
NMI
SUMMIT
2024
An Energetic View:
Mitochondrial Nutrition
for Fatigue, the Brain,
& Healthy Ageing
Saturday 12th October
Featuring Dr. Joseph Pizzorno, Lorraine Nicolle, Claire Sehinson,
Professor Robert Thomas, Dr. Deanna Minich
An event by:
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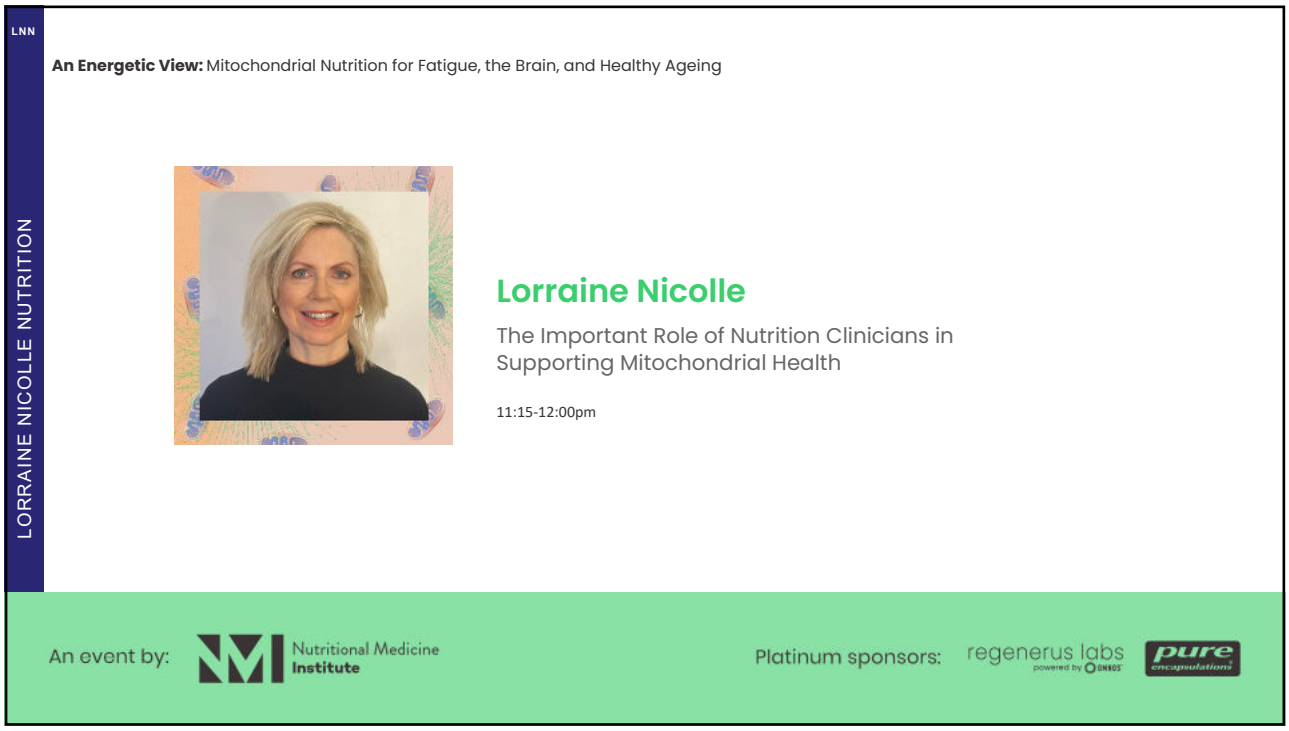
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LORRAINE NICOLLE NUTRITION
An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing
Lorraine Nicolle
The Important Role of Nutrition Clinicians in
Supporting Mitochondrial Health
11:15-12:00pm
An event by:
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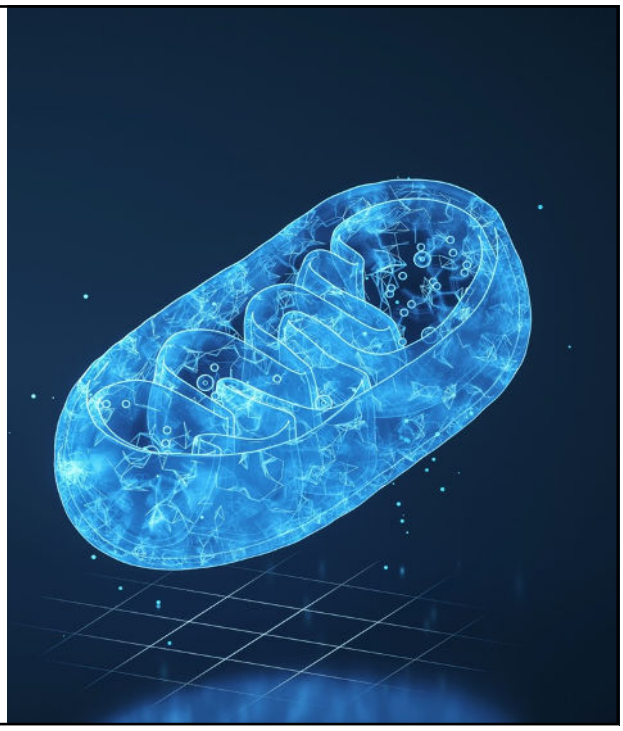
The Important Role of Nutrition Clinicians in Supporting Mitochondrial Health

