Aging Exercise and Mitochondrial Disease MitoAction 2023.

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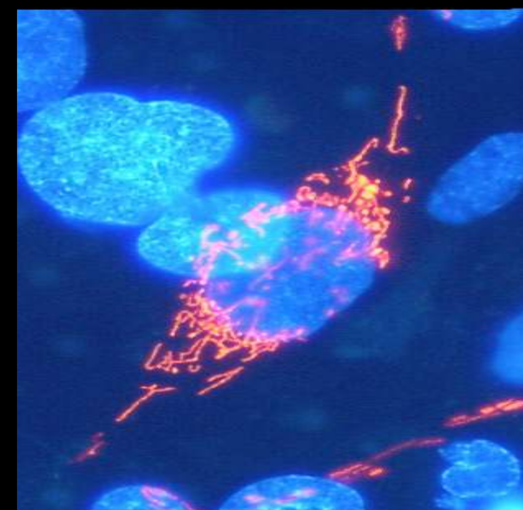


Disclosures

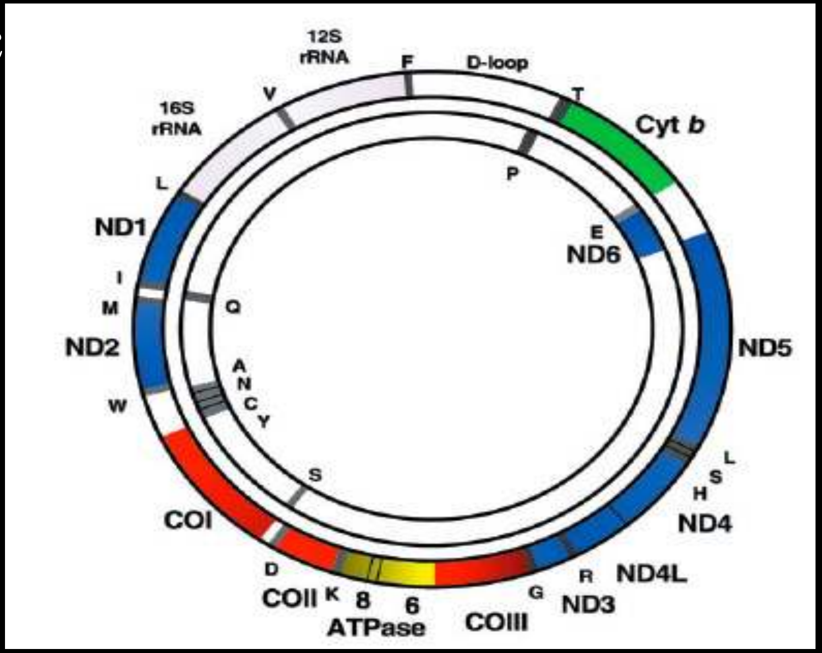
- Sanofi/Genzyme – speaker honorarium 2009, 2010-21.
- Ultragenyx – GNE study 2016-2018.
- Amicus Therapeutics – clinical trial 2019-2022.
- Janssen - speaker honoraria 2017.
- Genzyme - research funding, 2011; clinical trial 2019-2022, speaker honoraria 2017-22, Ad Board, 2021-22.
- Founder and CEO of Exerkine Corporation/Stayabove Nutrition.

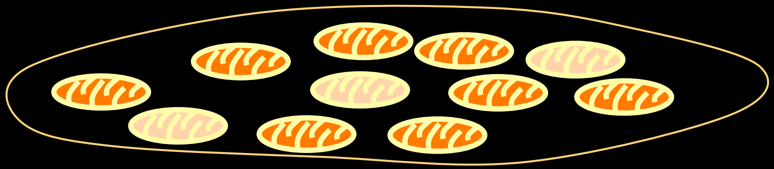
Summary

- Human aging/sarcopenia.
- Endurance exercise in human aging.
- Resistance exercise in human aging.
- Nutritional Supplementation for Sarcopenic Obesity.

Mitochondrial Disorders – Review.

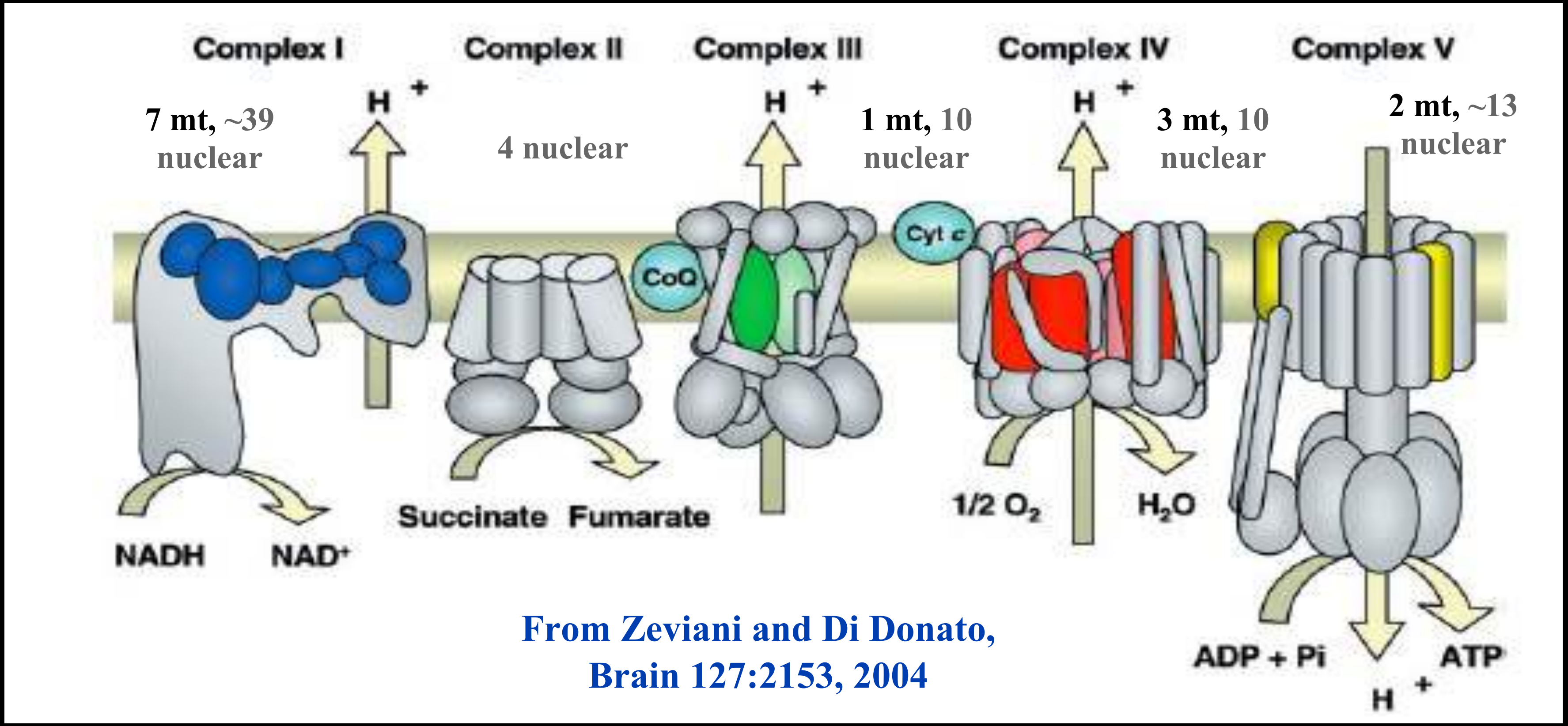
- 2 billion y ago – purple photosynthetic bacteria.
- Has its own mtDNA (37 genes) - + 38 (MOTS-c).
- Most proteins encoded by nDNA - ~ 1,300 total.
- Maternal inheritance.
- Heteroplasmy, replicative segregation.
- Mostly exons.
- Less effective DNA repair:
  - ~ 13 fold more mutations.





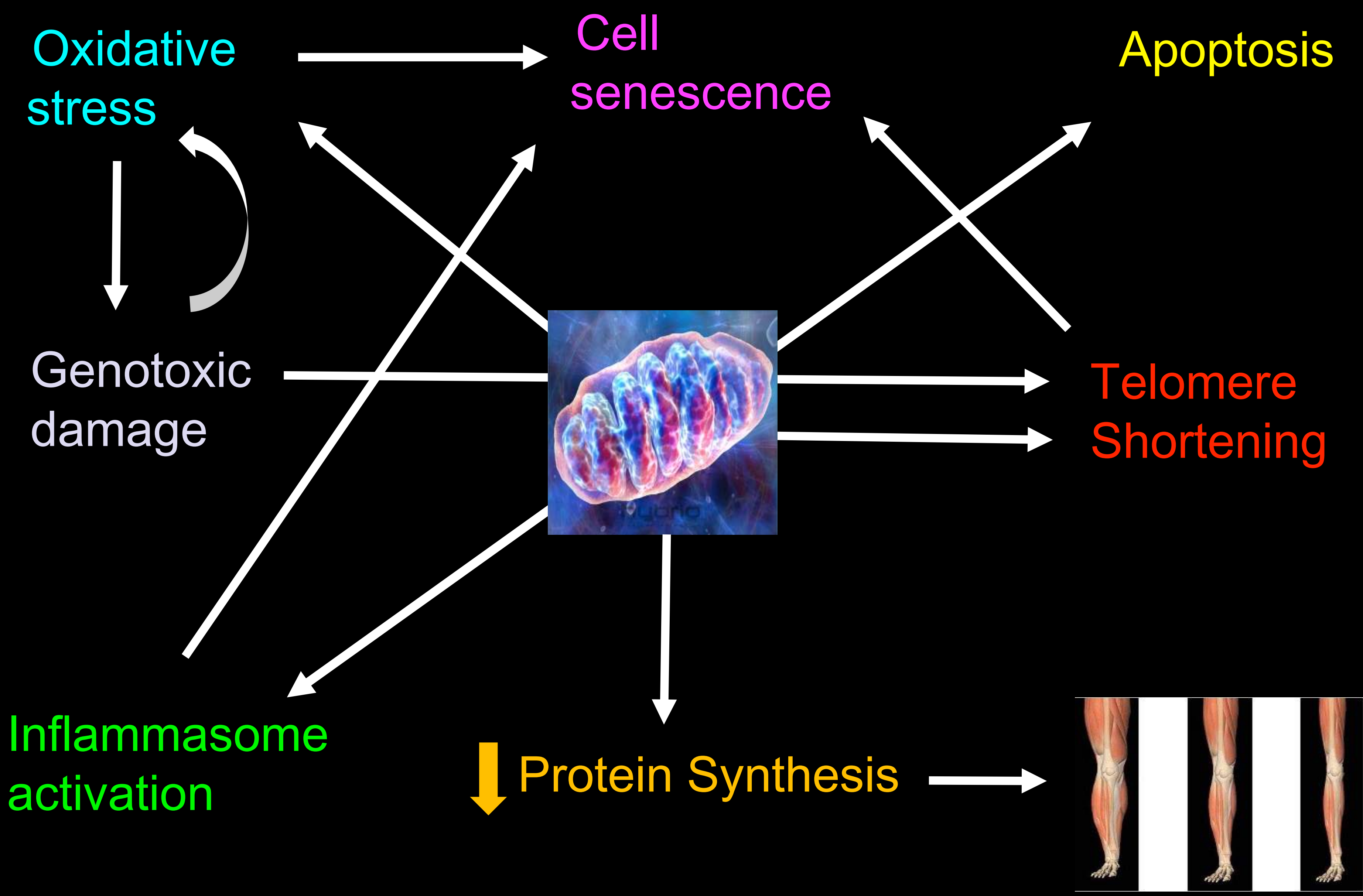
Electron Transport Chain

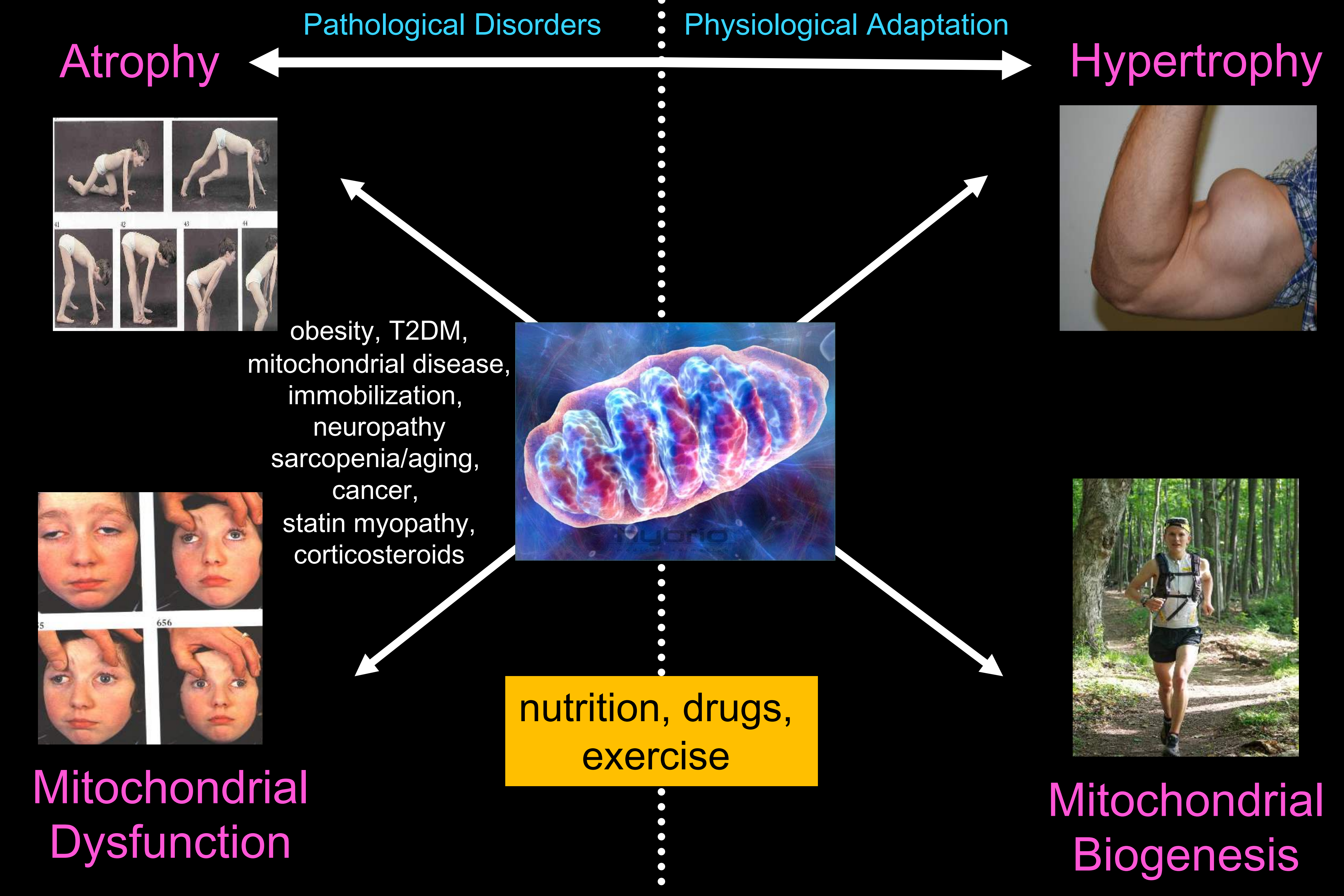
- **Formation ETC under dual genomic control.**
- **Series circuit I>III>IV and V conserved in vertebrates (13 sub-units).**

