar to HD.

+ creatine 1 + 2 %.

- ↓ – 3-NT accumulation.
- ↑ – PCr and ATP.
- ↑ – Striatal neurons.
  - – * confirmed in HD transgenic animals.



Cr + 3-NP 3-NP

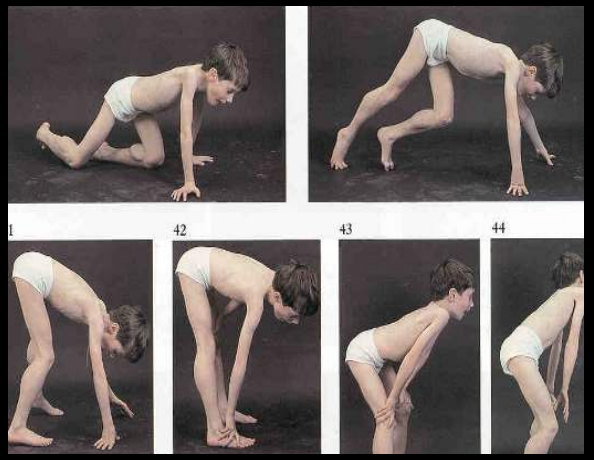
Creatine Monohydrate Improves Muscle Strength and Fat-free Mass in Duchenne Muscular Dystrophy.

(Tarnopolsky, MA, et al., *Neurology*, 2004).

N = 30, RCT, double blinded X 16 weeks.

Rx = CM 5 g/d.

MRC sum score, QOL, functional tasks, FFM (DEXA), QMA, CK activity, subjective, GGT, creatinine and urine (3-MH, 8-OH2-dG, N-telopeptides).



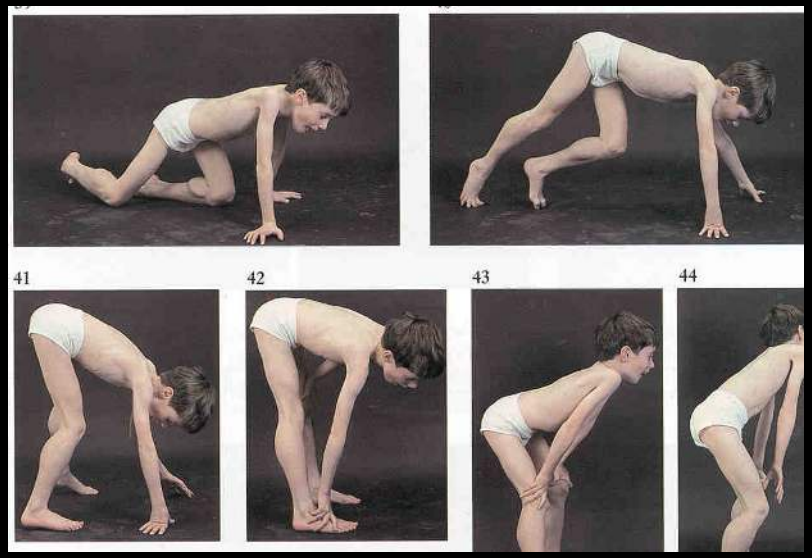
Creatine Monohydrate Improves Muscle Strength and Fat-free Mass in Duchenne Muscular Dystrophy.

(Tarnopolsky, MA, *Neurology*, 2004).

CrM vs PL:

- ⬇ Mega score loss.
- ⬆ Handgrip strength.
- ⬆ FFM (0.7 kg).
- ⬇ *N*-telopeptides.

Same effect with prednisone.



Benefit in Mitochondrial Disorders.

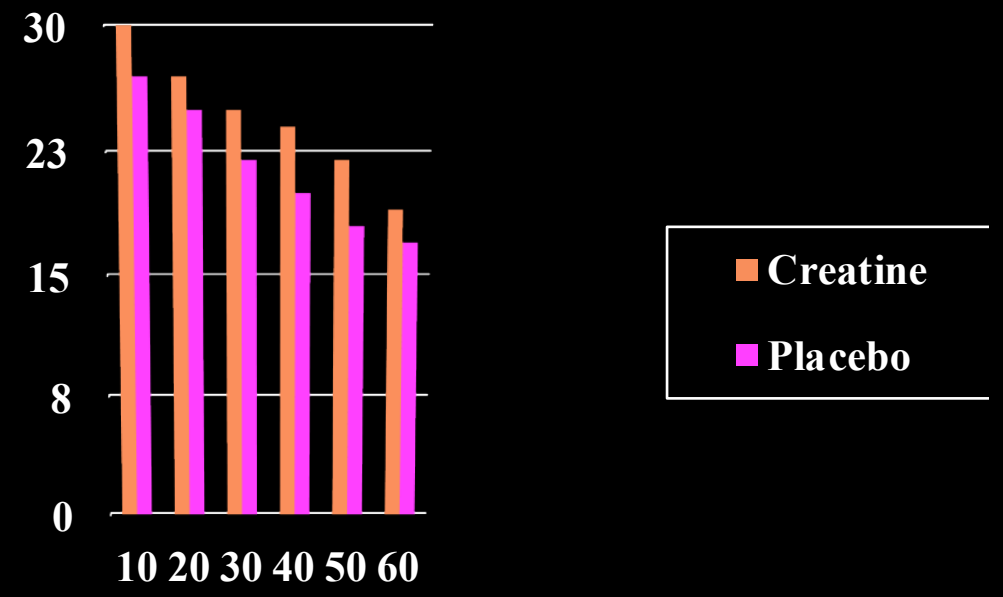
Tarnopolsky MA, et al, *Muscle Nerve*, 20:1502- 1509,1997.

N = 7, RCT, cross-over,

CM 10g/d X 2 week and 4 d/d X 1 week:

⇧ handgrip and dorsi-flexion power (~ 11 %).

➡ VO2max.