Lorraine Nicolle

MSc (Nutr.), PGCHE, BA (Hons), Dip.CIM, Dip.BCNH, mBANT, CNHC



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Affiliations and Declarations of Interest

Affiliations:

- Visiting Lecturer: Uni Northampton, CNELM, ION
- Clinical Supervisor: CPD-UK
- Nutrition Education Lead: Pharma Nord UK
- Co-founder and Nutritionist: My Menopause Companion
- Editorial Board Member: NMI

Declarations of Interest:

- No relevant declarations of interest

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Learning outcomes/clinical takeaways

1. Understand ***when*** we should consider mitochondrial function as a point of leverage in improving a client's Quality of Life
2. Consider which nutrition and lifestyle inputs can ***hamper*** mitochondrial function
3. Become familiar with which nutritional cofactors are essential for mitochondrial ***structure and function***
4. Gain insight into nutrition and lifestyle interventions that stimulate ***mitogenesis and mitophagy***

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When should we consider mitochondrial function as a point of leverage in improving a client's QoL?

1. Relevant sxs / dxs
2. Biomarkers that give clues from commonly used functional lab tests
3. Info from using a systems biology approach

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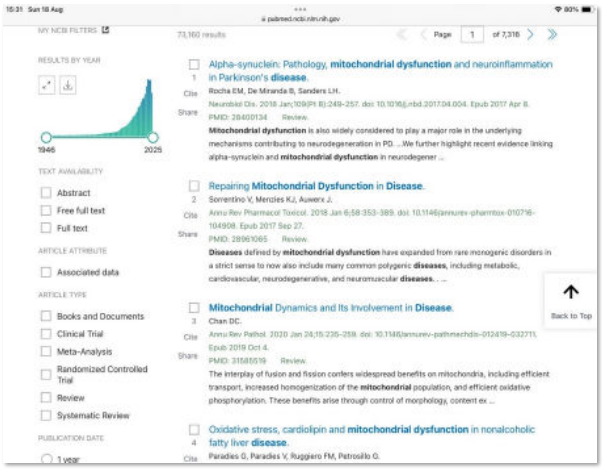
When the client has a diagnosed chronic illness

- Compromised mito fission, fusion and mitophagy →
- ↓ ATP production and ↓ control of apoptosis; ↑ mtROS → inflammation
- > 73,000 Pubmed search results for 'mitochondrial dysfunction in disease'
- This provides an opportunity: chronic illness research tells us we need to support mito function



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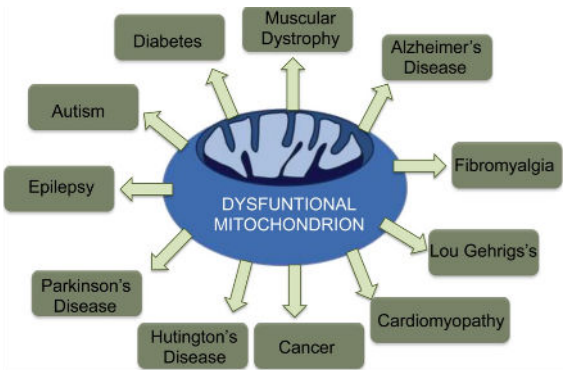
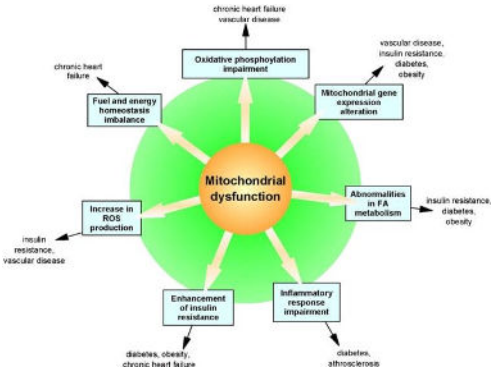
Types of conditions that **signal a likely need for mito support**