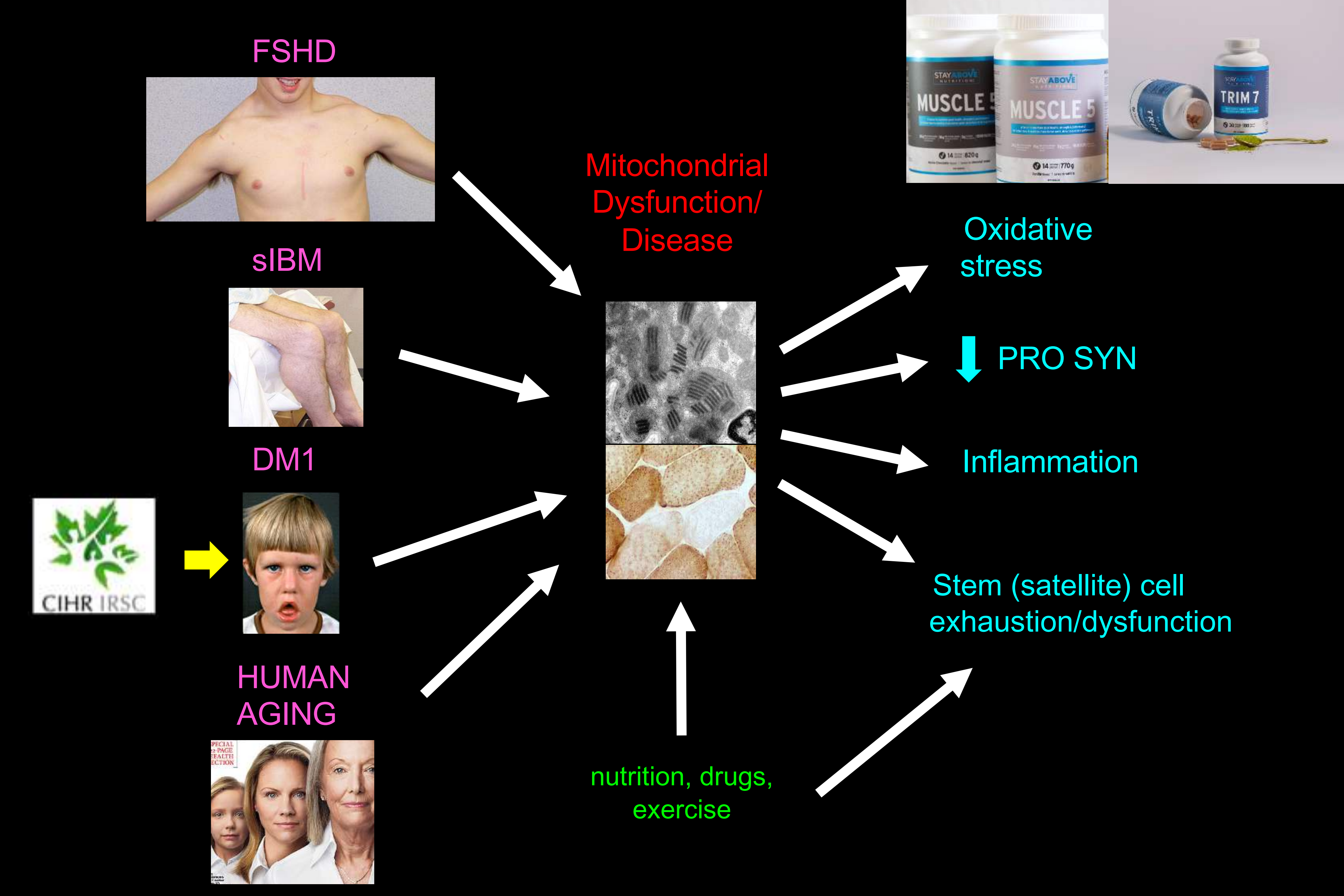


From Zeviani and Di Donato, Brain 127:2153, 2004

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



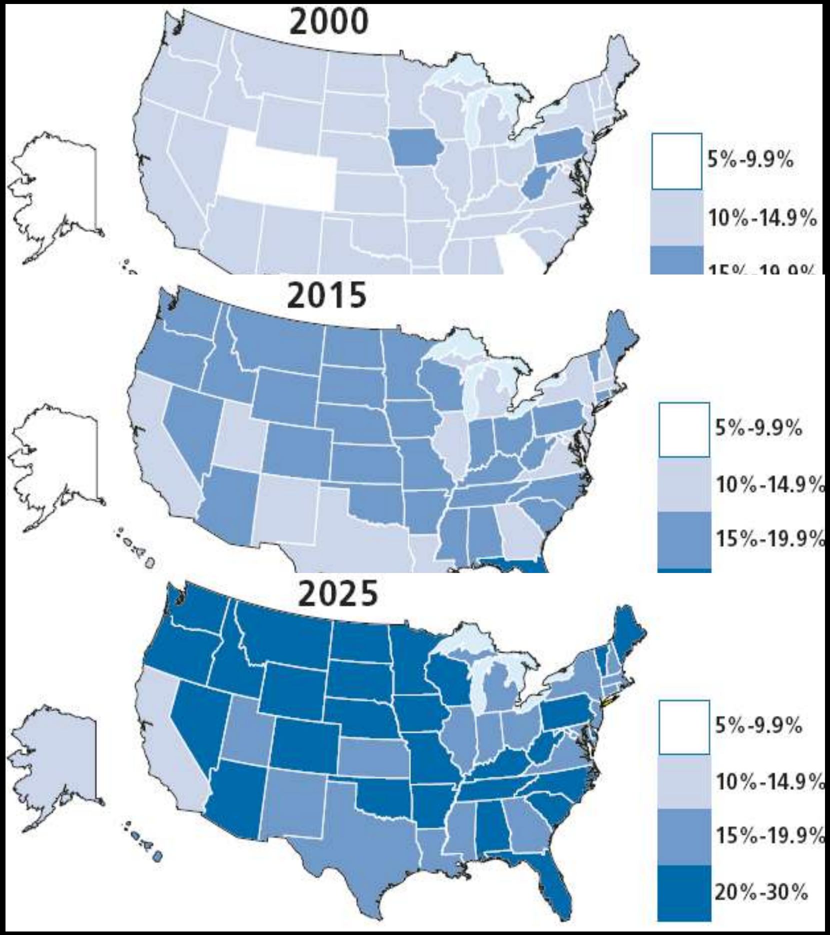

Pathological Disorders
Physiological Adaptation
Atrophy
Hypertrophy
obesity, T2DM,
mitochondrial disease,
immobilization,
neuropathy
sarcopenia/aging,
cancer,
statin myopathy,
corticosteroids
nutrition, drugs,
exercise
Mitochondrial
Dysfunction
Mitochondrial
Biogenesis



FSHD
sIBM
DM1
CIHR IRSC
HUMAN AGING
Mitochondrial Dysfunction/ Disease
nutrition, drugs, exercise
STAY ABOVE
MUSCLE 5
STAY ABOVE
MUSCLE 5
TRIM 7
Oxidative stress
PRO SYN
Inflammation
Stem (satellite) cell exhaustion/dysfunction

What is Sarcopenia of aging?

- "paucity of flesh".
- Muscle atrophy and weakness (2 SD < age normal).
- Functional impairment.
- Cost of sarcopenia = $ 40 billion/y in USA - 2019.
- ~ 10 % over age 70;
  ~ 30 % over age 80.



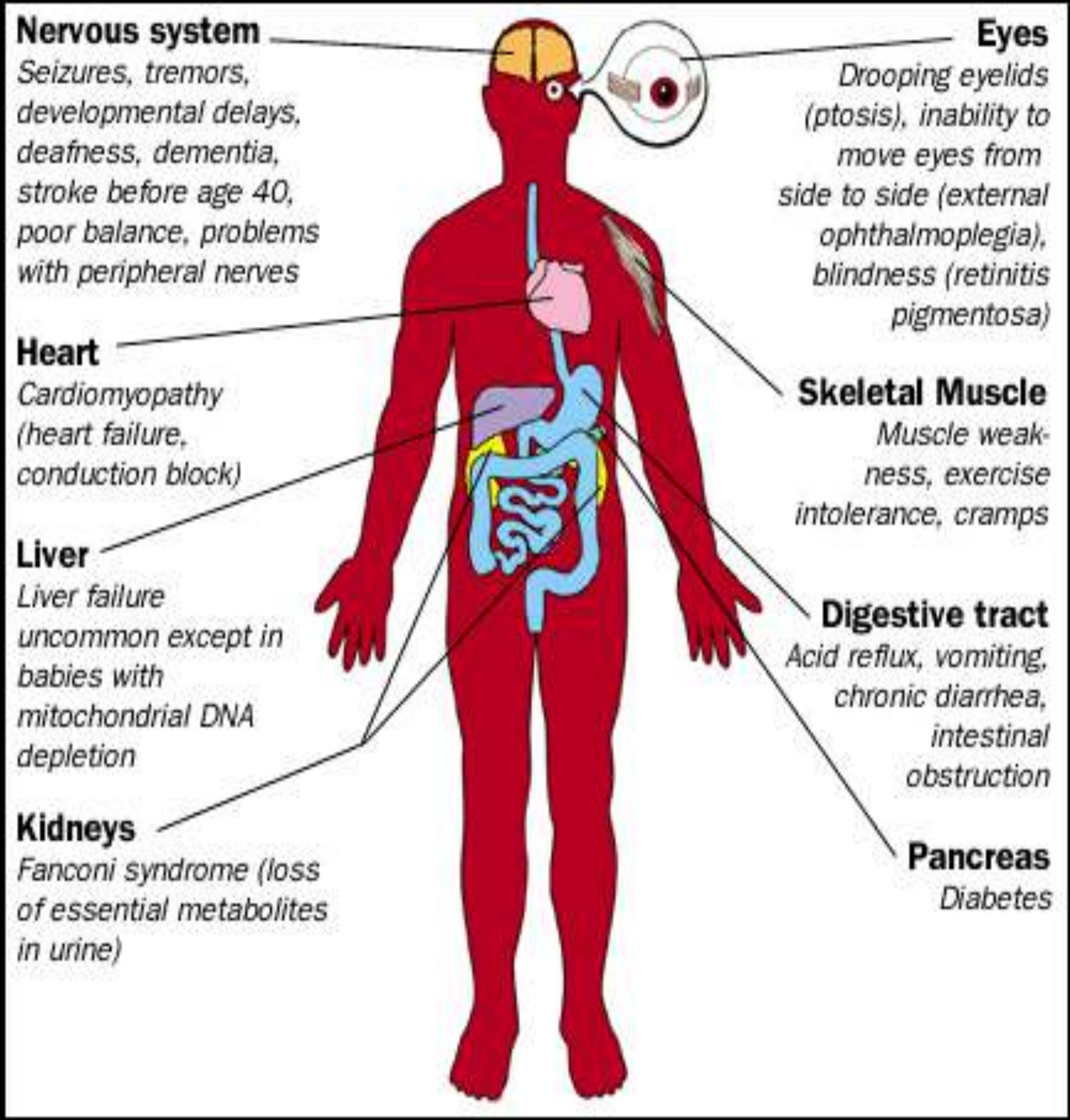
Causes of Aging/Sarcopenia

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

- Dennervation (α-motor neuron loss).
- Telomere shortening.
- Loss of proteostasis (↓ SYN/DEG).
- Genotoxic damage.
- Dys. nutrient sensing (anabolic resistance).
- Stem cell exhaustion/dysfunction.
- Oxidative stress.
- Altered inter-cellular communication.
- Chronic inflammation (Inflammaging).
- **Mitochondrial dysfunction.**

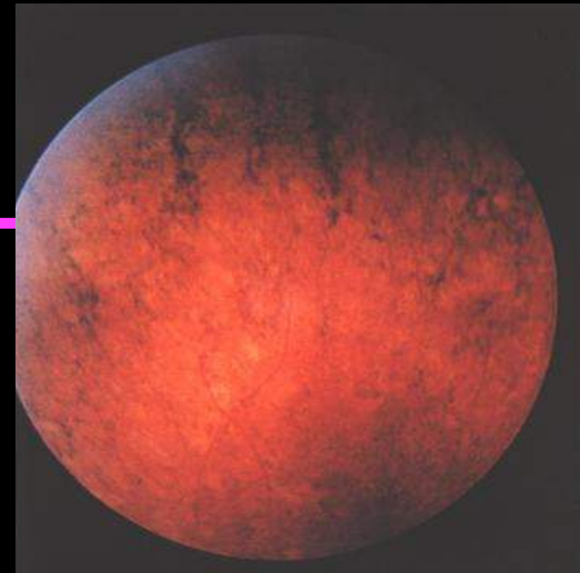
Mitochondrial Disorders

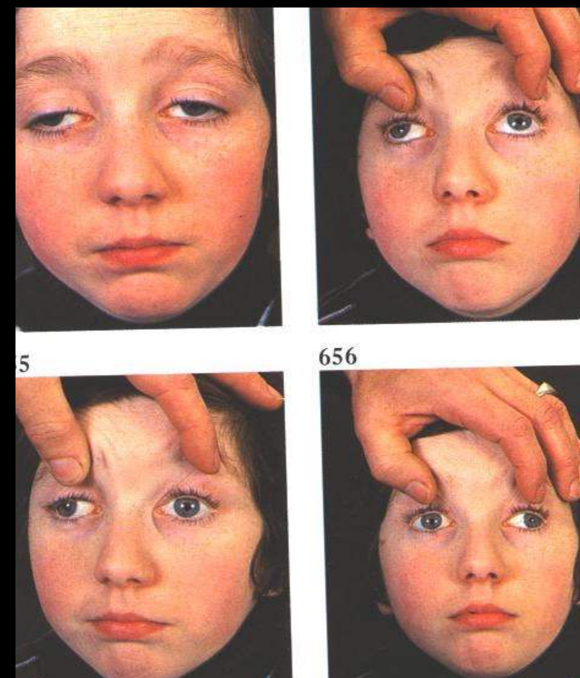
- Usually refers to disorders affecting the ETC.
- First mutations were discovered in the mtDNA as deletions (KSS) and LHON (11778) and MELAS (3243) in 1988.
- There are now > 200 known mtDNA mutations and an increasing number of nDNA mutations.



CLINICAL FEATURES

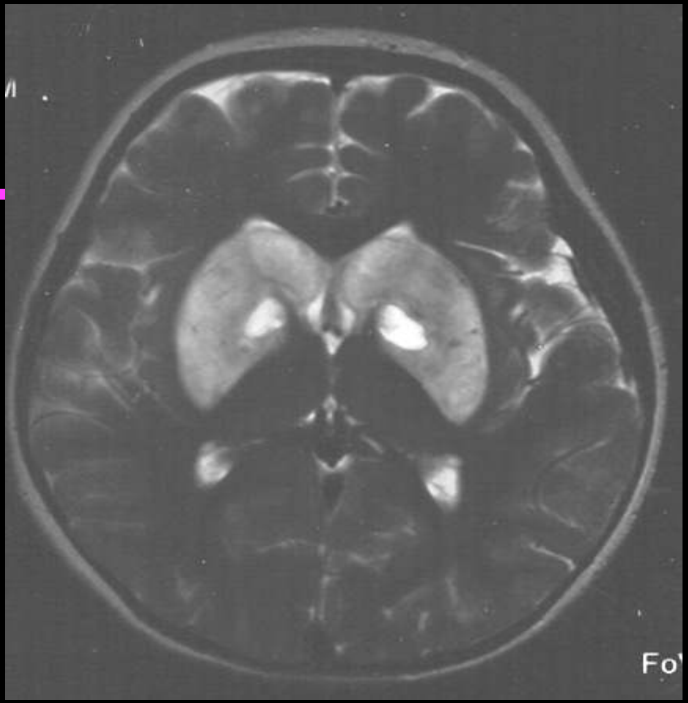
- Eyes/Hearing: Optic atrophy, PEO, retinitis pigmentosa/hypoacusis.
- Brain: Seizures, encephalopathy, dementia.
- Heart: Cardiomyopathy (hypertrophic, dilated, non-compaction).
- GI tract: Constipation, abdominal pain, pseudo-obstruction, hepatic failure.
- Renal: Renal tubular acidosis.
- Endocrine: Type 2 diabetes.
- Muscle: Weakness, exercise intolerance.





Mitochondrial Diagnosis

- Multi-system history.
- Family history (maternal – rule IN) .
- Lactate (SEN = 0.65; SPEC = >0.90).
- Urine – organic acids (ethylmalonic, 3-methylglutaconic, lactate, TCAi).
- Plasma amino acids (alanine).
- MRI/MRS/Exercise testing.
- Plasma GDF-15.
- Muscle histology/EM.
- Muscle enzymology.
- Specific point mutations.



•**Definite**

•**Probable**

•**Possible**

•**Unlikely**

Mitochondrial Disease R_x Strategies

General Issues

1. Avoid stressors (heat, dehydration, prolonged fasting, excessive exercise, etc.).
2. Check sleep (abnormal delta waves, apnea, no stage 3 or 4, nocturnal myoclonus, Sz, RLS) – melatonin (0.1 mg/kg/d).
3. Check for contractures, treat spasticity, AFOs for DF weakness.
4. Pain – not common – identify the generator (Neurogenic = TCAs, gabapentin, etc.; don't forget about MSK).
5. Optimize nutrition for growth – G-tube is often very beneficial if sub-optimal intake is present (also allows for optimal delivery of supplements and medications).

Habitual Diet – General suggestions – Continued.

Avoid fasting for prolonged periods (> 10 h).

More frequent meals.