Creatine in Mitochondrial Disorders

Study	N	Dose	Outcome	S.E.s
Komura, 2003	5	0.08 - .35 g/kg/d, 4y	+ 12.1 %	nil
Barisic, 2002	1	20g>5g/d X 28mo	+ CNS, MRS	? Renal
Cacic, 2001	1	~ 0.15 g/kg/d	+ symptoms	nil
Klopstock, 2000	16	20g/d X 4 weeks	+ 23 % (N.S.)	nil
Borchert, 1999	4	0.15 – 0.2 g/kg/d	+ symptoms	nil
Tarnopolsky, 1997	7	10g/d > 4g/d (3 wk)	+ high intensity	nil
Hagenfeldt, 1994	1	5 g/d	+ exerc./HA	nil

Mitococktail

- Given that there are several final common pathways of mitochondrial dysfunction – targetting most of them should be more beneficial. Tarnopolsky and Beal. *Ann Neurol,* 2001.
- Examples:
  - Chemotherapy (ALL survival rates).
  - *mdx* mouse (Payne, E, *Muscle Nerve,* 2006).
- ? Mitochondrial disease?

Potential use in *mdx* model

Group	Average Peak Grip Strength	Grip Strength Fatigue	Rotarod	Creatine Kinase Activity	Retrop. Fat Pad	Total Creatine Gluteus	Internal Myonuclei (Gluteus)
HMB	7	7 *	5	**1** †	7	7	6 *
CrM	5	6 *	**2** *	7	4 *	**2**	5 *
LA	4	**2** *	5	**3**	5 *	**3**	4 *
CLA	5	4 *	7	6	**1** *	6	7
PRED	**3**	4 *	4	4	6	5	**2** *
COMB	**2** *	**3** *	**1** *	5	**3** *	4	**3** *
COMB + PRED	**1** *	**1** *	**3**	**1** †	**2** *	**1**	**1** *

Payne, et al, *Muscle Nerve*, 2006.

Mitococktail (Matthews, *Neurology*, 43:884-, 1993).

- N = 16 (4 deletions, 3 point mutations, 4 > 71 y).
- 1 > several 2 month periods (open):
  - COQ10 300 mg/d
  - Vitamin K (60 mg tid); MVI, thiamine 100 mg; riboflavin 25 mg, vitamin C 500 mg)
- No effect on lactate, exercise testing or muscle PCr/Pi.

Mitococktail (Marriage, *Mol Gen Metab.*, 81:263-, 2004).

- N = 12 (6 LHON; 3 CPEO, 3 misc.).
- Pre, 3,6,12 months (open):
  - COQ10 @ 5 mg/kg (~ 210 mg/d); carnitine 500 mg/d; B complex (1,2,3,5,6,12, folate), vitamin K (0.4 mg/kg), vitamin C 1000 mg)
- CoQ10 – increased 5 fold:
  - Increased ATP production in lymphocytes at 12 months, no effect on lactate.

BENEFICIAL EFFECTS OF CREATINE, CoQ_{10}, AND LIPOIC ACID IN MITOCHONDRIAL DISORDERS

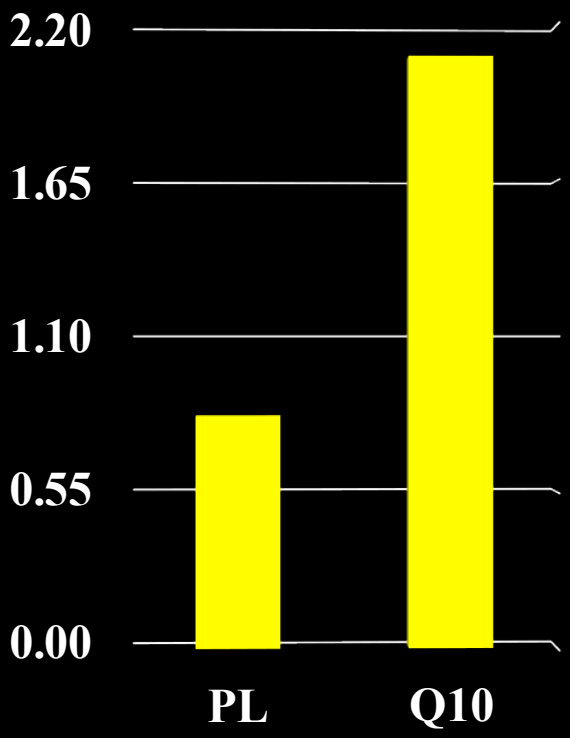
M. CHRISTINE RODRIGUEZ, BSc,[1] JAY R. MacDONALD, MD, PhD,[2] DOUGLAS J. MAHONEY, PhD,[2] GIANNI PARISE, PhD,[1] M. FLINT BEAL, MD,[3] and MARK A. TARNOPOLSKY, MD, PhD[4]

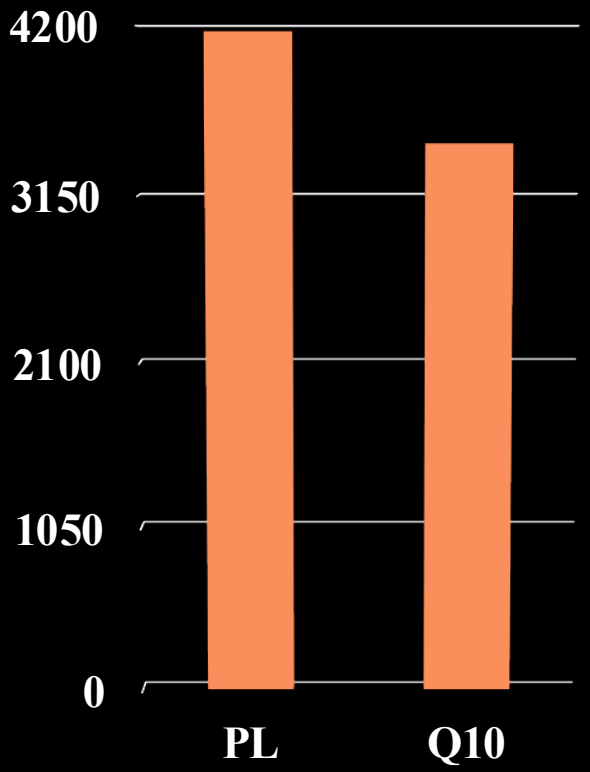
Rodriguez, et al., *Muscle and Nerve,* 35:235-, 2007.

- 2 month RCT, 2 month W/O, cross-over.
- CoQ10 120 mg bid + 150 mg Vit E.
- Creatine 3 g/d.
- **Alpha lipoic acid** 300 mg bid
- **N** = 16 patients with definite mitochondrial disease (MELAS, MERRF, KSS, CPEO, LHON, Misc. (i.e., m.9035T>C).