Mito dysfunction contributes to all these chronic illnesses



Mito dysfunction is at the root of a network of *metabolic* abnormalities



Marcovina SM, Sirtori C, et al (2013). Translating the basic knowledge of mitochondrial functions to metabolic therapy: role of L-carnitine. Transl Res. 2013 Feb;161(2):73-84, Wen R, Banik B, Pathak RK, et al. Nanotechnology inspired tools for mitochondrial dysfunction related diseases. Adv Drug Deliv Rev. 2016 Apr 1;99(Pt A):52-69

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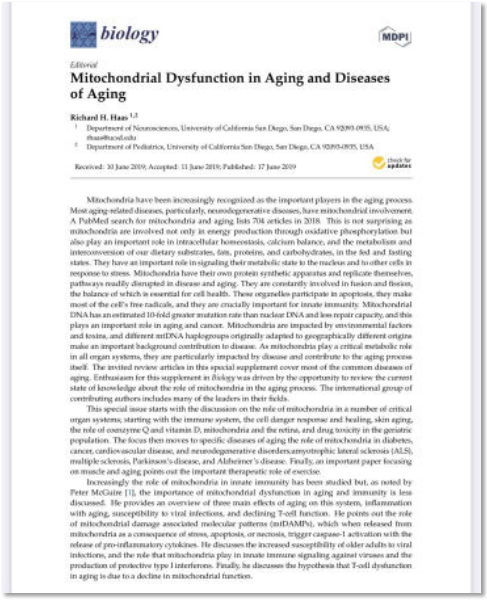
Also diseases related to…

- Declining skeletal muscle
- Neurodegeneration
- Declining immune function

Haas RH. Mitochondrial Dysfunction in Aging and Diseases of Aging. Biology (Basel). 2019 Jun 17;8(2):48.



biology

MDPI

Editorial

Mitochondrial Dysfunction in Aging and Diseases of Aging

Richard H. Haas [1,2]

1 Department of Neurosciences, University of California San Diego, San Diego, CA 92093-0935, USA; rhaas@ucsd.edu

2 Department of Pediatrics, University of California San Diego, San Diego, CA 92093-0935, USA

Received: 30 June 2019; Accepted: 11 June 2019; Published: 17 June 2019

Mitochondria have been increasingly recognized as the important players in the aging process. Most aging-related diseases, particularly, neurodegenerative diseases, have mitochondrial involvement. A PubMed search for mitochondria and aging lists 704 articles in 2018. This is not surprising as mitochondria are involved not only in energy production through oxidative phosphorylation but also play an important role in intracellular homeostasis, calcium balance, and the metabolism and interconversion of our dietary substrates, fats, proteins, and carbohydrates, in the fed and fasting states. They have an important role in signaling their metabolic state to the nucleus and to other cells in response to stress. Mitochondria have their own protein synthetic apparatus and replicate themselves, pathways readily disrupted in disease and aging. They are constantly involved in fusion and fission, the balance of which is essential for cell health. These organelles participate in apoptosis, they make most of the cell's free radicals, and they are crucially important for innate immunity. Mitochondrial DNA has an estimated 10-fold greater mutation rate than nuclear DNA and less repair capacity, and this plays an important role in aging and cancer. Mitochondria are impacted by environmental factors and toxins, and different mtDNA haplogroups originally adapted to geographically different origins make an important background contribution to disease. As mitochondria play a critical metabolic role in all organ systems, they are particularly impacted by disease and contribute to the aging process itself. The invited review articles in this special supplement cover most of the common diseases of aging. Enthusiasm for this supplement in Biology was driven by the opportunity to review the current state of knowledge about the role of mitochondria in the aging process. The international group of contributing authors includes many of the leaders in their fields.