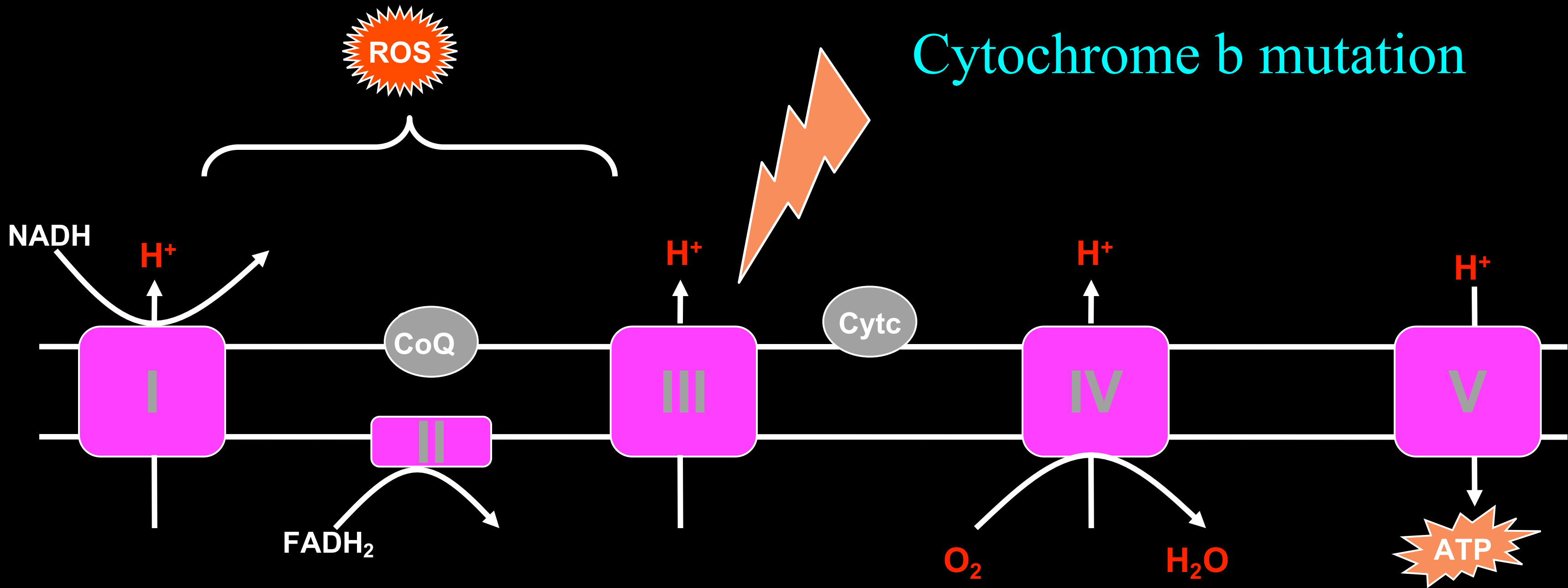
Consider high fat in complex I with seizures or PDH deficiency.

Treat iron, vitamin D, vitamin B12, folate, vitamin E, and copper deficiency (ferritin > 50).

Avoid alcohol > 2 drinks/day maximum.

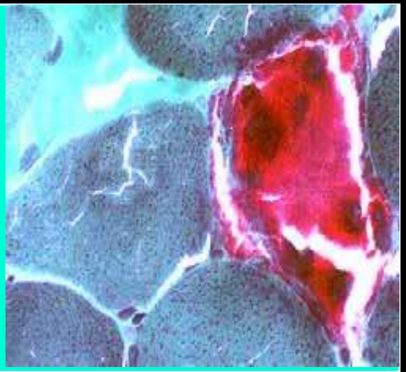
Avoid MSG and other migraine triggers (red wine, aged cheese, etc.) in MELAS patients with migraines.

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)

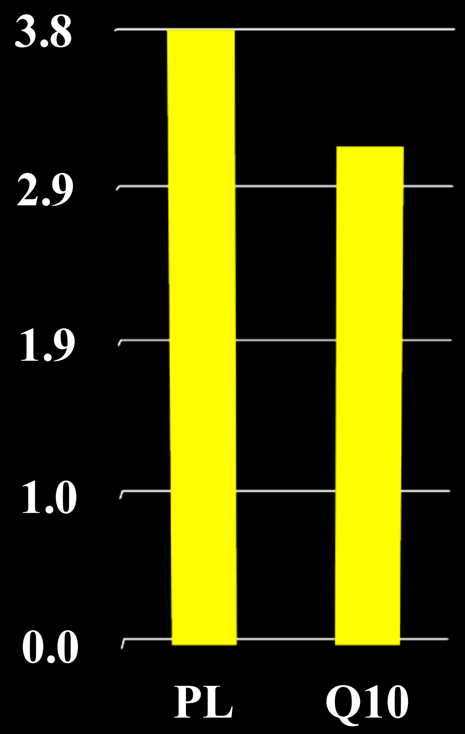
BENEFICIAL EFFECTS OF CREATINE, CoQ_{10}, AND LIPOIC ACID IN MITOCHONDRIAL DISORDERS

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]

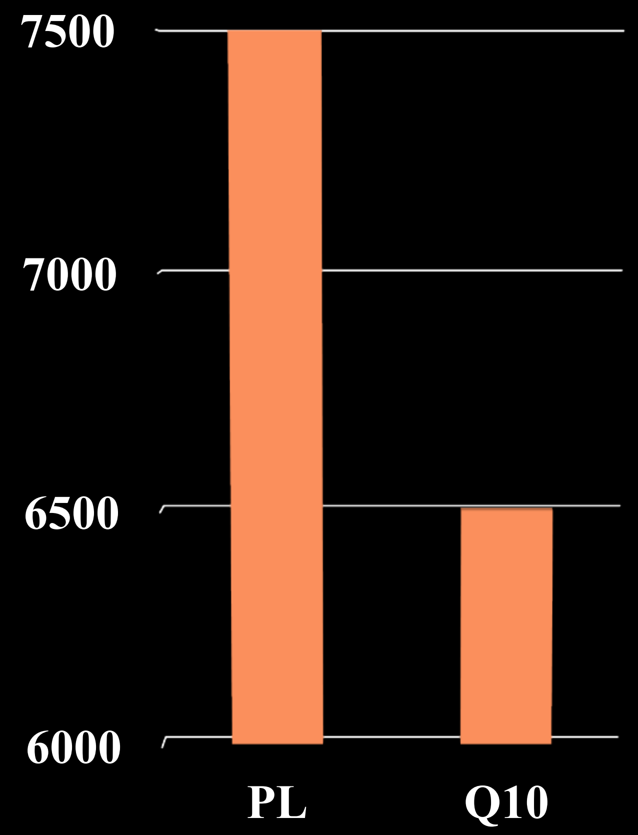
Rodriguez, et al., *Muscle and Nerve,* 35:235-, 2007.

- 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



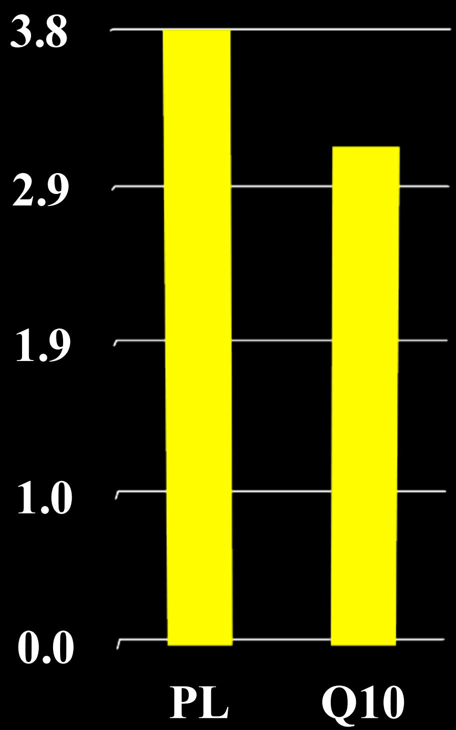
Lactate (mmol/L), $P < 0.05$



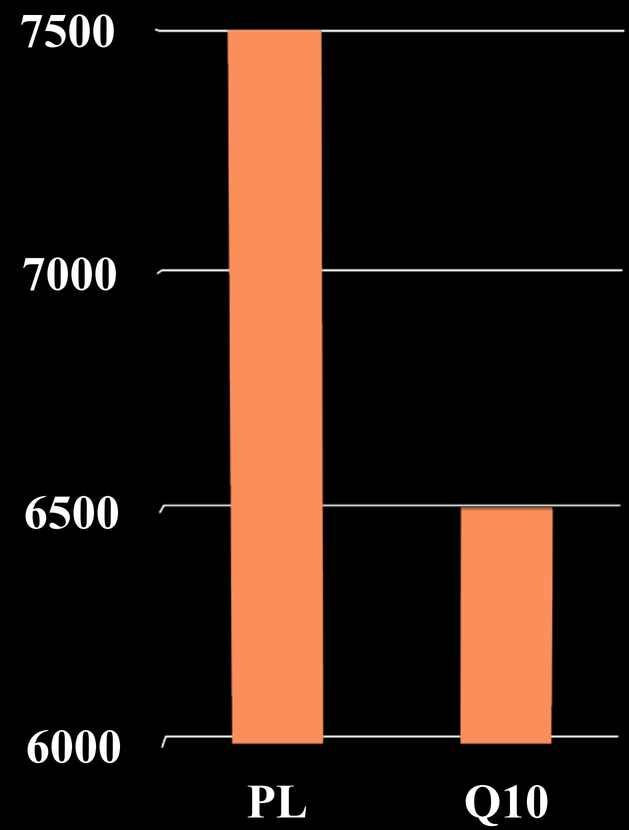
8-isoprostanes (umol/g creatinine), $P < 0.05$

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

Mitochondrial Cocktail



Lactate (mmol/L), P < 0.05



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

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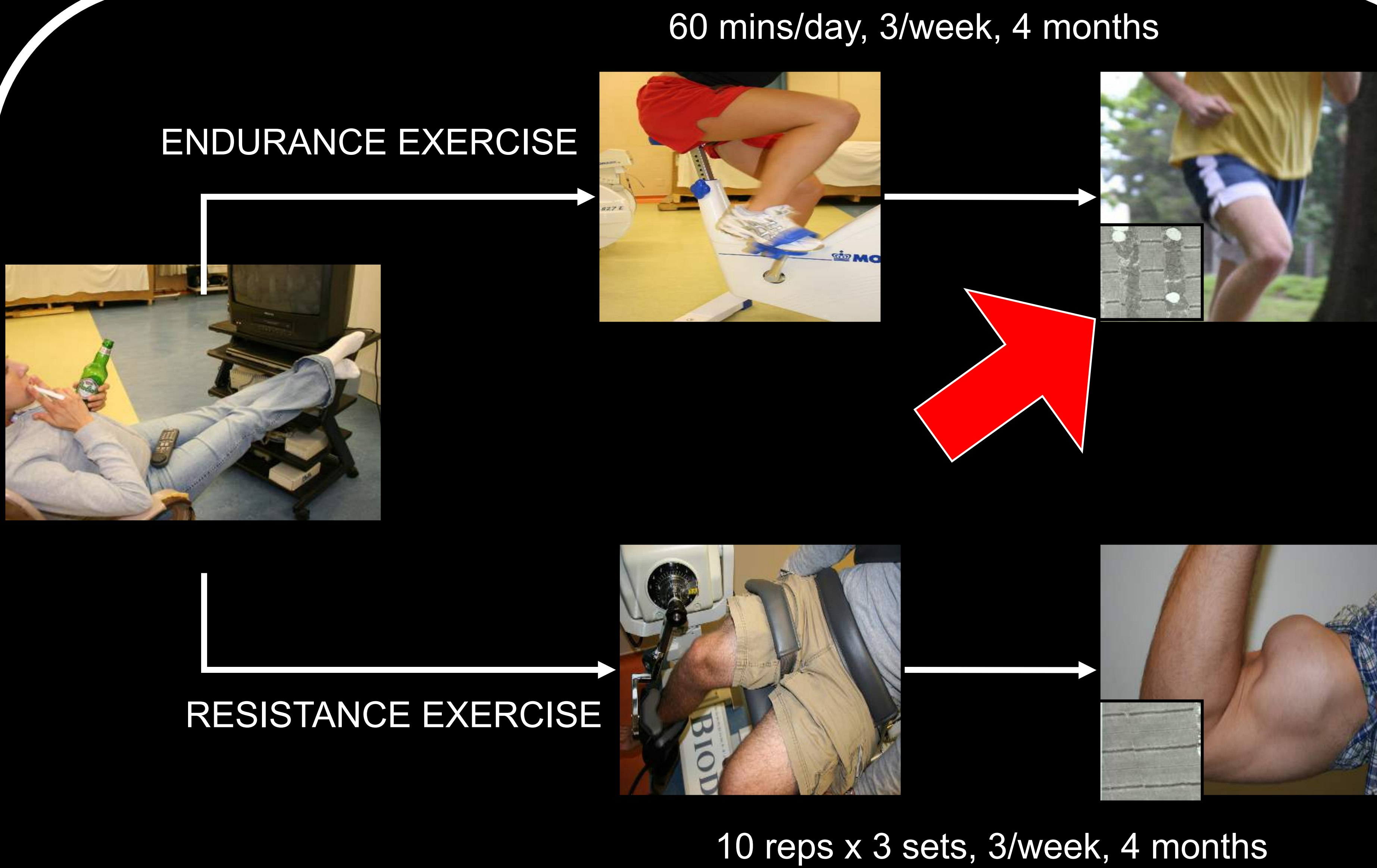
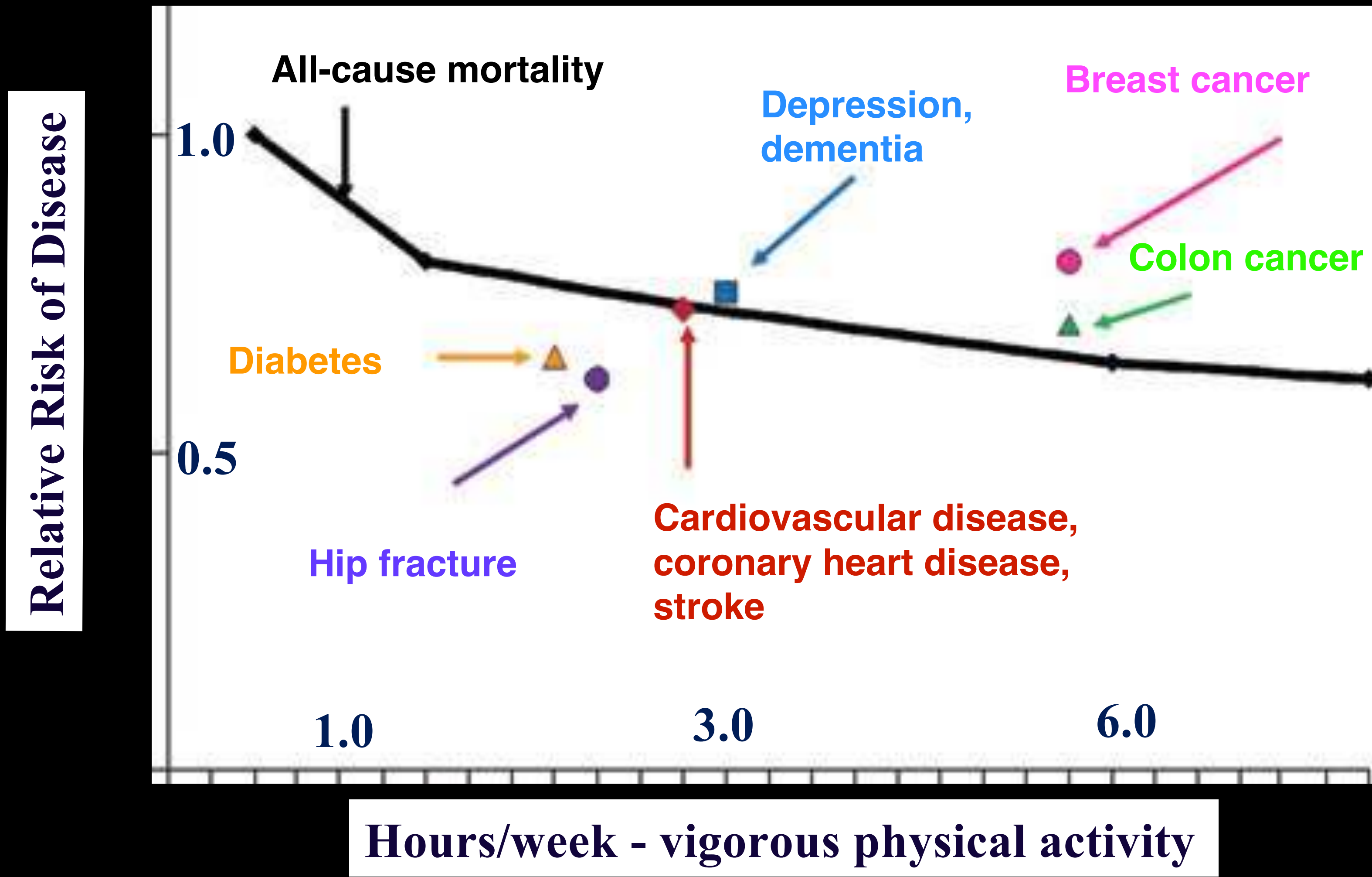


Contractile Activity Determines Phenotype

Physical Activity for Health

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



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Aging, acute and chronic endurance exercise – metabolomic analysis.