Mitochondrial Cocktail

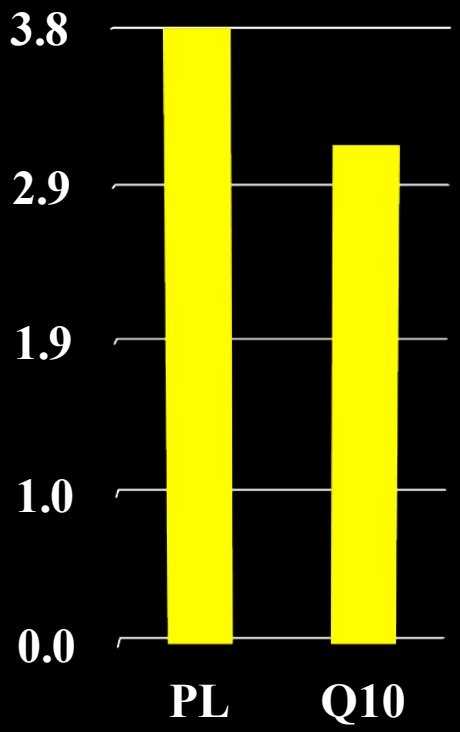
Rodriguez, et al., *Muscle and Nerve,* 35:235-, 2007.



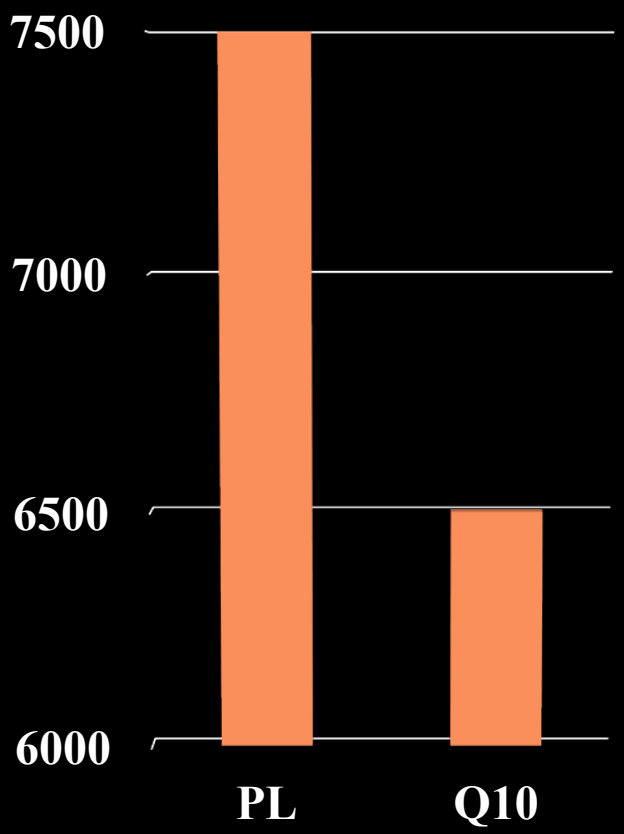


CoQ10 (ug/mL), $P < 0.001$ 8-OH-2dG (ng/g creatinine), $P = 0.065$

Mitochondrial Cocktail



Lactate (mmol/L), $P < 0.05$



8-isoprostanes (umol/g creatinine), $P < 0.05$

Rodriguez, et al., *Muscle and Nerve,* 35:235-, 2007.

Mitochondrial Disorders - CoQ10 Rx (3 – 5 mg/kg/d).

- POSITIVE: Reichmann, 1998 (9), Matsuo, 1999 (2), Barbiroli, 1999 (10), Barbiroli, 1997 (6), Chen, 1997 (8), Schoffner, 1989 (1), Nishikawa, 1989 (10), Bresolin, 1988 (7), Ogasahara, 1986 (5), Bendahan, 1992 (2), Ikejiri, 1996 (1), Ogasahara, 1985 (1), Yamamoto, 1987 (1), Desnulle, 1988 (1), Ihara, 1989 (2), Abe, 1999 (2), Chan, 1998 (9). (78)
- NO EFFECT: Matthews, 1993 (16), Gold, 1996 (8). (24)
- SAFETY: Shults, et al, Arch Neurol, 2002 – PD – safe and well tolerated up to 1,200 mg/d. Matthews – some GI side effects; children with COQ10 deficiency – very high doses.
- FORMULATION: We used ubiquinone not ubiquinol.

A RANDOMIZED TRIAL OF COENZYME Q_{10} IN MITOCHONDRIAL DISORDERS

ELISA I. GLOVER, PhD,[1] JOAN MARTIN, MSc,[2] AMY MAHER, PhD,[1] REBECCA E. THORNHILL, PhD,[4] GERALD R. MORAN, PhD,[3,4] and MARK A. TARNOPOLSKY, MD, PhD[1,2]

[1] Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
[2] Department of Medicine, 2H26 Division of Neuromuscular and Neurometabolic Disorders, McMaster University Medical Center, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada
[3] Department of Radiology, McMaster University, Hamilton, Ontario, Canada
[4] Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, Ontario, Canada

Glover, et al., *Muscle and Nerve,* **42**:739-, 2010.

- **2 month RCT, 2 month W/O, cross-over.**
- **CoQ10 600 mg bid.**
- **N = 30 patients with definite mitochondrial disease (N = 15 - MELAS, N = 15 - MERRF, KSS, CPEO, LHON, Misc.).**
- **MRS (brain), lactate, oxidative stress, cycle ergometry.**