This special issue starts with the discussion on the role of mitochondria in a number of critical organ systems, starting with the immune system, the cell danger response and healing, skin aging, the role of coenzyme Q and vitamin D, mitochondria and the retina, and drug toxicity in the geriatric population. The focus then moves to specific diseases of aging the role of mitochondria in diabetes, cancer, cardiovascular disease, and neurodegenerative disorders amyotrophic lateral sclerosis (ALS), multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Finally, an important paper focusing on muscle and aging points out the important therapeutic role of exercise.

Increasingly the role of mitochondria in innate immunity has been studied but, as noted by Peter McGuire [1], the importance of mitochondrial dysfunction in aging and immunity is less discussed. He provides an overview of three main effects of aging on this system, inflammation with aging, susceptibility to viral infections, and declining T-cell function. He points out the role of mitochondrial damage associated molecular patterns (mtDAMPs), which when released from mitochondria as a consequence of stress, apoptosis, or necrosis, trigger caspase-1 activation with the release of pro-inflammatory cytokines. He discusses the increased susceptibility of older adults to viral infections, and the role that mitochondria play in innate immune signaling against viruses and the production of protective type I interferons. Finally, he discusses the hypothesis that T-cell dysfunction in aging is due to a decline in mitochondrial function.

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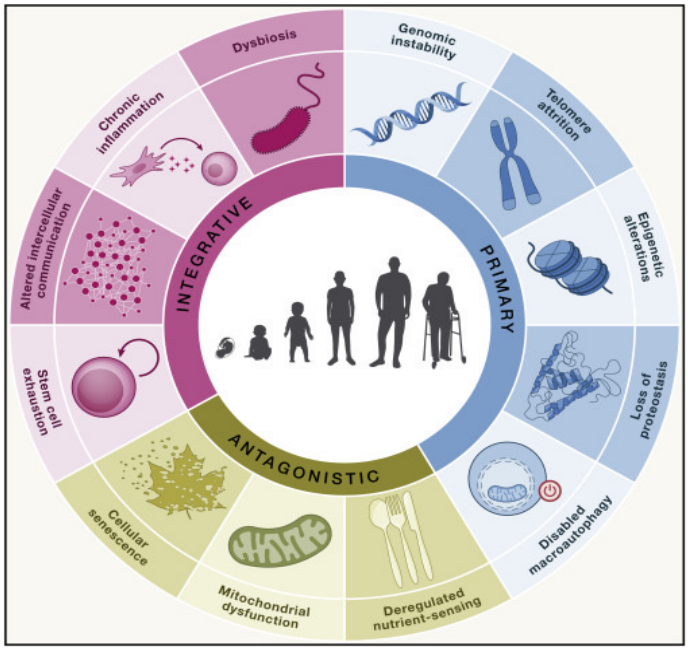
But also *anyone* concerned with healthy ageing, not just those with a chronic illness

As mito dysfunction is one of the hallmarks of ageing of current interest to researchers

(And another hallmark of ageing is disabled autophagy/mitophagy, which is how mitochondria stay strong)

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of ageing: An expanding universe. Cell. 2023 Jan 19;186(2):243-278.



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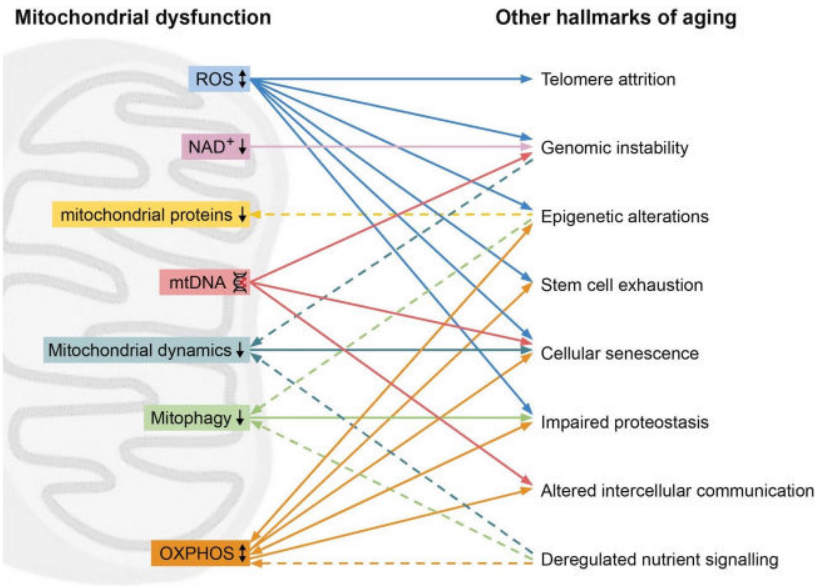
Mito dysfunction affects all other hallmarks of ageing