Experimental Design:

- Young (20-40) Sedentary: N=6
- Young (20-40) Athletic: N=8
- Old (65+) Athletic: N=13
- Old (60+) Sedentary-baseline: N=14
- Old (60+) Sedentary-post END exercise: N=14

LC-MS/MS analysis:

- LC-MS/MS on an ABSCIEX 5500 triple quadrupole mass spectrometer according to published methods (Naviaux, et al. 2016. PMID: 27573827).
- 612 metabolites were targeted and 477 metabolites were above the LLOQ

Nederveen, et al., MS in preparation, 2022

Aging, acute and chronic endurance exercise – metabolomic analysis.

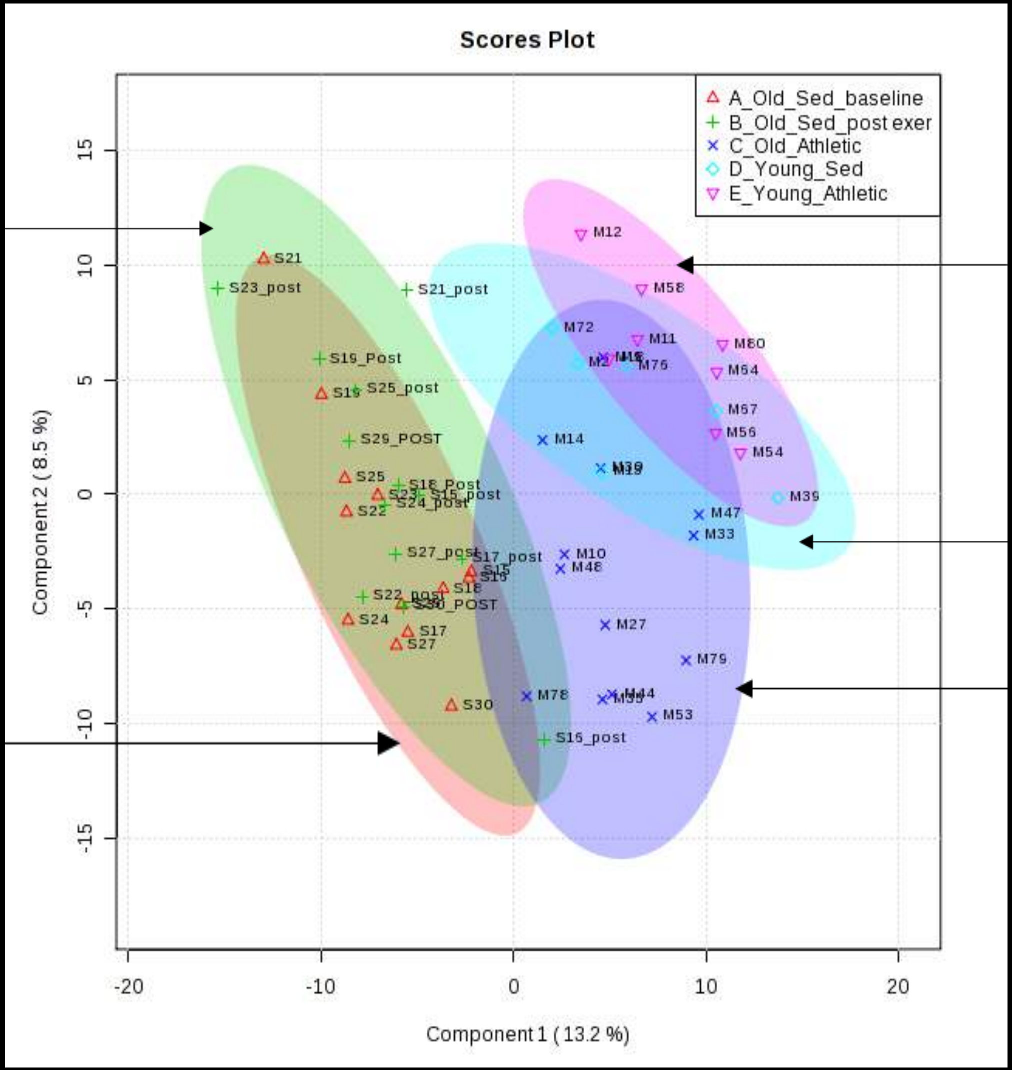
Old_Sed_Post

Young Athletic

Young Sedentary

Old Athletic

Old_Sed_Baseline



Nederveen, et al., MS in preparation, 2022

Aging, acute and chronic endurance exercise – metabolomic analysis.

Main pathways affected with aging *per se*:

1. ↓ deoxyguanosine nucleotides (dGUOK pathway).
   MITOCHONDRIAL DYSFUNCTION
2. ↑ medium and long chain acyl-carnitine species
   MITOCHONDRIAL FAO DYSFUNCTION
3. ↓ sphingomyelin species, eg. SM(d18:1/24:0)
   EXOSOME MARKER
4. ↓ specific phosphatidyl choline species, eg PC(16:0/18:1)
5. ↑ free 7-methylguanosine (7mG capping to activate mRNA)
   REDUCED PRO SYNTHESIS.

Nederveen, et al., MS in preparation, 2022

Sphingolipids are the top distinguishing pathway with chronic training and 3 months of exercise training.

No.	Pathway Name	Measured Metabolites in the Pathway (N)	Expected Pathway Proportion (P = N/612)	Expected Hits in Sample of 70 (P * 70)	Observed Hits in the Top 70 Metabolites	Fold Enrichment (Obs/Exp)	Impact (Sum VIP Score)	Fraction of Impact (VIP) Explained (% of 130.3245)	Increased (Athl/Sed>1)	Decreased (Athl/Sed<1)
1	Sphingolipid Metabolism	73	0.119	8.3	24	2.9	44.2	33.9%	24	0
2	Phospholipid Metabolism	98	0.160	11.2	12	1.1	22.5	17.3%	12	0
3	Purine Metabolism	37	0.060	4.2	5	1.2	11.8	9.0%	5	0
4	Cholesterol, Cortisol, Non-Gonadal Steroid Metabolism	22	0.036	2.5	6	2.4	11.3	8.7%	6	0
5	Glycolysis and Gluconeogenesis	14	0.023	1.6	3	1.9	5.4	4.1%	0	3
6	Microbiome Metabolism	31	0.051	3.5	3	0.8	5.3	4.0%	3	0
7	Eicosanoid and Resolvin Metabolism	29	0.047	3.3	2	0.6	3.4	2.6%	0	2
8	Ganglioside Metabolism	17	0.028	1.9	2	1.0	3.3	2.5%	2	0
9	Fatty Acid Oxidation and Synthesis	38	0.062	4.3	2	0.5	3.3	2.5%	2	0
10	Tyrosine and Phenylalanine Metabolism	4	0.007	0.5	1	2.2	2.1	1.6%	1	0
11	Vitamin D (Calciferol) Metabolism	3	0.005	0.3	1	2.9	2.0	1.5%	1	0
12	Vitamin E (Tocopherol) Metabolism	1	0.002	0.1	1	8.7	2.0	1.5%	1	0
13	Vitamin C (Ascorbate) Metabolism	3	0.005	0.3	1	2.9	1.9	1.4%	0	1
14	Oxalate, Glyoxylate Metabolism	3	0.005	0.3	1	2.9	1.9	1.4%	0	1
15	1-Carbon, Folate, Formate, Glycine, Ser	7	0.011	0.8	1	1.2	1.8	1.4%	1	0
16	Cardiolipin Metabolism	8	0.013	0.9	1	1.1	1.7	1.3%	1	0
17	Phytanic, Branch, Odd Chain Fatty Acid	1	0.002	0.1	1	8.7	1.7	1.3%	0	1
18	Vitamin B3 (Niacin, NAD+) Metabolism	8	0.013	0.9	1	1.1	1.6	1.2%	0	1
19	Vitamin B2 (Riboflavin) Metabolism	3	0.005	0.3	1	2.9	1.6	1.2%	1	0
20	Bioamines and Neurotransmitter	13	0.021	1.5	1	0.7	1.5	1.2%	0	1

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}.

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.

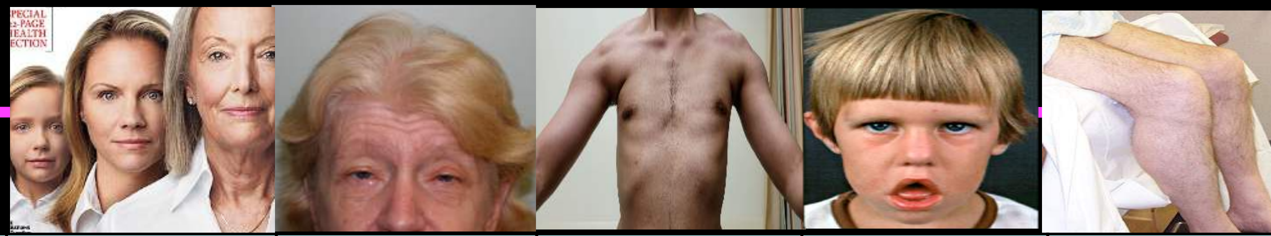
Jeppesen T., et al., Brain 129:3402-, 2006

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

Many questions remain regarding exercise and MD



Phenotype

Molecular

Variable	AGING	MITO	FSD	DM1	sIBM
Strength	↑	↑	→	→	↑
Endurance	↑	↑	↑	↑	→
QOL	↑	↑	+,-	?	?
Body Composition Index (lean/fat)	↑	↑	?	↑	?
Mitochondrial Function	↑	↑	?	?	?
Oxidative stress	↓	?	?	?	?
Inflammation	↓	?	?	?	?

The Journal of Clinical Investigation CLINICAL MEDICINE

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

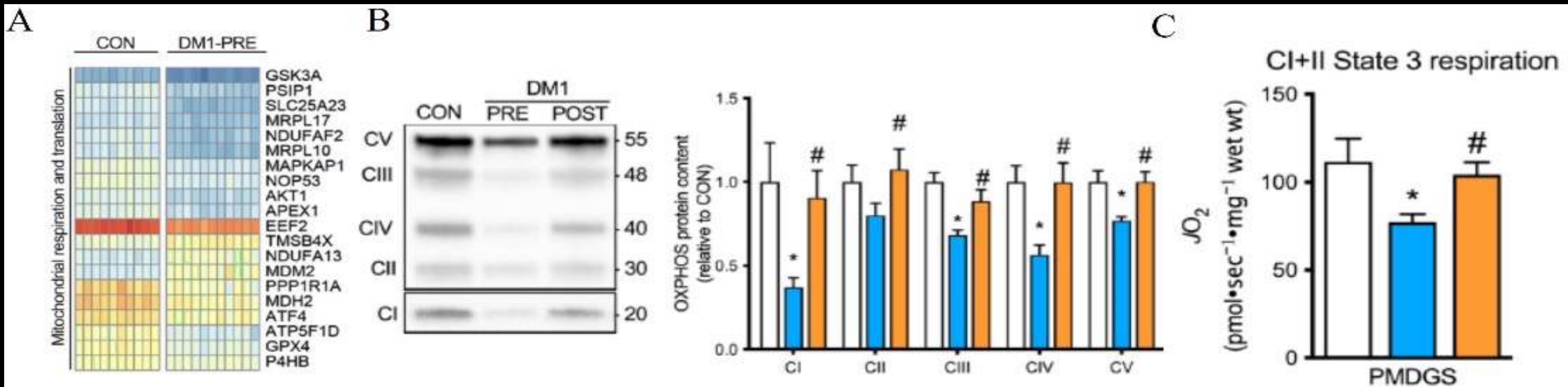
Andrew I. Mikhail,[1] Peter L. Nagy,[2] Katherine Manta,[3] Nicholas Rouse,[2] Alexander Manta,[1] Sean Y. Ng,[1] Michael F. Nagy,[2] Paul Smith,[2] Jian-Qiang Lu,[4] Joshua P. Nederveen,[3] Vladimir Ljubicic,[1] and Mark A. Tarnopolsky[3,5]

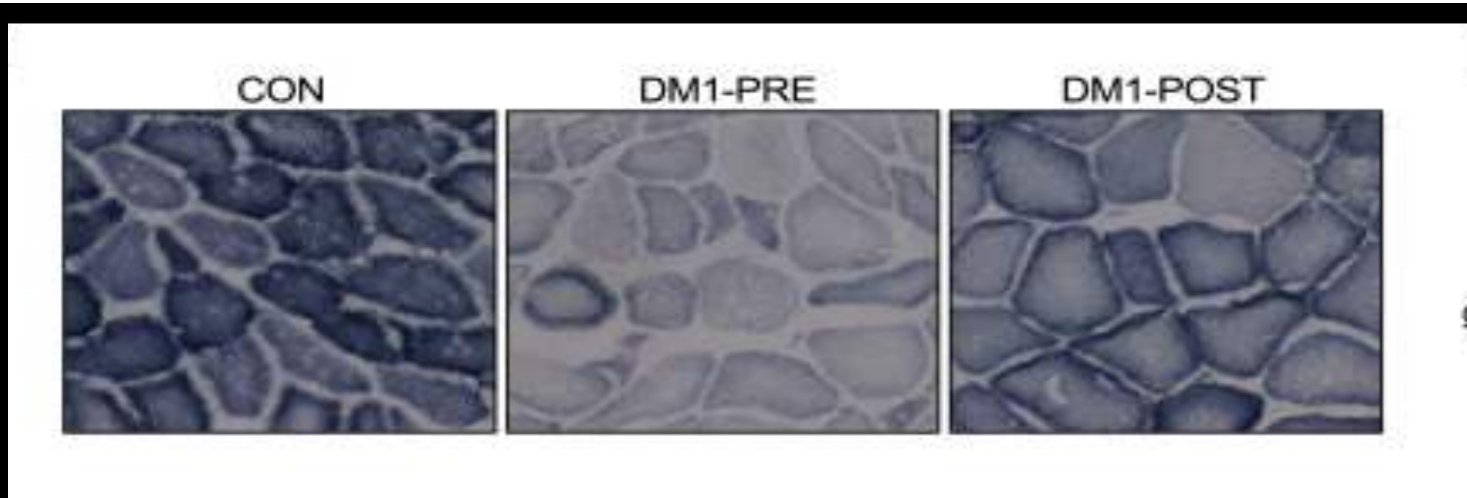
[1]Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada. [2]Praxis Genomics LLC, Atlanta, Georgia, USA. [3]Department of Pediatrics, McMaster University Children's Hospital, Hamilton, Ontario, Canada. [4]Department of Pathology and Molecular Medicine/Neuropathology, McMaster University,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

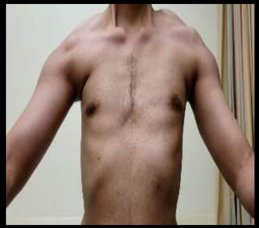
- Safe – histopathology, CK, cardiac, joint.
- Increase function (6MWT – 47 m, TUG, 5XSTS).
- ~ 30 % VO_{2peak}.
- 1.6 kg (4.3 %) LBM.