A RANDOMIZED TRIAL OF COENZYME Q_{10} IN MITOCHONDRIAL DISORDERS

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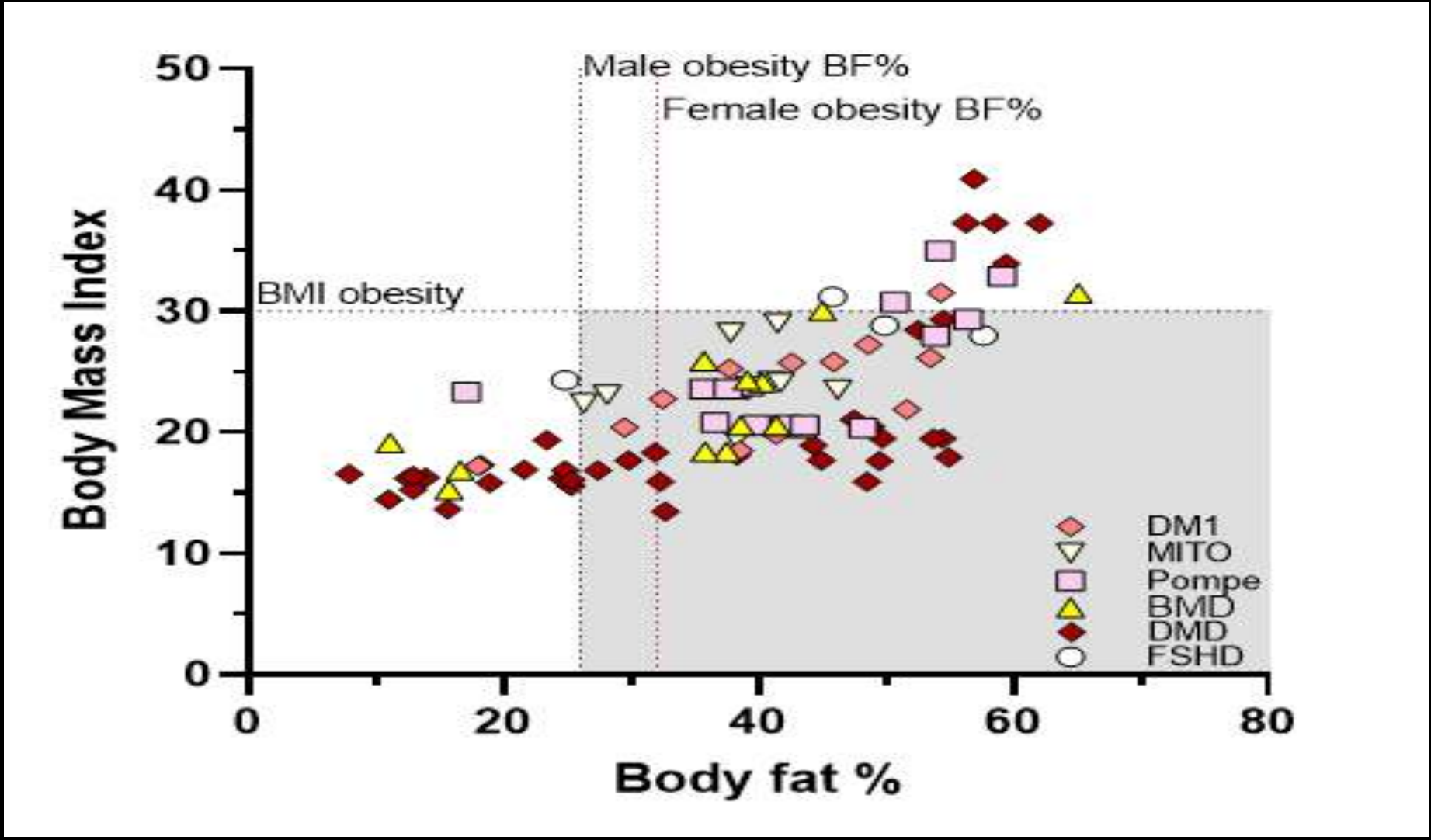
[1] Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
[2] Department of Medicine, 2H26 Division of Neuromuscular and Neurometabolic Disorders, McMaster University Medical Center, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada
[3] Department of Radiology, McMaster University, Hamilton, Ontario, Canada
[4] Department of Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, Ontario, Canada

Glover, et al., *Muscle and Nerve,* **42**:739-, 2010.

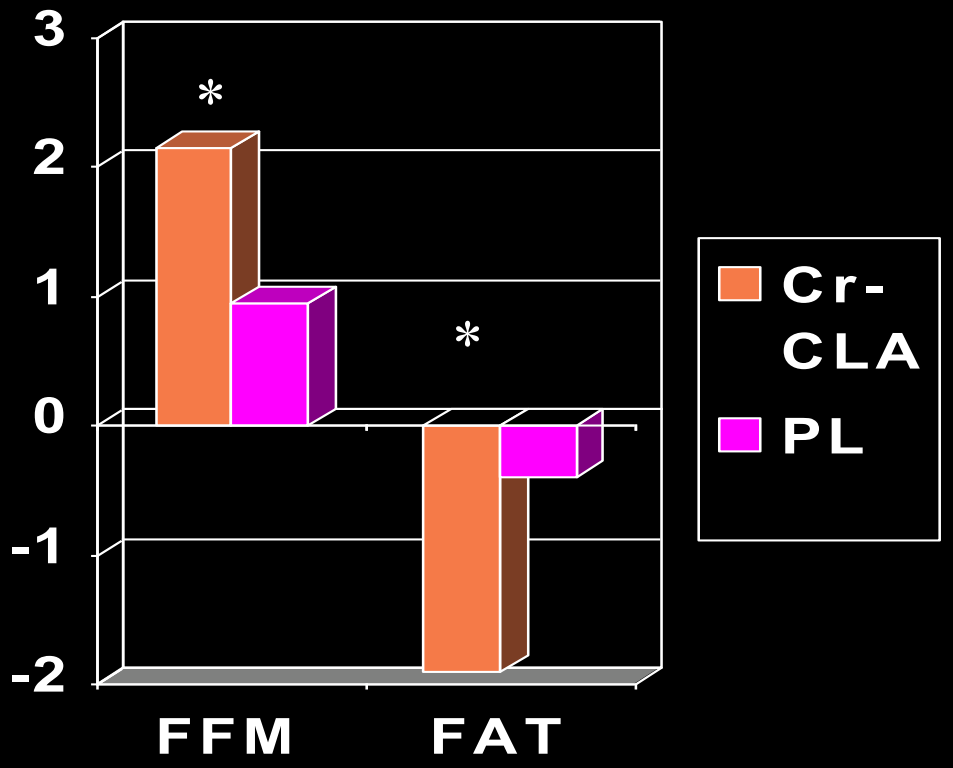
- **No effect on lactate or oxidative stress.**
- **Small improvement in cycle ergometry.**
- **Small decrease in choline compounds in brain.**

Sarcopenic Obesity – Mito. Disease and MD



RT, CrM/CLA in older adults (2005)

- N = 20 men (72 y).
- N = 20 women (69 y).
- CrM – 5 g + 2 g dextrose/d.
- CLA – 50:50 mix of c9, t11: t10, c12 @ 6 g/d.
- RCT:
  - 6 mo, 2 X/week supervised wt.