Van der Rijt S, Molenaars M, McIntyre RL, Janssens GE, Houtkooper RH. Integrating the Hallmarks of Aging Throughout the Tree of Life: A Focus on Mitochondrial Dysfunction. *Front Cell Dev Biol*. 2020;8:594416.

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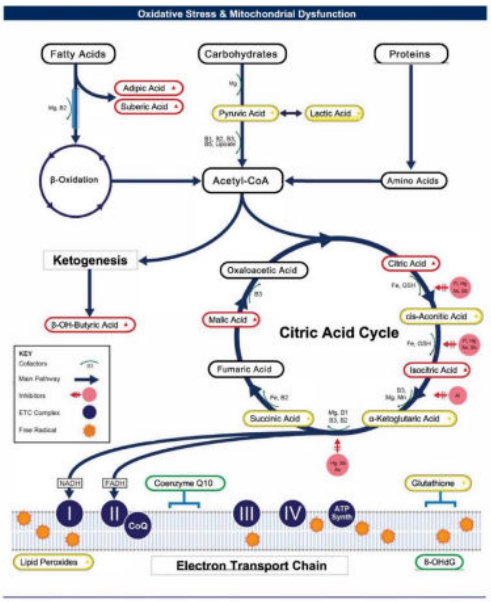
Biomarkers that can give us clues

- Some standard, e.g., HbA1c, TC:HDL…
- Organic acid markers. E.g.
  - Elevated lactate and/or pyruvate: is the pyruvate carrier getting pyruvate into the mitochondria? Requires B vitamins
  - Elevated adipic and/or suberic acid: are fatty acids getting into the mito for beta oxidation? Requires carnitine, B2, Mg
  - Elevated Krebs cycle intermediates – several cofactors are required



Graphic: NutrEval Support Guide, from https://www.gdx.net/uk/core-uk/support-guides-uk/NutrEval-Support_guide.pdf

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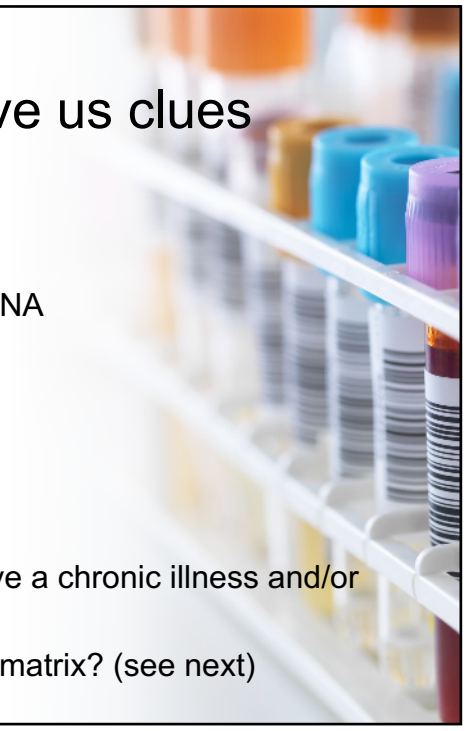
Other biomarkers that can give us clues



- **Oxidative stress markers**:
  - Lipid peroxides for mito double membrane
  - 8-hydroxy-deoxyguanosine (8-OHdG) for mtDNA
- **Antioxidants:**
  - Blood levels of GSH and CoQ10
  - Functional GSH (pyroglutamic acid)
- **And the all-important case history:**
  - We've already considered: does the client have a chronic illness and/or are they chronically fatigued?
  - But also: what clues can be gleaned from the matrix? (see next)