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

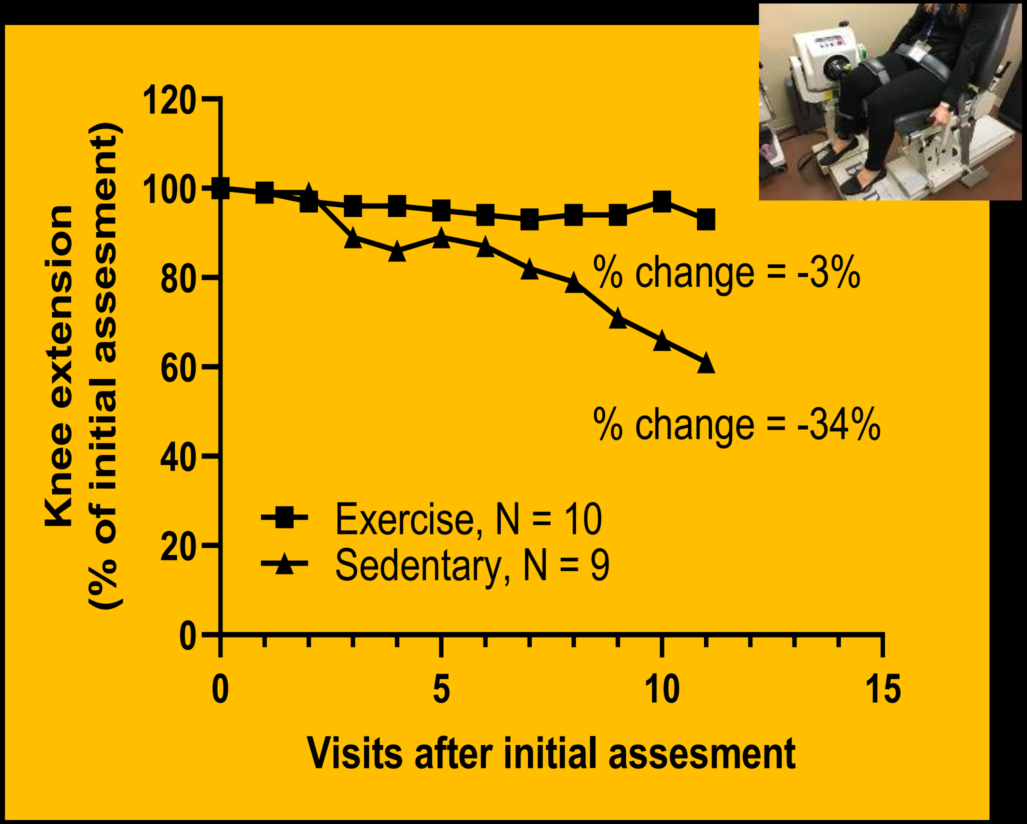
ABSTRACT

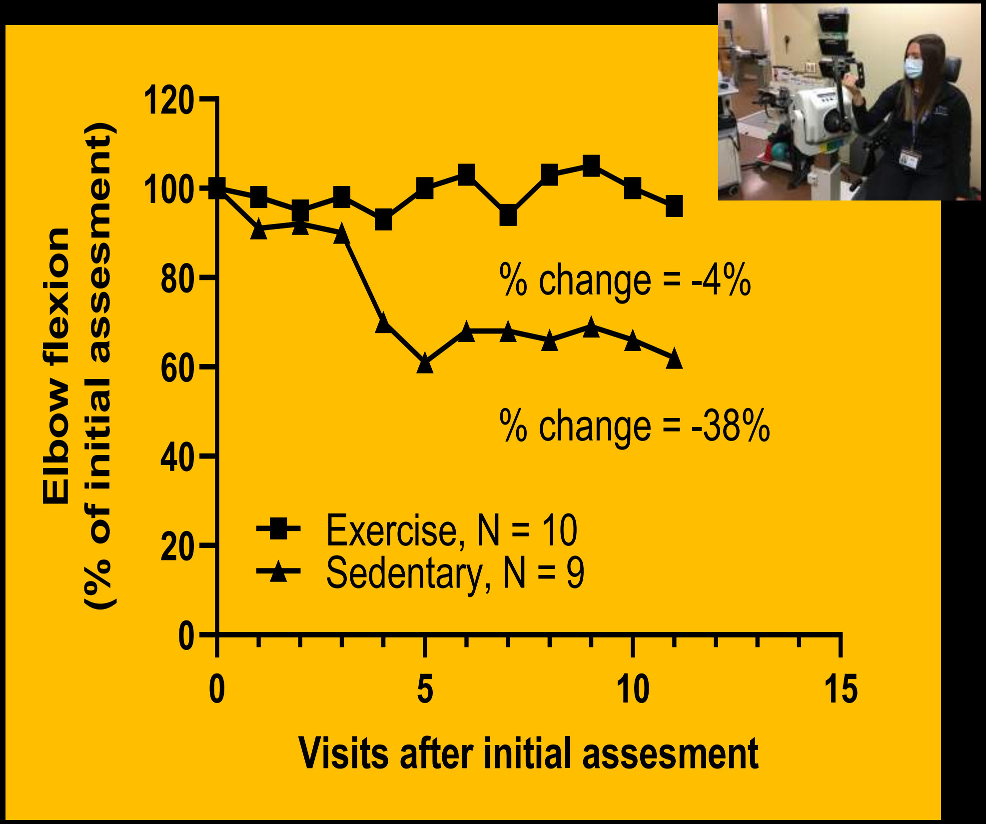
Brady LI, MacNeil LG, Tarnopolsky MA: Impact of habitual exercise on the strength of individuals with myotonic dystrophy type 1. Am J Phys Med Rehabil 2014;93:739–750.

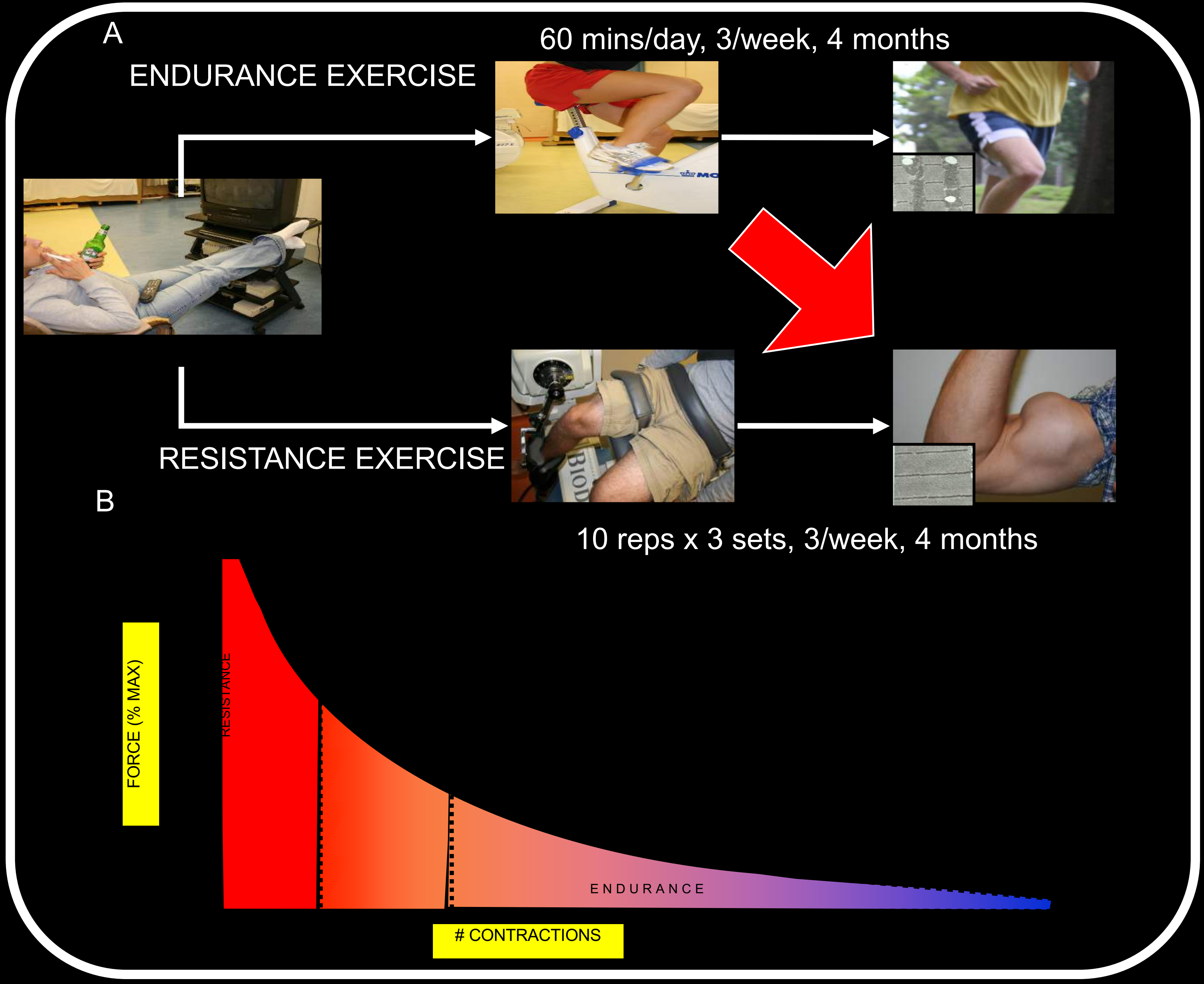
Exercise is Medicine!



FSHD – demethylation of DUX4 = oxidative stress and MITOCHONDRIAL DYSFUNCITON



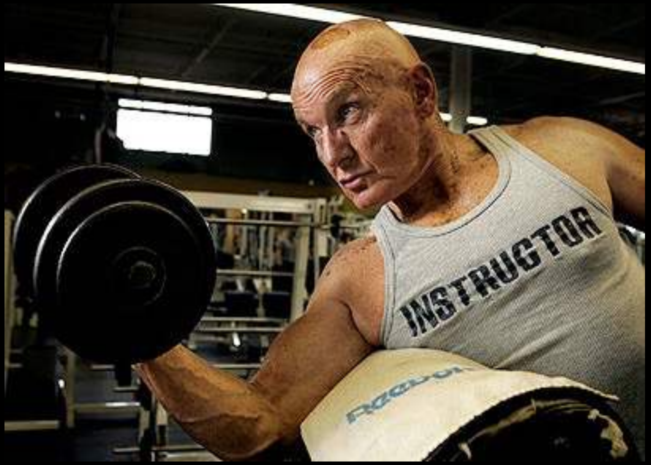



A
60 mins/day, 3/week, 4 months
ENDURANCE EXERCISE
RESISTANCE EXERCISE
B
10 reps x 3 sets, 3/week, 4 months
FORCE (% MAX)
RESISTANCE
ENDURANCE
CONTRACTIONS

Mitochondrial Adaptation and Exercise in Older Adults:

6 months of whole-body RESISTANCE exercise training

- 2x per week of supervised sessions
- One set (50% of 1 RM) to three sets (75% of NEW 1 RM)



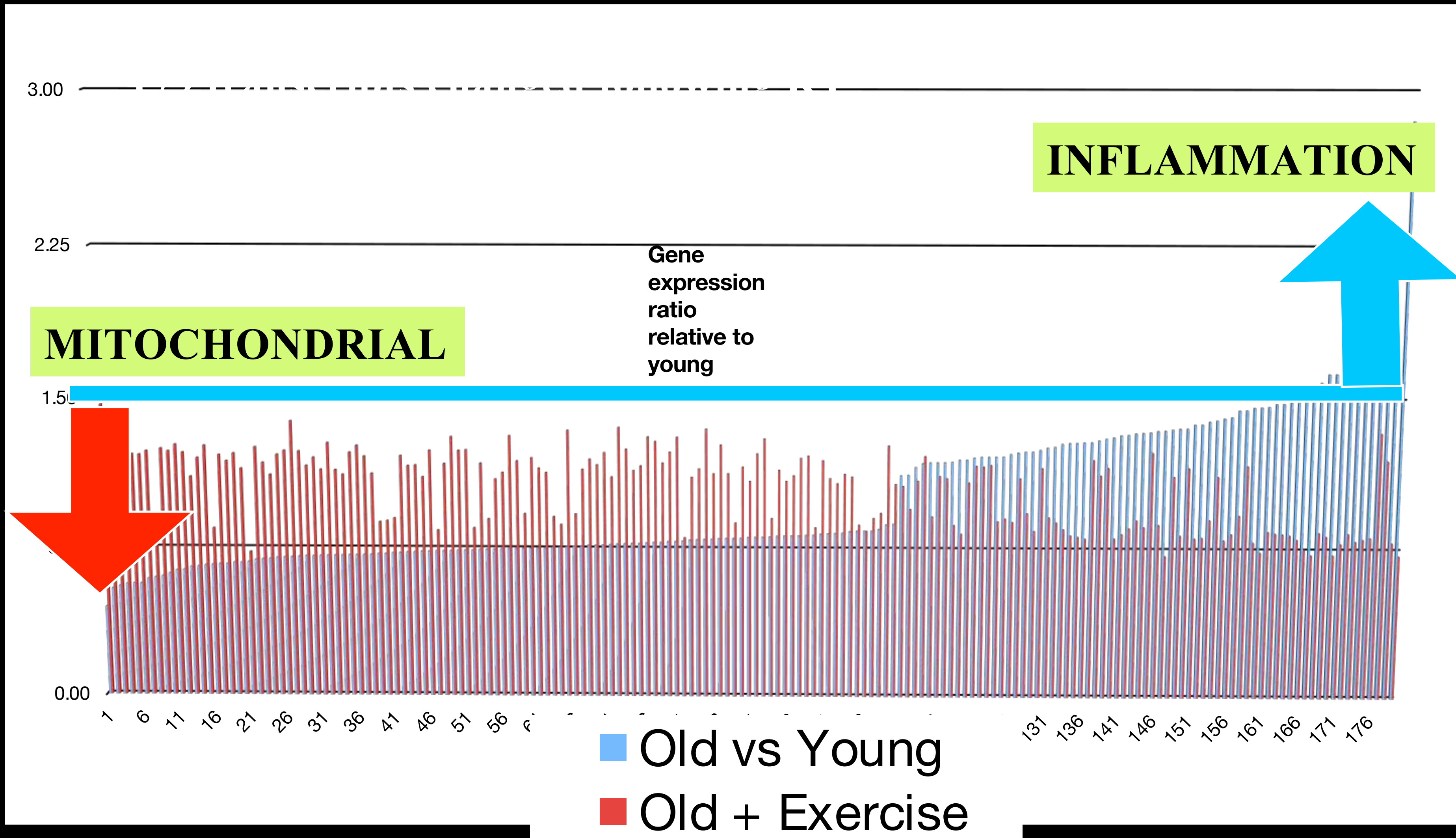
70 ± 5 y

♀ = ♂

- **Muscle biopsies** – taken from the *vastus lateralis* in the post-absorptive state – PRE and POST training.

Tarnopolsky et al., *PLoS ONE*, 2007

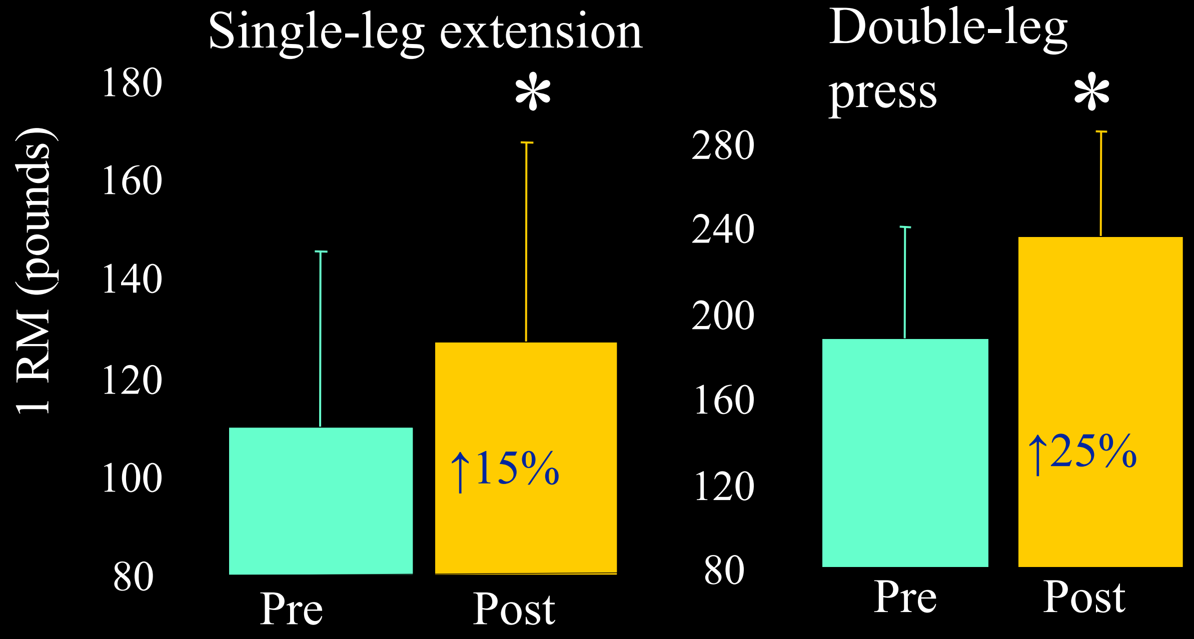
Exercise reverses aging.