Tarnopolsky , M, et al, *PLoS ONE*, Oct., 2007

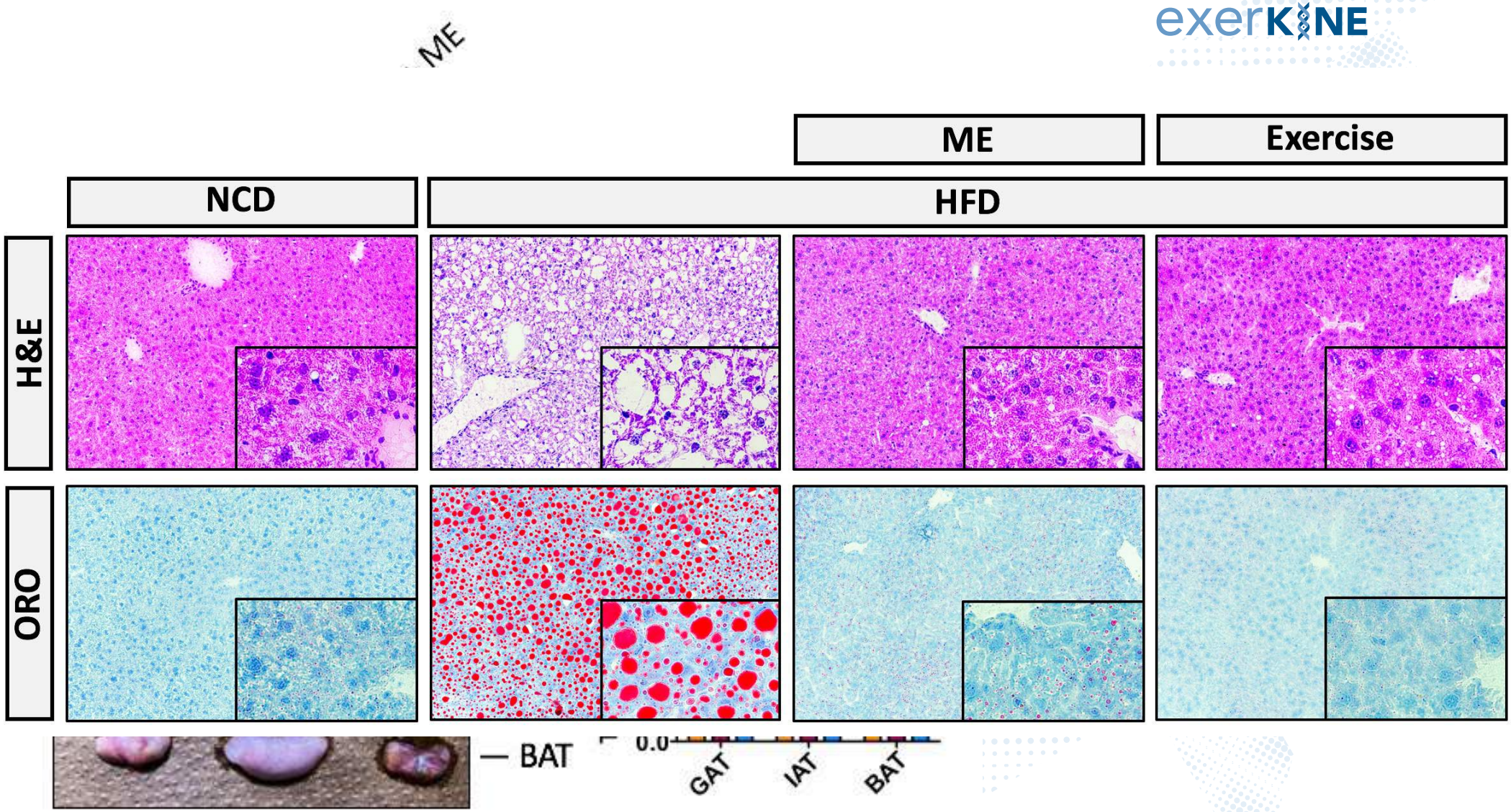
Multi-nutrient supplement for obesity, NAFLD, T2DM – TRIM7.

- High fat fed vs. chow fed.
- 30 day intervention (+/- EX):
- EX = 3 X/wk @ 15 m/min.
- Wt. loss:
  - components (green tea and green coffee, forskolin).
- Mito. enhancer:
  - ALA, COQ10, vitamin E, + beet root (nitrates).