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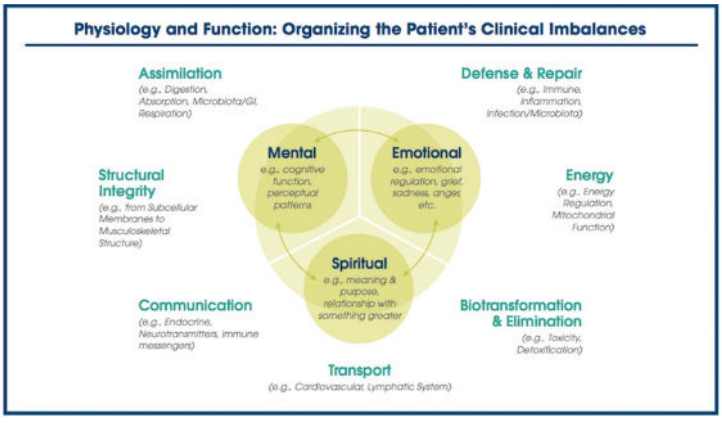
Looking wider

Using a **systems approach** (with the aid of your preferred matrix – IFM or another) makes RNTs ideally placed to identify and intervene in ***underlying body system imbalances*** contributing to any mitochondrial dysfunction



Functional Medicine Matrix: Organizing Clinical Imbalances | IFM [Internet]. The Institute for Functional Medicine. Available from: https://www.ifm.org/news-insights/toolkit-functional-medicine-matrix/

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Many body **system imbalances** can hamper mitochondrial function

Examples:

- Oxidative stress damages mitochondrial membranes and mtDNA
- Poor biotransformation increases mito-damaging toxic load
- Insulin resistance inhibits mitophagy by disrupting nutrient sensing pathways
- Loss of membrane structural integrity affects ETC (situated on inner membrane)
- Long term stress → hampers mito function via the Cell Danger Response (CDR)
- Gut dysbiosis and/or intestinal hyperpermeability (can affect metabolic health, toxic load and inflammation)
- Most body system imbalances → inflammation; and inflammation inhibits mitophagy

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Clinical action plan:

Is it worth supporting mitochondrial function in your client?

Take the client's case history

Are there any relevant sxs or diagnosed dxs that typically have a mitochondrial component? (E.g. metabolic and/or neurodegenerative)

Functional testing

Are there any relevant biomarkers out of range?

What is out of balance on the matrix (where is the ink)?

Anything that can hamper mitochondrial function?

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Perceived threats

- Mitochondria trigger mtROS and inflammation *when they sense danger*
- Mito control ATP synthesis and thus also control whether the cell should focus on either:
  - 'Peacetime' metabolism (energy production), or
  - **Cellular defence** (ROS + inflammation):
    - Termed the '**cell danger response** - CDR' by Naviaux
- Mito can't do both roles simultaneously
- CDR is a normal adaptation in function – but it can get stuck

Naviaux RK. Incomplete Healing as a Cause of Aging: The Role of Mitochondria and the Cell Danger Response. Biology (Basel). 2019 May 11;8(2):27, Naviaux RK. Perspective: Cell danger response Biology-The new science that connects environmental health with mitochondria and the rising tide of chronic illness. Mitochondrion. 2020 Mar;51:40-45.

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Perceived threats

- Purpose of CDR (switching mito function in chronic illness, toxicity or infection) is to protect cells from damage
  - E.g. to prevent viruses and other microbes replicating by hijacking mito ATP
  - CDR reduces O2 usage for OXPHOS (ATP) and instead drives O2 into the cytosol to form ROS to kill viruses /pathogens /chemicals...
- Defence mode manifests as **fatigue**, due to ↓ATP and ↑ immune response/inflammation/oxidation
- Body normally gets itself out of this defence mode but can get stuck in situations of chronic stress/infection/toxicity – see examples of damaging inputs on next slides →

Naviaux RK. Incomplete Healing as a Cause of Aging: The Role of Mitochondria and the Cell Danger Response. Biology (Basel). 2019 May 11;8(2):27, Naviaux RK. Perspective: Cell danger response Biology-The new science that connects environmental health with mitochondria and the rising tide of chronic illness. Mitochondrion. 2020 Mar;51:40-45.