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)



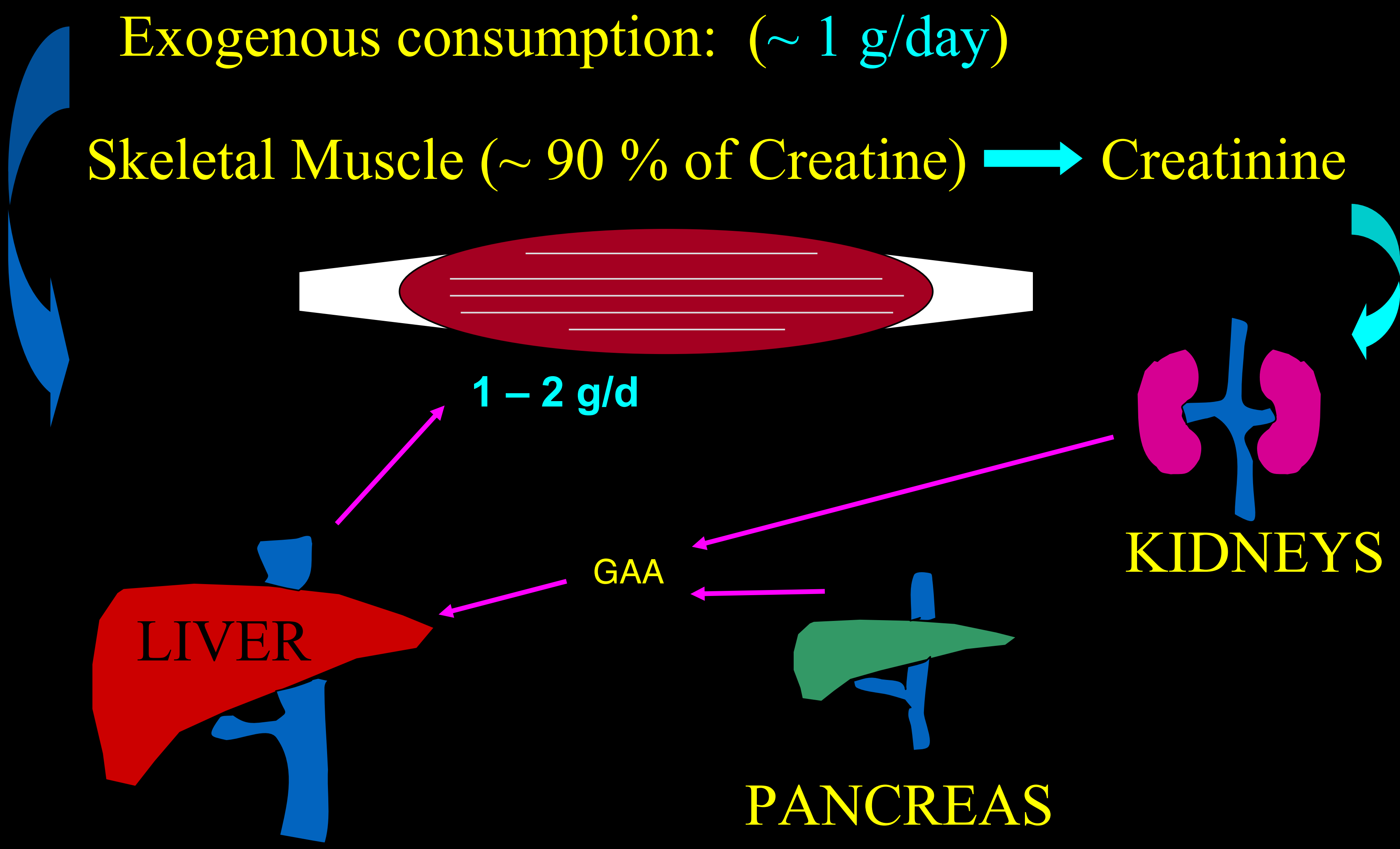
CK pre: 187 ± 115 U/L
CK post: 166 ± 159 U/L

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

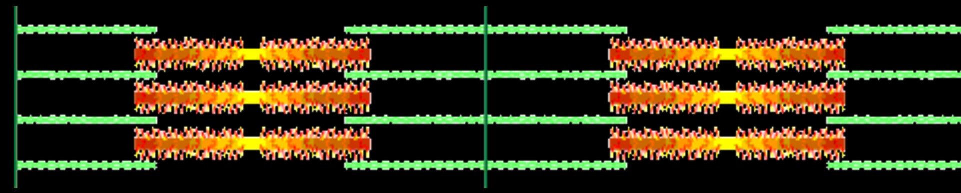
Can supplements enhance exercise Benefits?

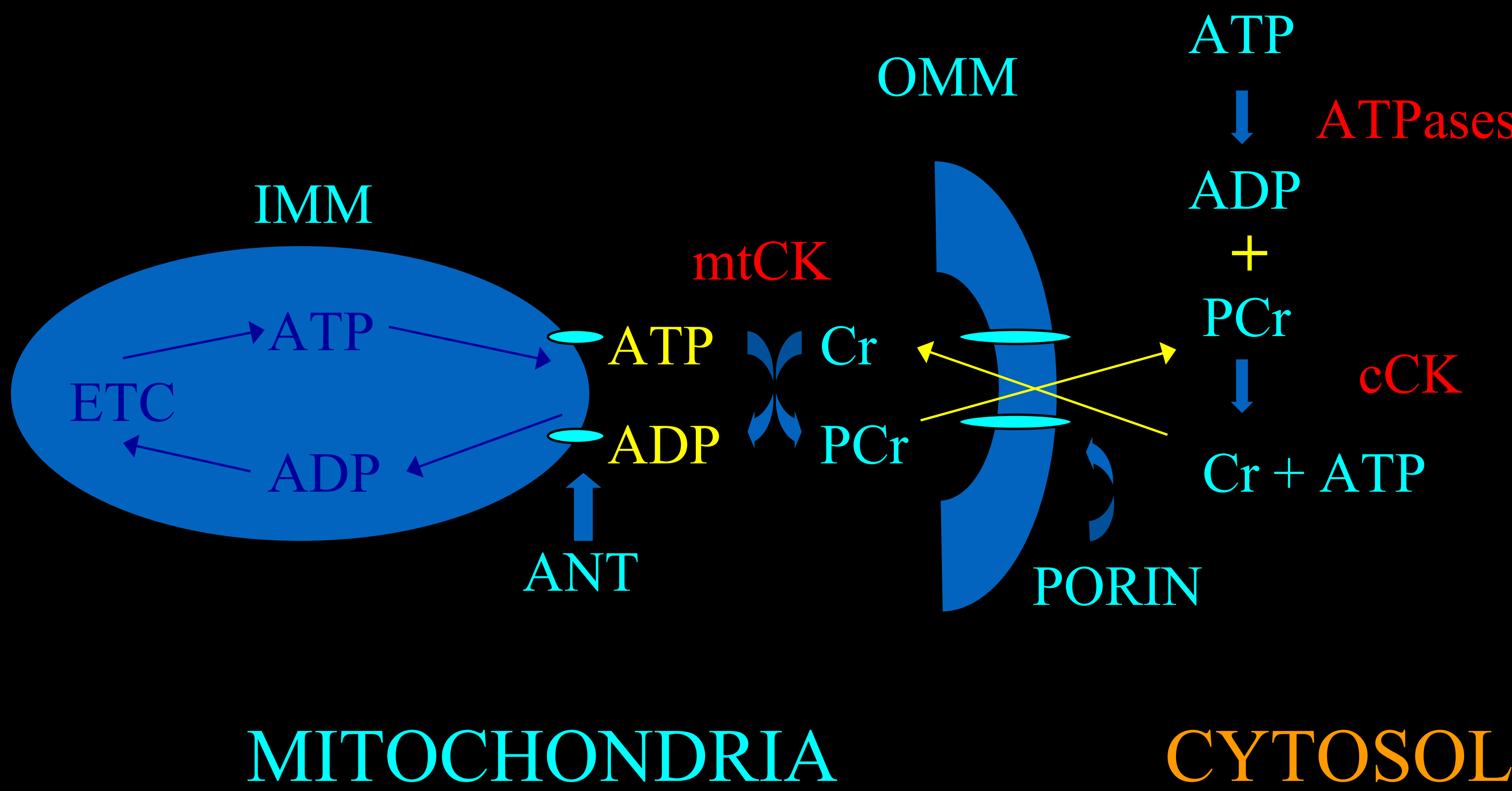
- Creatine and aging.
- Protein and aging.
- Sarcopenic obesity.

Creatine in the body:



Cr-PCr Metabolism





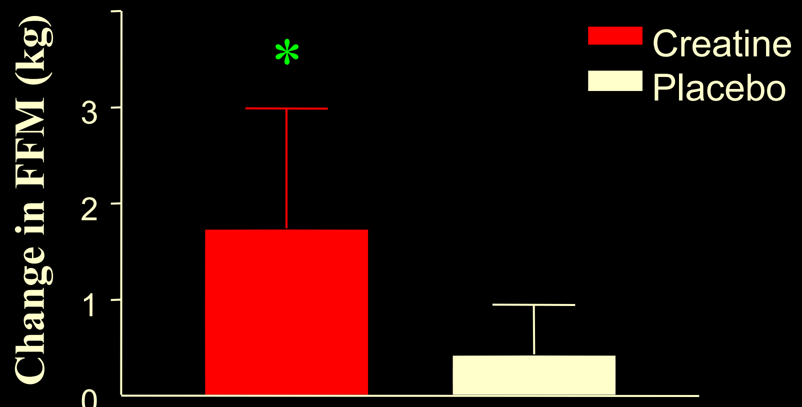
RT and CrM in older adults

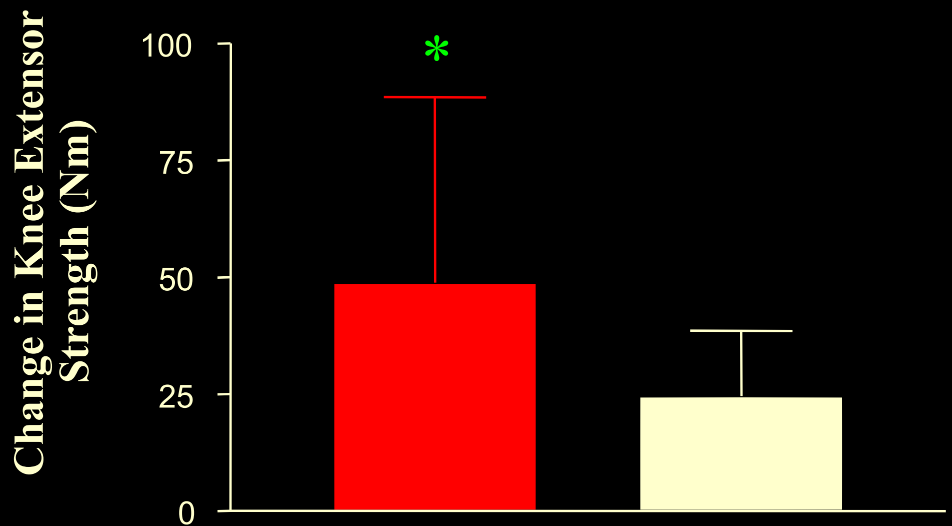
15 men (68 y); 15 women (69 y)

14 weeks RT program (3X/wk)

No effect at all on % BF.

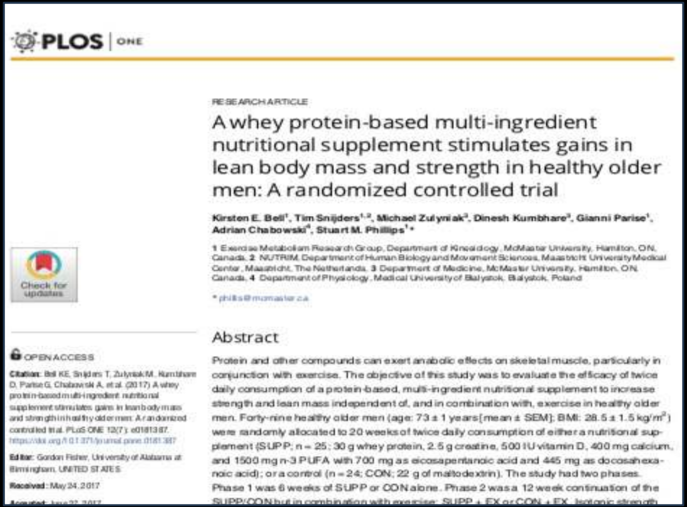
No side effects noted





Brose, A, et al., *J. Gerontol.*, 58:11-19, 2003

Multi-ingredient nutritional supplement (Muscle5)



PLOS | ONE

RESEARCH ARTICLE

A whey protein-based multi-ingredient nutritional supplement stimulates gains in lean body mass and strength in healthy older men: A randomized controlled trial

Kirsten E. Bell[1], Tim Snijders[1,2], Michael Zulyniak[3], Dinesh Kumbhare[3], Gianni Parise[1], Adrian Chabowski[4], Stuart M. Phillips[1]*

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OPEN ACCESS

Citation: Bell KE, Snijders T, Zulyniak M, Kumbhare D, Parise G, Chabowski A, et al. (2017) A whey protein-based multi-ingredient nutritional supplement stimulates gains in lean body mass and strength in healthy older men: A randomized controlled trial. PLoS ONE 12(7): e0181387. https://doi.org/10.1371/journal.pone.0181387

Editor: Gordon Fisher, University of Alabama at Birmingham, UNITED STATES

Received: May 24, 2017

Abstract

Protein and other compounds can exert anabolic effects on skeletal muscle, particularly in conjunction with exercise. The objective of this study was to evaluate the efficacy of twice daily consumption of a protein-based, multi-ingredient nutritional supplement to increase strength and lean mass independent of, and in combination with, exercise in healthy older men. Forty-nine healthy older men (age: 73 ± 1 years [mean ± SEM]; BMI: 28.5 ± 1.5 kg/m^2) were randomly allocated to 20 weeks of twice daily consumption of either a nutritional supplement (SUPP; n = 25; 30 g whey protein, 2.5 g creatine, 500 IU vitamin D, 400 mg calcium, and 1500 mg n-3 PUFA with 700 mg as eicosapentanoic acid and 445 mg as docosahexanoic acid); or a control (n = 24; CON; 22 g of maltodextrin). The study had two phases. Phase 1 was 6 weeks of SUPP or CON alone. Phase 2 was a 12 week continuation of the

- Whey + calcium + vitamin D + creatine + omega 3 (fish oil) vs collagen placebo.
- ⬆ - strength, LBM, composite cognition.
- ⬇ - TGs and inflammation (TNF, IL-6, CRP).
    - *Front Aging Neurosci.* 2019 May 9;11:107;
    - *Appl Physiol Nutr Metab.* 2018 Mar;43(3):299-302

nutrients

MDPI

Article

A Five-Ingredient Nutritional Supplement and Home-Based Resistance Exercise Improve Lean Mass and Strength in Free-Living Elderly

Mats I. Nilsson [1,2], Andrew Mikhail [1,3], Lucy Lan [1], Alessia Di Carlo [1], Bethanie Hamilton [1], Kristin Barnard [1], Bart P. Hettinga [2], Erin Hatcher [1], Milla G. Tarnopolsky [1], Joshua P. Nederveen [1], Adam L. Bujak [2], Linda May [1] and Mark A. Tarnopolsky [1,2,*]