Nederveen, et al., ***Nutrients*, 2021, 13, 3726.**

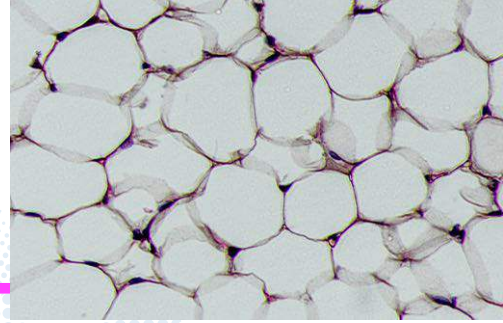
TRIM7 – Metabolic Enhancer

exerKINE

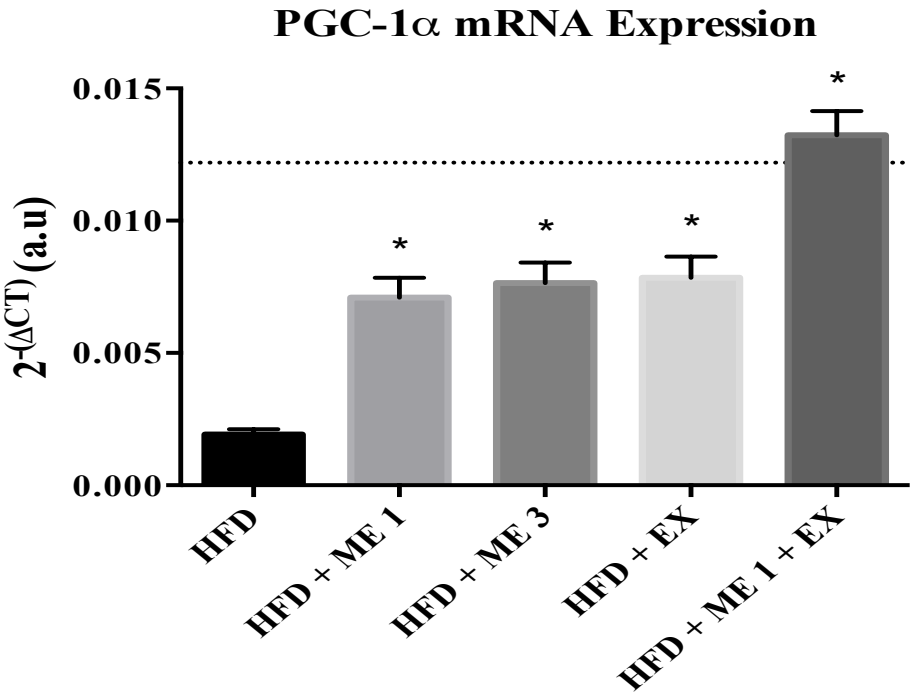


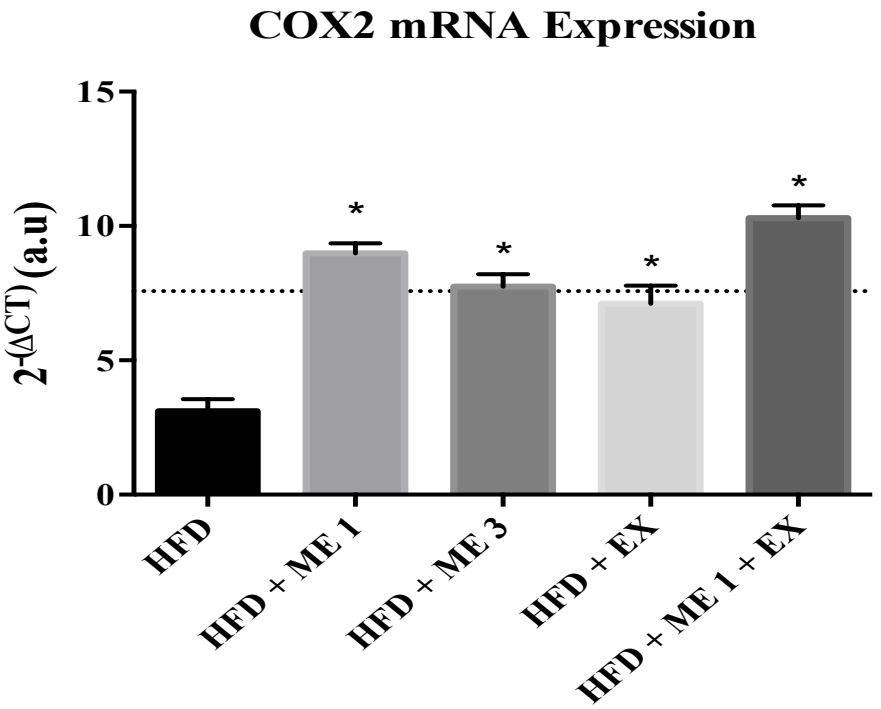
Nederveen, et al., ***Nutrients,*** **2021, 13, 3726.**