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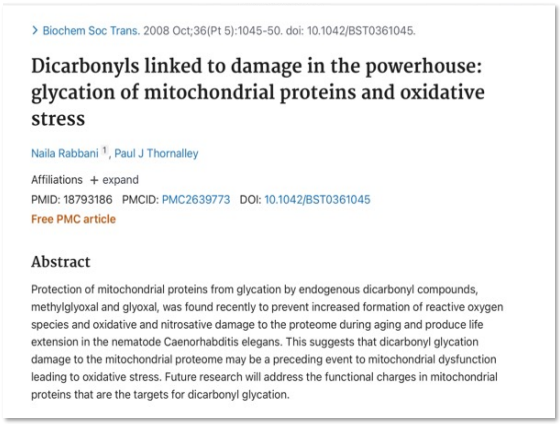
AGE products damage mito and → oxidative stress
[Glycation reaction]



> Biochem Soc Trans. 2008 Oct;36(Pt 5):1045-50. doi: 10.1042/BST0361045.

Dicarbonyls linked to damage in the powerhouse: glycation of mitochondrial proteins and oxidative stress

Naila Rabbani [1], Paul J Thornalley

Affiliations + expand

PMID: 18793186 PMCID: PMC2639773 DOI: 10.1042/BST0361045

Free PMC article

Abstract

Protection of mitochondrial proteins from glycation by endogenous dicarbonyl compounds, methylglyoxal and glyoxal, was found recently to prevent increased formation of reactive oxygen species and oxidative and nitrosative damage to the proteome during aging and produce life extension in the nematode Caenorhabditis elegans. This suggests that dicarbonyl glycation damage to the mitochondrial proteome may be a preceding event to mitochondrial dysfunction leading to oxidative stress. Future research will address the functional charges in mitochondrial proteins that are the targets for dicarbonyl glycation.

Fructose damages liver mitochondria, contributing to metabolic dxs

> Nutrients. 2017 Mar 24;9(4):323. doi: 10.3390/nu9040323.

Fructose-Rich Diet Affects Mitochondrial DNA Damage and Repair in Rats

Federica Cioffi [1], Rosalba Senese [2], Pasquale Lasala [3], Angela Ziello [4], Arianna Mazzoli [5], Raffaella Crescenzo [6], Giovanna Liverini [7], Antonia Lanni [8], Fernando Goglia [9], Susanna Iossa [10]

Affiliations + expand

PMID: 28338610 PMCID: PMC5409662 DOI: 10.3390/nu9040323

Free PMC article

Abstract

Evidence indicates that many forms of fructose-induced metabolic disturbance are associated with oxidative stress and mitochondrial dysfunction. Mitochondria are prominent targets of oxidative damage; however, it is not clear whether mitochondrial DNA (mtDNA) damage and/or its lack of repair are events involved in metabolic disease resulting from a fructose-rich diet. In the present study, we evaluated the degree of oxidative damage to liver mtDNA and its repair, in addition to the state of oxidative stress and antioxidant defense in the liver of rats fed a high-fructose diet. We used male rats feeding on a high-fructose or control diet for eight weeks. Our results showed an increase in mtDNA damage in the liver of rats fed a high-fructose diet and this damage, as evaluated by the expression of DNA polymerase γ, was not repaired; in addition, the mtDNA copy number was found to be significantly reduced. A reduction in the mtDNA copy number is indicative of impaired mitochondrial biogenesis, as is the finding of a reduction in the expression of genes involved in mitochondrial biogenesis. In conclusion, a fructose-rich diet leads to mitochondrial and mtDNA damage, which consequently may have a role in liver dysfunction and metabolic diseases.

Keywords: fructose-rich diet; mitochondrial DNA (mtDNA); mitochondrial biogenesis; oxidative damage; repair mechanisms.

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Being **sedentary** → loss of skeletal muscle mass, mito dysfunction and increased oxidative damage to muscle

J Gerontol A Biol Sci Med Sci. 2009 Sep;64(9):927-39. doi: 10.1093/gerona/glp066. Epub 2009 May 22.

Impact of lifelong sedentary behavior on mitochondrial function of mice skeletal muscle

Pedro A Figueiredo [1], Scott K Powers, Rita M Ferreira, Francisco Amado, Hans J Appell, José A Duarte