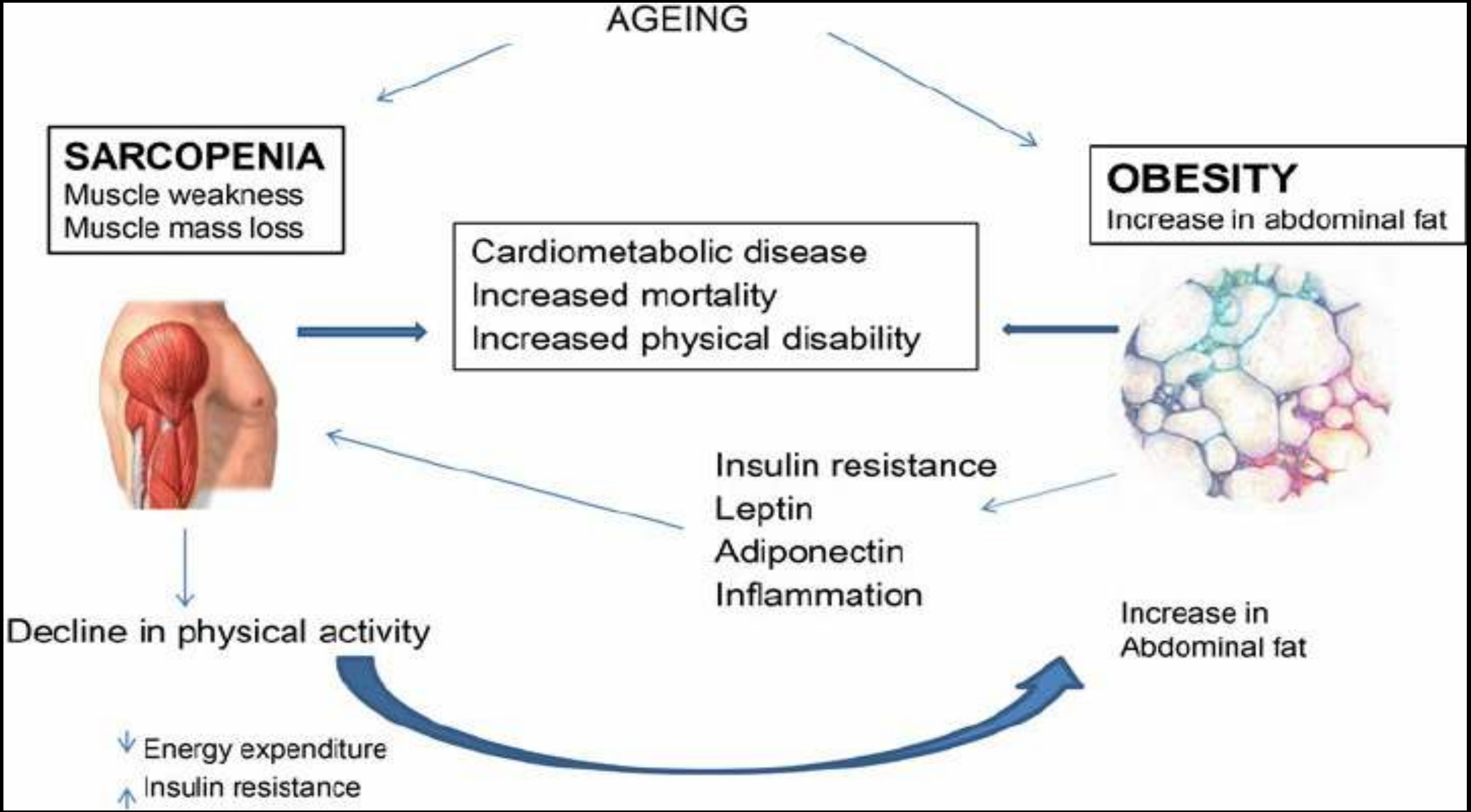
check for updates

Received: 11 July 2020; Accepted: 3 August 2020; Published: 10 August 2020

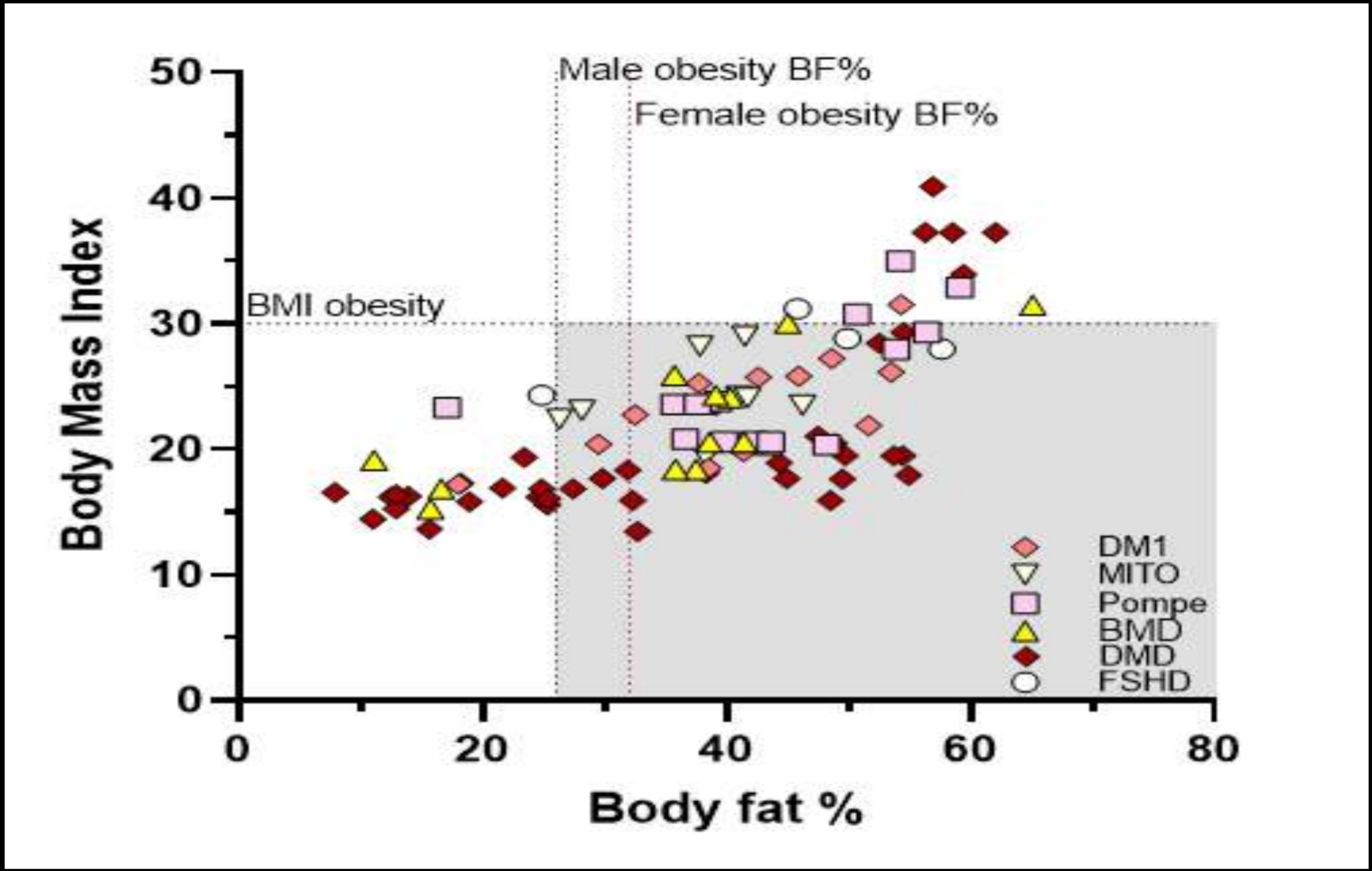
Abstract: Old age is associated with lower physical activity levels, suboptimal protein intake, and desensitization to anabolic stimuli, predisposing for age-related muscle loss (sarcopenia). Although resistance exercise (RE) and protein supplementation partially protect against sarcopenia under controlled conditions, the efficacy of home-based, unsupervised RE (HBRE) and multi-ingredient supplementation (MIS) is largely unknown. In this randomized, placebo-controlled and double-blind trial, we examined the effects of HBRE/MIS on muscle mass, strength, and function in free-living, older men. Thirty-two sedentary men underwent twelve weeks of home-based resistance band training (3 d/week), in combination with daily intake of a novel five-nutrient supplement

- Whey + casein (Ca) + vit. D + creatine +omega 3 (fish oil) vs collagen placebo.
- ⬆ - LBM, LBM/fat ratio, strength, 5- time sit-to stand.
    - Nilsson at al, *Nutrients* 2020, 12, 2391.

Sarcopenic Obesity - ? Treatment options

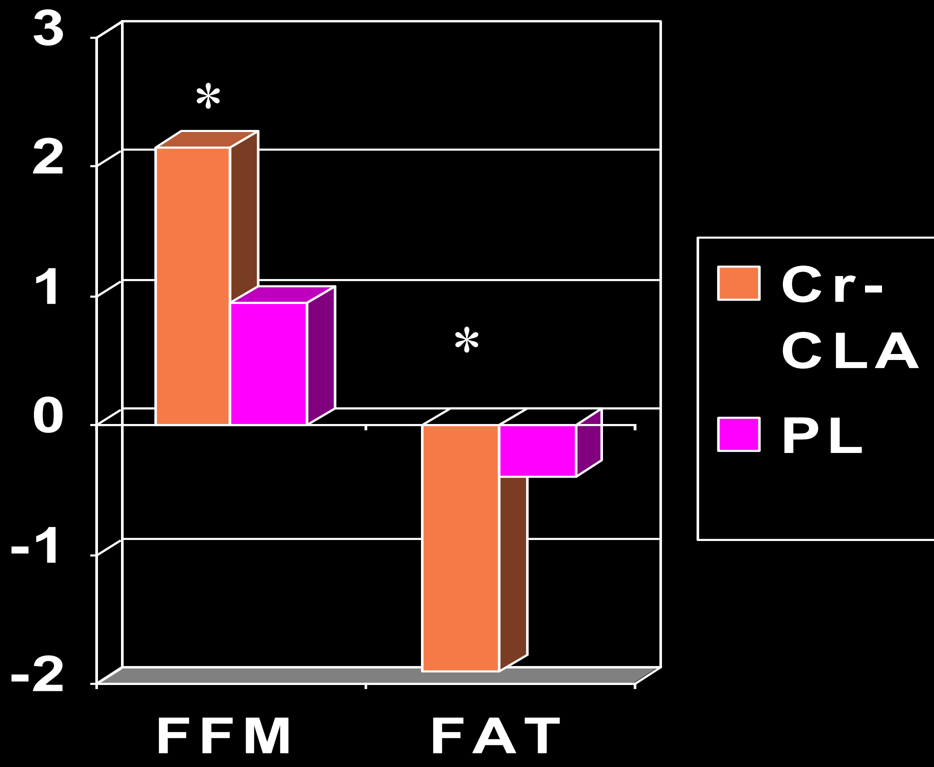


Sarcopenic Obesity – Aging and MD



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 weight training.



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

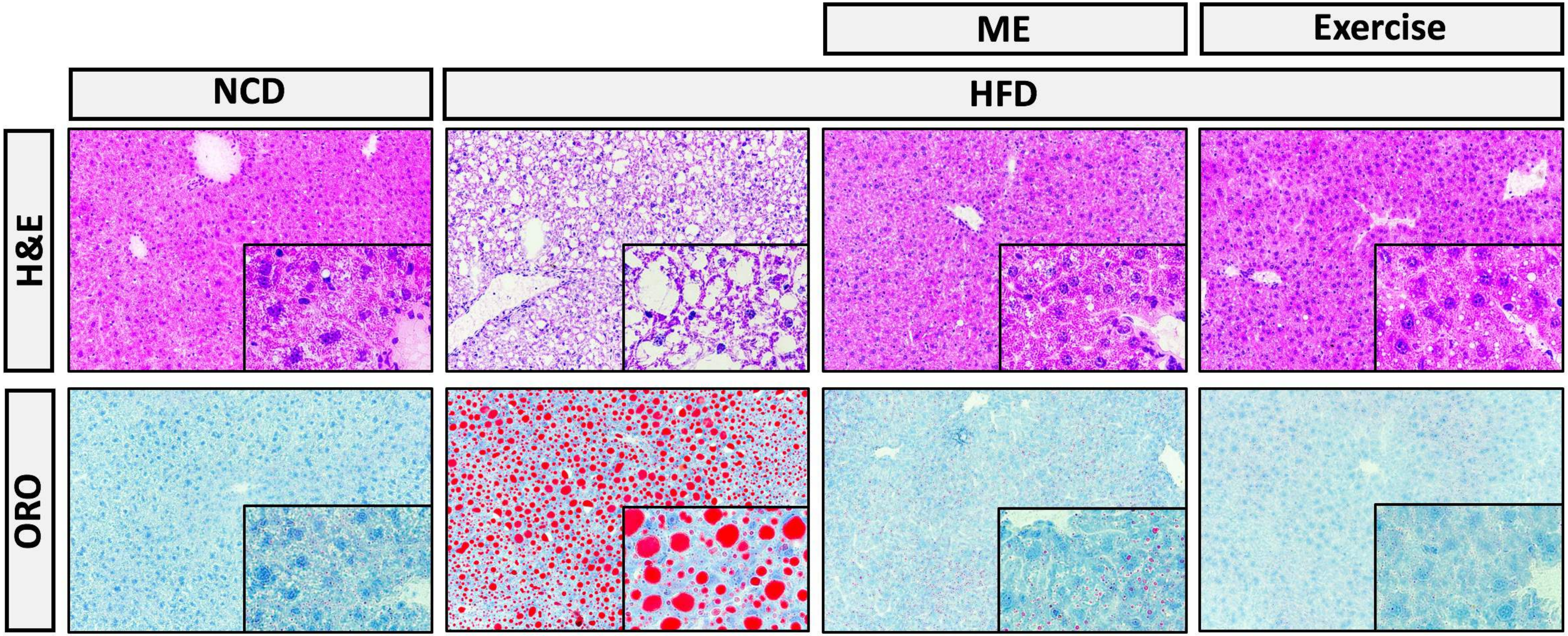
Multi-nutrient supplement for obesity, NAFLD, T2DM – TRIM7/ME3.

- 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.**

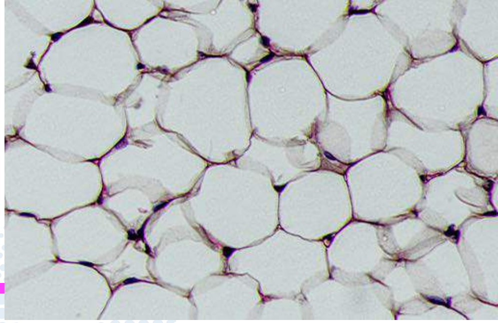
TRIM7 – Metabolic Enhancer

ME

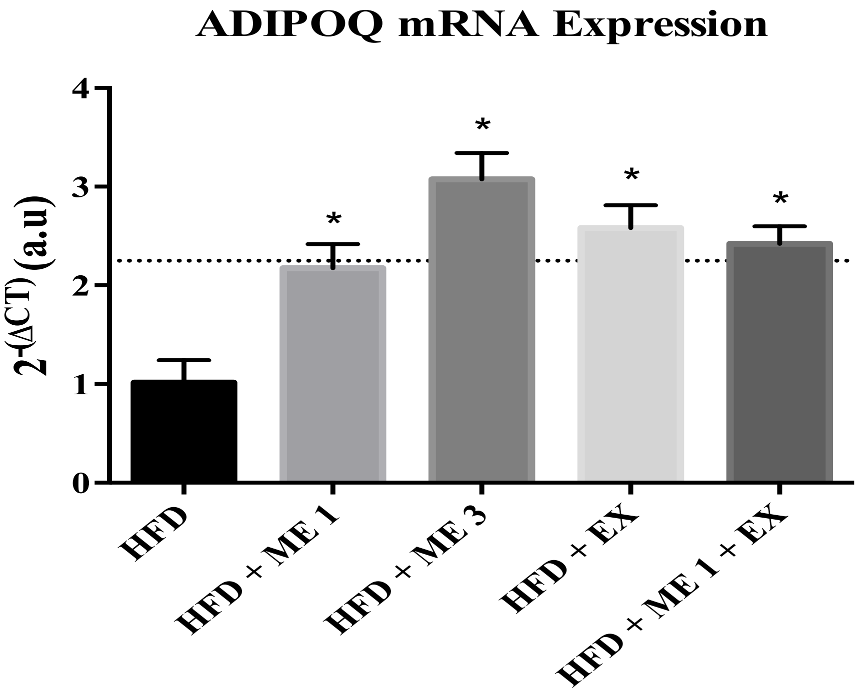


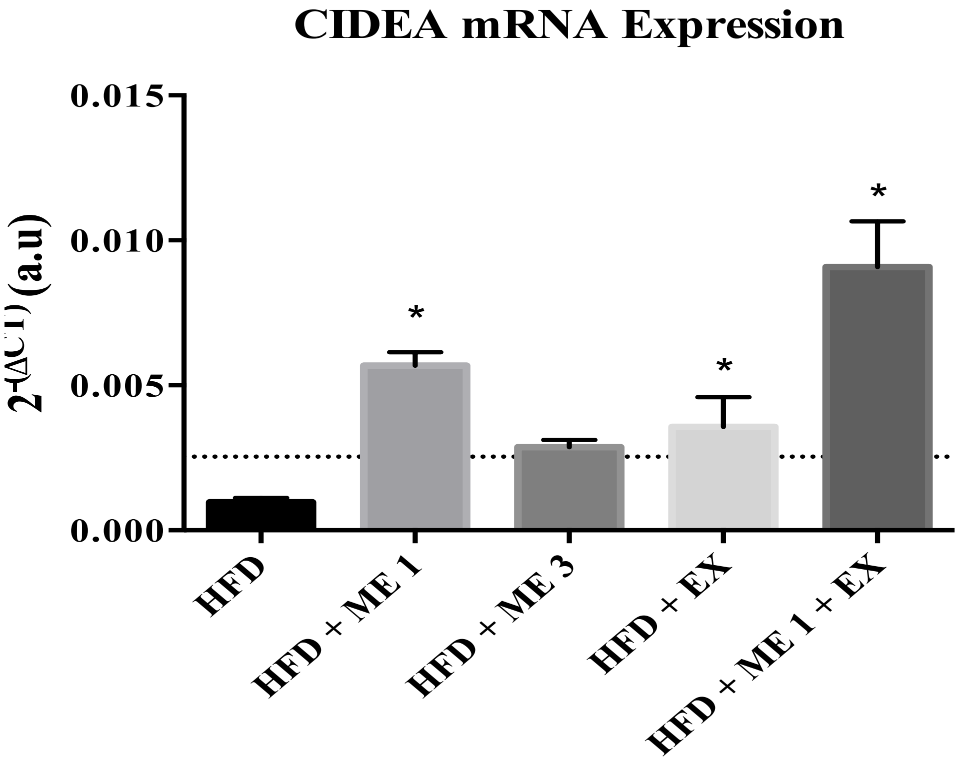
Nederveen, et al., ***Nutrients*, 2021, 13, 3726.**

Metabolic Enhancer - Browning



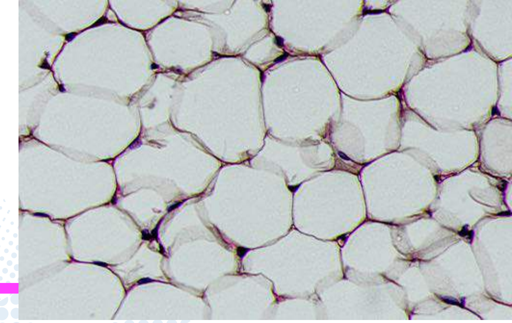
Mechanism = White adipose tissue browning