Metabolic Enhancer – Mitochondrial Biogenesis



Mechanism = White adipose tissue browning

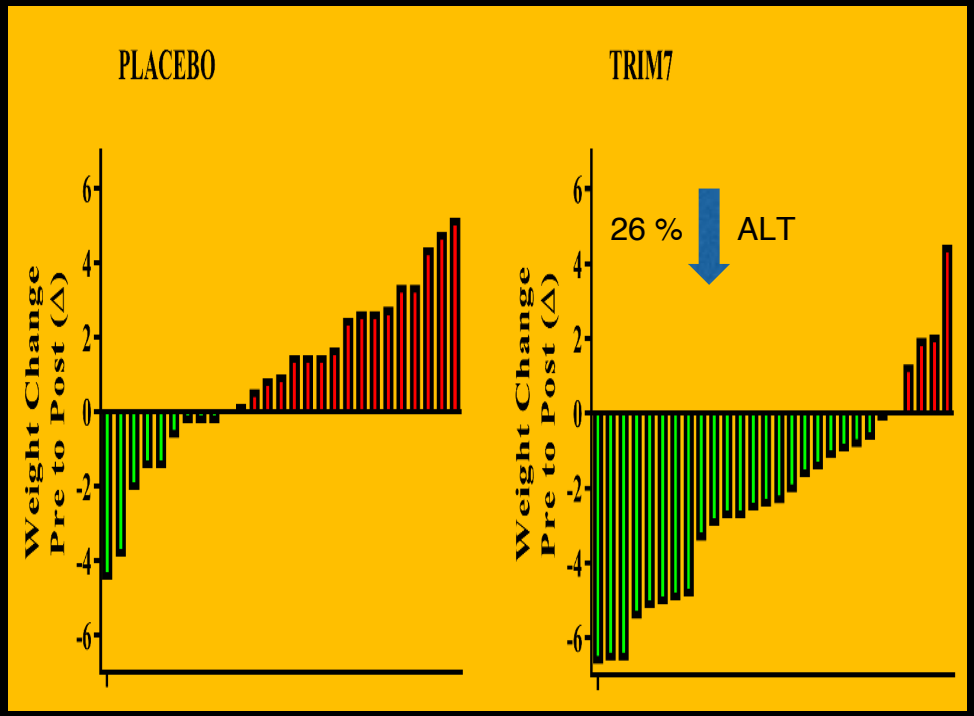




Nederveen, et al., ***Nutrients,*** **2021, 13, 3726.**

TRIM7 – RCT

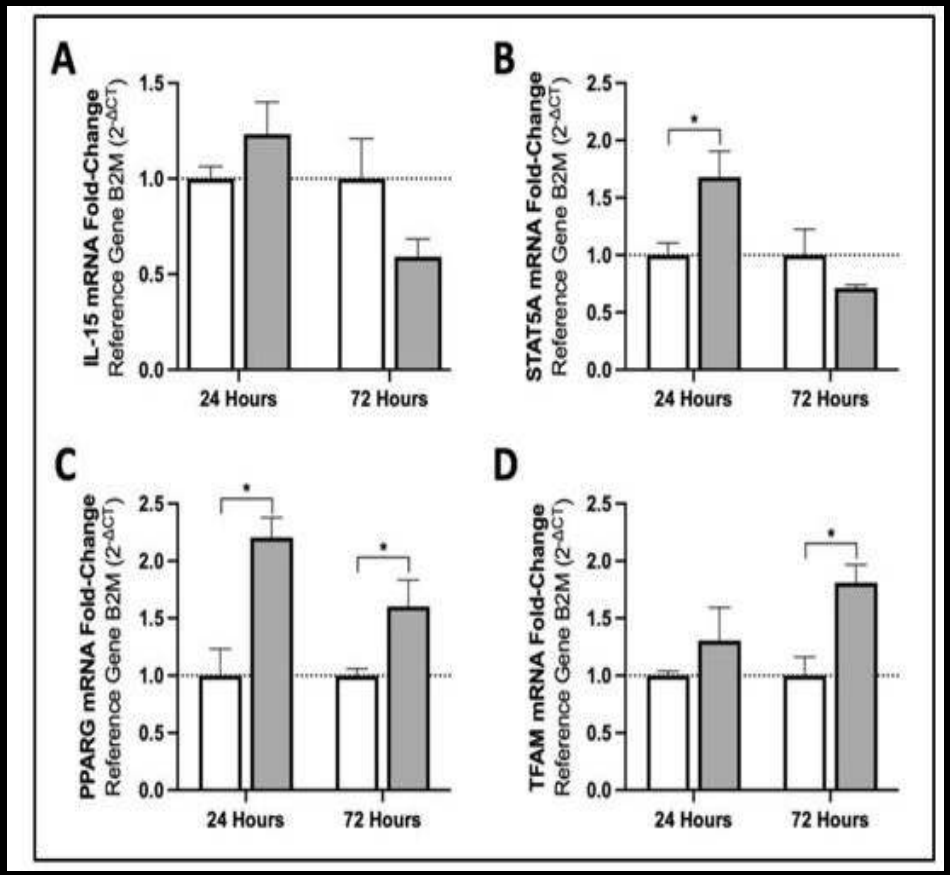
- N = 60 overweight and obese men and women (20 – 55 y).
- 3 months of supplement (Trim7) vs placebo.
- Primary endpoint = weight loss.
- Secondary = Body Composition Index (BCI) = muscle mass (kg)/adipose (kg) by DEXA.



Nederveen, J., et al., MS in preparation, 2022.

New Mito Cocktail in Older Adult Fibroblasts

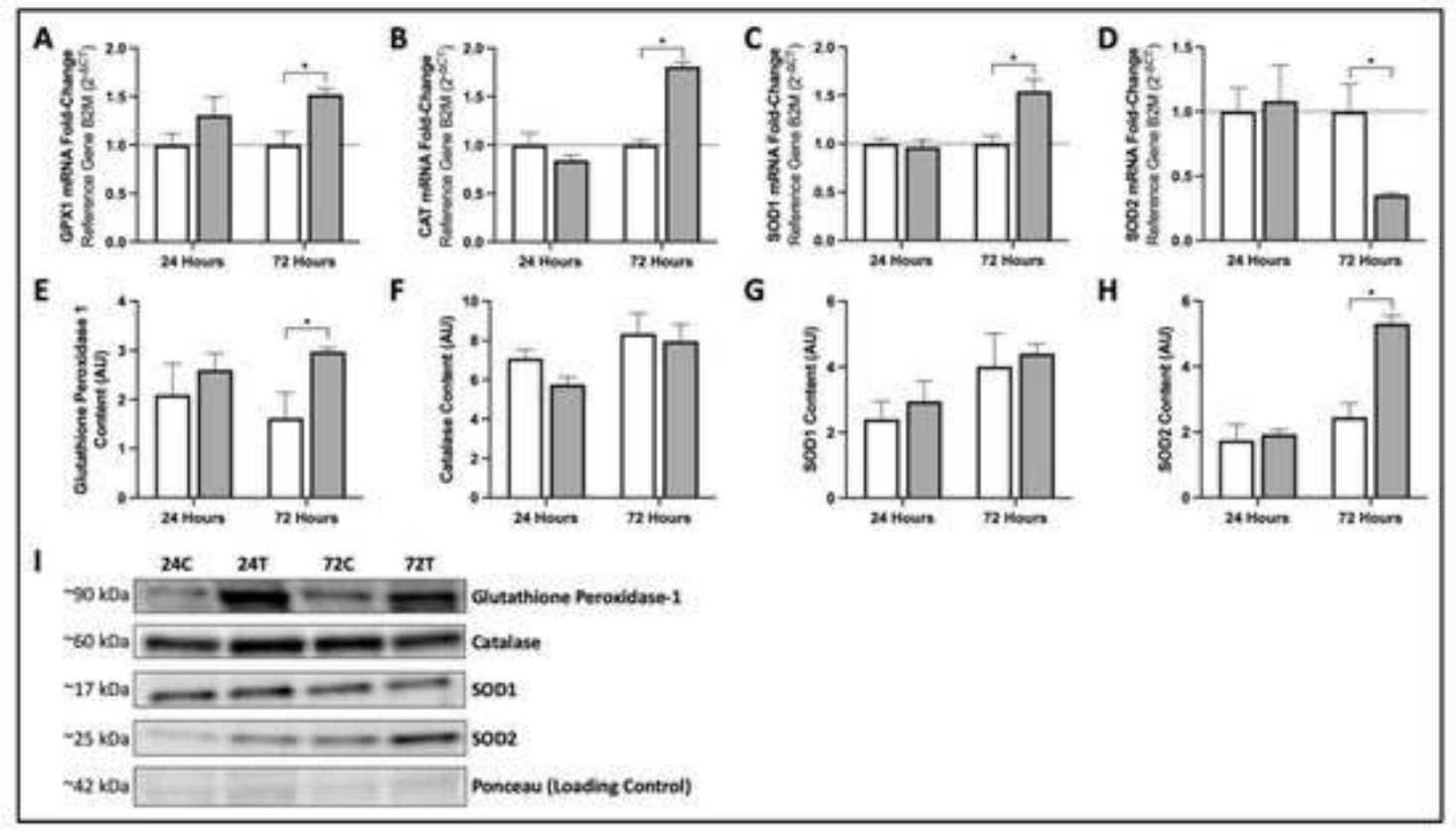
- Aging = mitochondrial dysfunction + oxidative stress.
- N = 3 older women dermal fibroblasts.
- Treatment with culture media +/- novel mitochondrial cocktail:
  - CoQ10, α-LA, vitamin E, vitamin C, resveratrol, curcumin, zinc, lutein and astaxanthin, vitamin D and copper and biotin.



Rebalka, I., et a., Cosmetics, 2022

New Mito Cocktail in Older Adult Fibroblasts

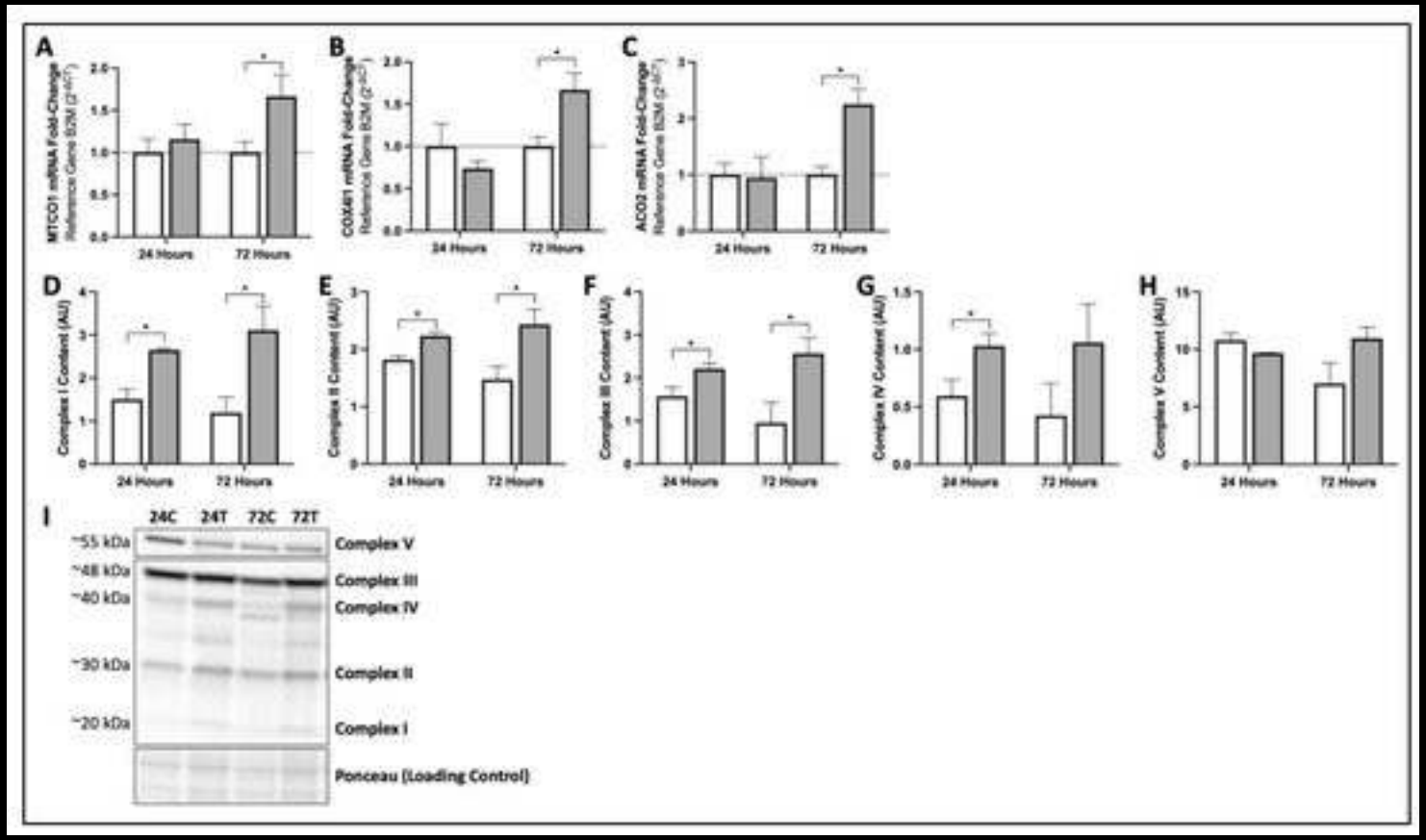
- mRNA and Western blot for Anti-oxidant Proteins.



Rebalka, I., et a., Cosmetics, 2022

New Mito Cocktail in Older Adult Fibroblasts

- Western blot for Mito. Proteins.



Rebalka, I., et a., Cosmetics, 2022

Leber Hereditary Optic Neuropathy (LHON)

Painless, ceco-central visual loss.

Unilateral > bilateral.

May be some recovery.

Males (~ 80 %) > females (17-B-estradiol).

Triggers: smoking, ? Sunlight, menopause.

m.3460G>A; m.11778G>A, m.14484T>C (mildest).

Leber Hereditary Optic Neuropathy (LHON)

Treatment:

- Mito cocktail vs. idebenone.
- Higher doses in the 18 – 24 mo. after loss > 50 %.
- Avoid sunlight.
- ID at risk individuals – prevention!
- Eye checks (glaucoma).
- ? ERT at menopause.
- MitoCanada study for a novel multi-ingredient supplement for LHON and complex 1 Leigh.

Thanks

- The lab:

Dr. J. Nederveen
Mr. A. Mikhail
Mr. B. Hettinga
Dr. M. Nilsson
Dr. I. Rebelka

- The clinic:
  - **Ms. Erin Hatcher**
  - **Ms. Linda Brandt**
  - **Ms. Lauren Brady**
  - **Ms. Kristin Barnard**

- Collaborators:

Dr. C. Perry
Dr. B. Naviaux
Dr. J. Bourgeois
Dr. R. Austin

- **Warren Lammert and Family.**
- **Dan Wright and Family.**
- **McMaster Children's Hospital and Hamilton Health Sciences Foundation.**