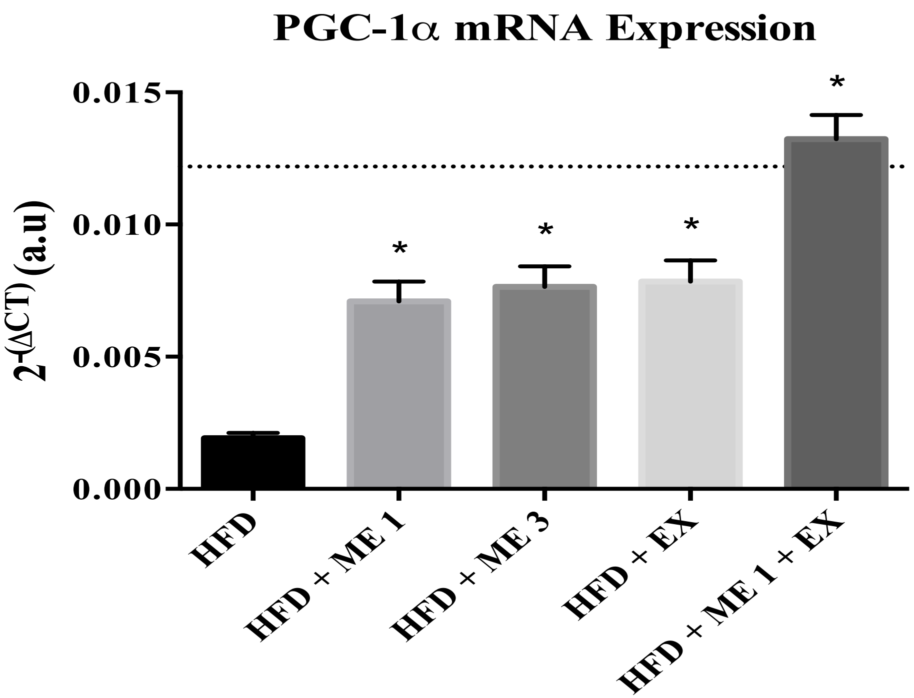


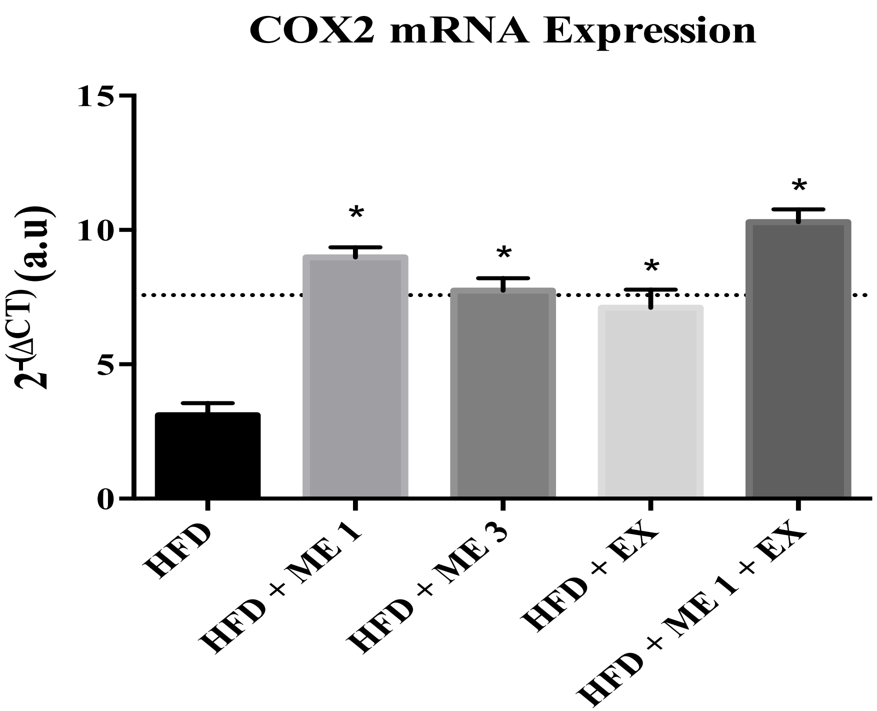
Nederveen, et al., ***Nutrients***, **2021, 13, 3726.**

Metabolic Enhancer – Mitochondrial Biogenesis



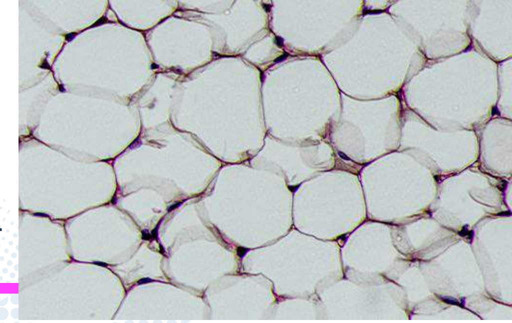
Mechanism = White adipose tissue browning



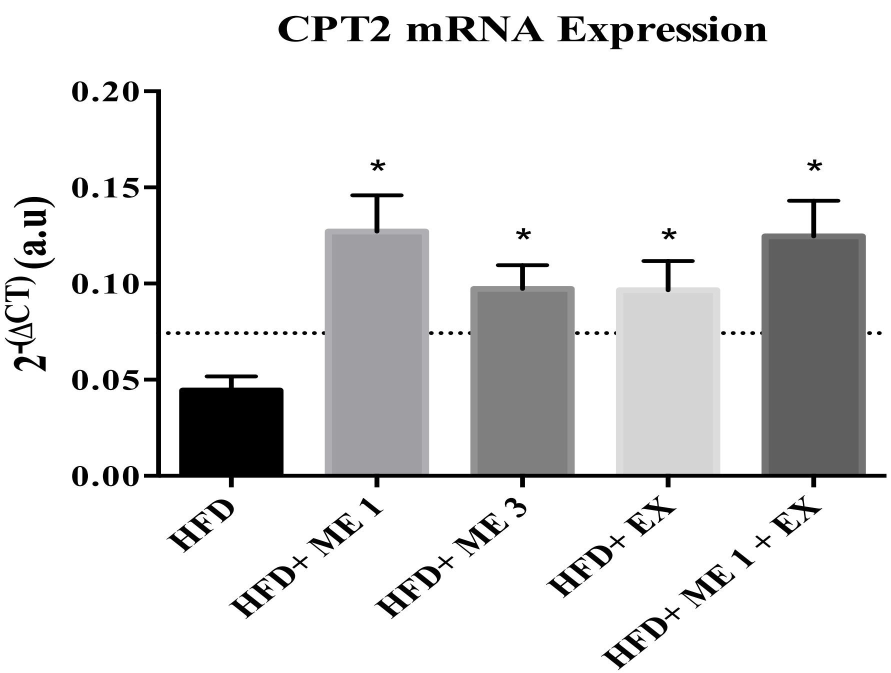


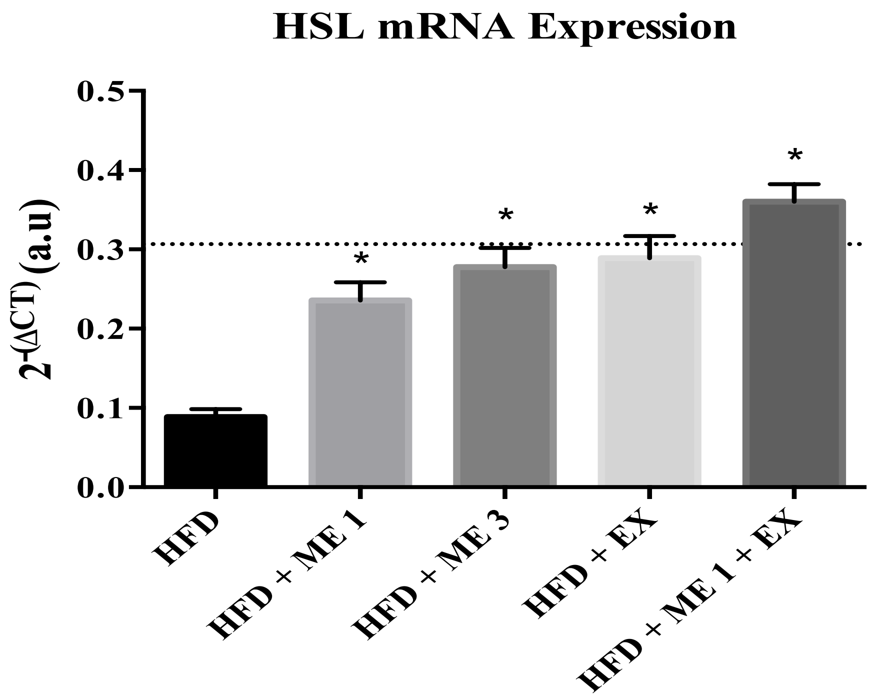
Nederveen, et al., ***Nutrients*, 2021, 13, 3726.**

Metabolic Enhancer – Lipid Oxidation



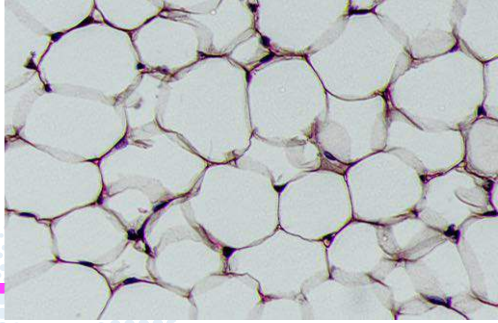
Mechanism = White adipose tissue browning

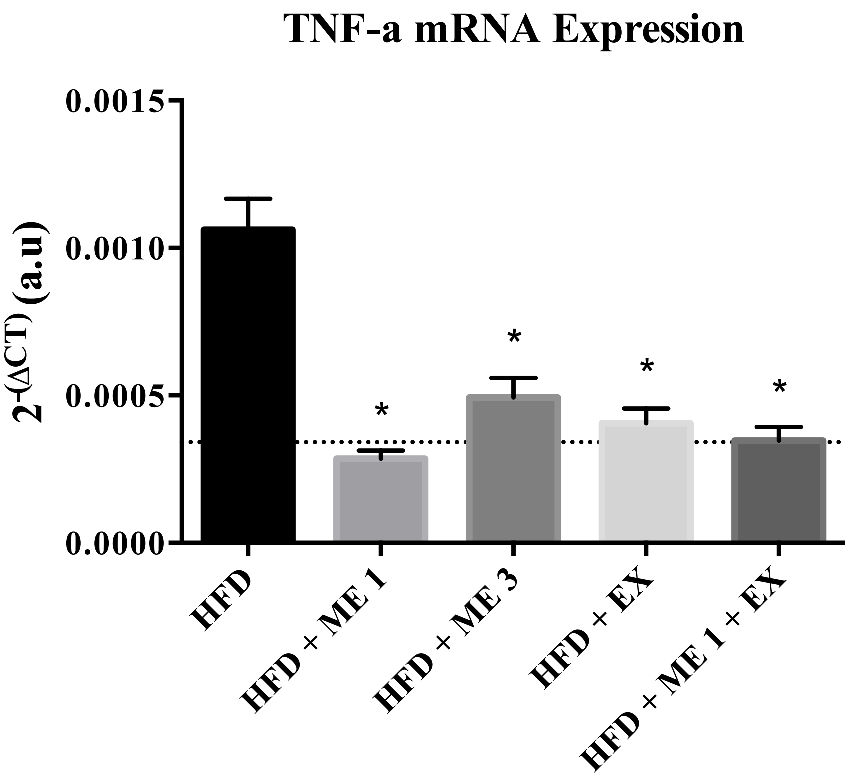


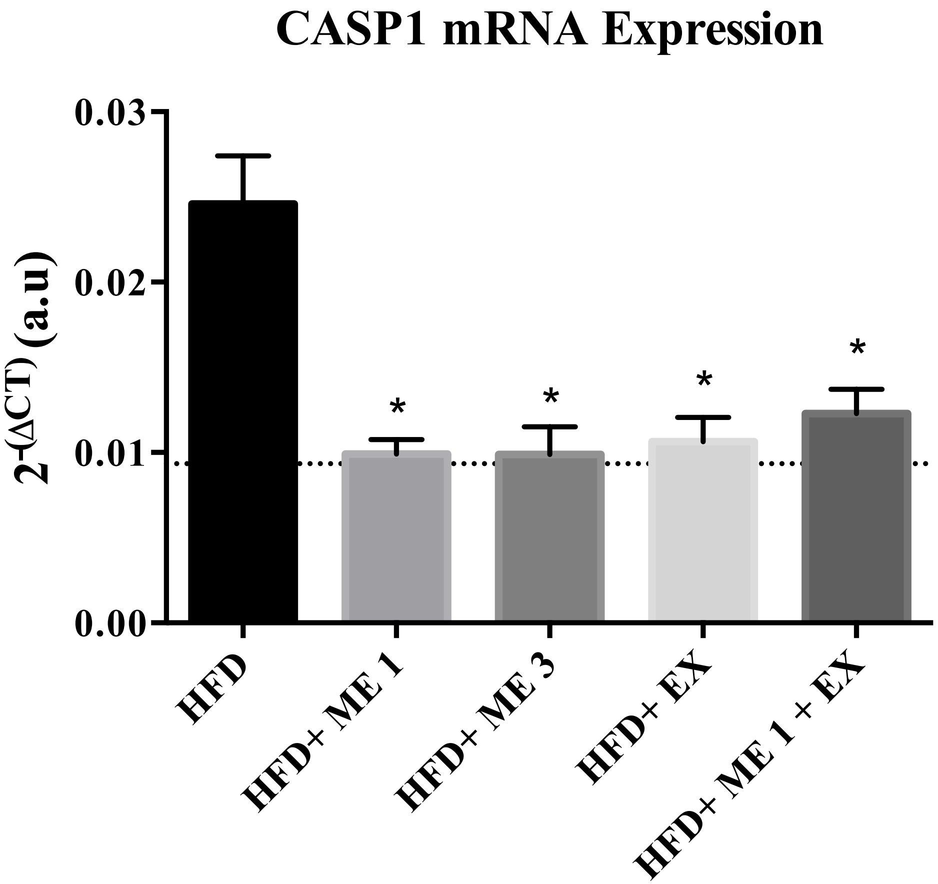


Nederveen, et al., ***Nutrients,*** **2021, 13, 3726.**

Metabolic Enhancer – Inflammation



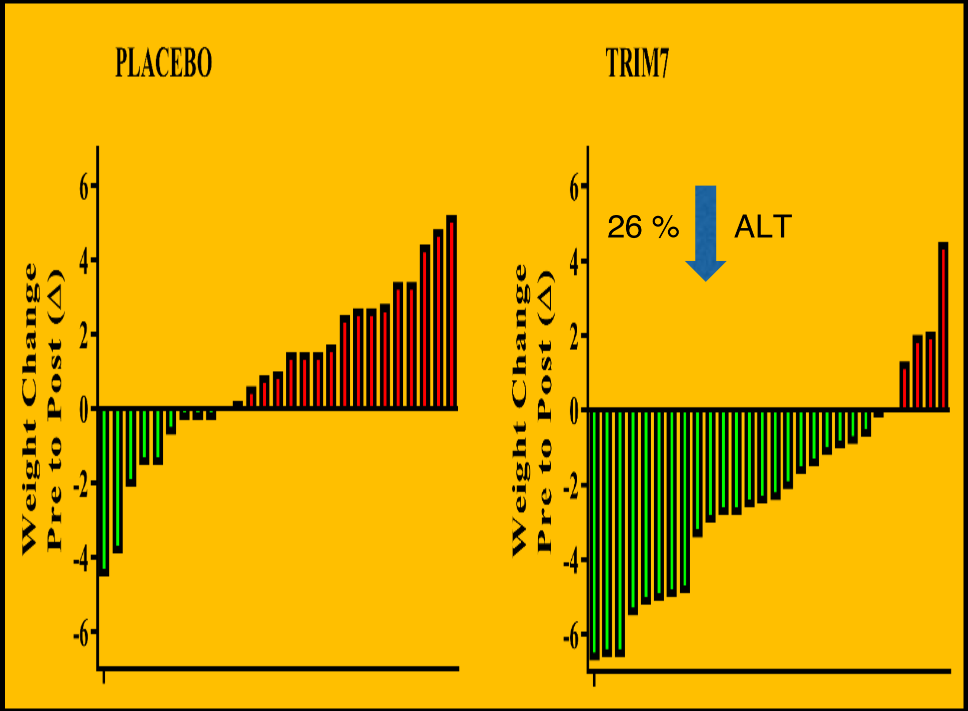




Nederveen, et al., ***Nutrients*, 2021, 13, 3726.**

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 Review, Nutrients, 2023.

Thanks

- The lab:

Dr. J. Nederveen
Mr. B. Hettinga
Dr. M. Nilsson
Dr. J. Crane
Dr. L. MacNeil
Mr. D. Xhuti

- Collaborators:

Dr. B. Naviaux
Dr. S. Melov
Dr. G. Parise
Dr. S. Phillips
Dr. J. Heisz
Dr. R. Austin

- Collaborators (cont.):
  - Dr. M. Devries

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

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