Affiliations + expand

PMID: 19465709 PMCID: PMC2981452 DOI: 10.1093/gerona/glp066

Free PMC article

Abstract

This study investigated the impact of lifelong sedentariness on skeletal muscle mass and mitochondrial function. Thirty C57BL/6 strain mice (2 months) were randomly divided into three groups (young-Y; old sedentary-OS; old active-OA). Young animals were sacrificed after 1 week of quarantine, and OS and OA groups were individually placed into standard cages and in cages with running wheels, respectively, until sacrifice (25 months). Body weights and hind-limb skeletal muscle wet weights were obtained from all groups. Mitochondrial respiratory functional measures (i.e., state 3 and 4 respiration, respiratory control ratio, and ratio of nanomoles of ADP phosphorylated by nanomoles of O2 consumed [ADP/O]) and biochemical markers of oxidative damage (aconitase activity, protein carbonyl derivatives, sulfhydryl groups) were measured in isolated mitochondrial suspensions. Our results reveal that lifelong sedentary behavior has a negative impact on the age-related loss of skeletal muscle mass and on the isolated mitochondrial function of mixed skeletal muscle of mice, which is associated with an increased oxidative damage to mitochondrial biomolecules.

Other mitochondrial hazards discussed in the literature

- Energy overload – see mechanisms →
- Toxic overload: metals, environmental pollution and/or certain pharmaceuticals (statins, Abx…)
- Circadian dysregulation: fusion, fission, mitophagy are influenced by clock genes; are aligned to the light/dark cycle
  - *'Disturbing the molecular clock…leads to abrogated mitochondrial rhythmicity and altered respiration'*
- Melatonin is also an important antioxidant

De Goede P, Wefers J, Brombacher EC, et al. Circadian rhythms in mitochondrial respiration. J Mol Endocrinol. 2018 Apr;60(3):R115-R130

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Energy overload as a mito toxin

- Excess caloric intake disrupts nutrient sensing pathways (e.g. AMPK, PGC1-a) that then inhibits mitophagy and mitogensis
- Also leads to obesity that increases mitochondrial fission in subcutaneous adipose tissue
  - These smaller, fragmented mito are less able to produce ATP (animal data)
  - This suppressed ATP production (energy expenditure) → more weight gain (vicious cycle)
- Excessive time in the fed state inhibits lipolysis and therefore mito flexibility (as glucose is burned in the fed state and is therefore the only fuel)
- Obesity → insulin resistance → **inflammation** → ↑ fission and ↓ mitophagy

Xia W, Veeragandham P, Cao Y, et al. Obesity causes mitochondrial fragmentation and dysfunction in white adipocytes due to RalA activation. Nat Metab. 2024 Feb;6(2):273-289

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Clinical action plan:

A checklist of things to reduce or avoid

- Sedentary living
- Caloric excess
- High starch / sugar / fructose diet
- Excess alcohol
- Trans/oxidised fats
- Poor sleep / night shifts
- Smoking
- Excess time in traffic / environmental toxins
- Advanced glycation end products
- Polypharmacy

Cioffi F, Senese R, Lasala P, et al. Fructose-Rich Diet Affects Mitochondrial DNA Damage and Repair in Rats. Nutrients. 2017 Mar 24;9(4):323, Figueiredo PA, Powers SK, Ferreira RM, Amado F, Appell HJ, Duarte JA. Impact of lifelong sedentary behavior on mitochondrial function of mice skeletal muscle. J Gerontol A Biol Sci Med Sci. 2009 Sep;64(9):927-39, Ghosh S, Kewalramani G, Yuen G, et al. Induction of mitochondrial nitrative damage and cardiac dysfunction by chronic provision of dietary omega-6 polyunsaturated fatty acids. Free Radic Biol Med. 2006 Nov 1;41(9):1413-24, Rabbani N, Thornalley PJ. Dicarbonyls linked to damage in the powerhouse: glycation of mitochondrial proteins and oxidative stress. Biochem Soc Trans. 2008 Oct;36(Pt 5):1045-50.

Many of these damage the mitochondria via ***oxidative stress***

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Case snippet: stubborn CFS

- Longstanding sxs (oedema, sore throat, raised glands, exhaustion, diarrhoea, GI discomfort, poor sleep), but all GP investigations were presented as ‘normal’
- Issues identified and addressed over several consultations: histamine intolerance, HPA hyperactivity, colonic dysbiosis, nutrient deficiencies (including mito nutrients)
- Fatigue somewhat improved but occasional ‘crashes’; continued elevated ESR (32) on repeated tests; bouts of oedema in face, arms, abdomen and legs whenever she diverts from core diet (AIP) or tries to reduce supplements
- Further testing then revealed… →

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Past exposure *and* recent immune response to ***Coxsackie*** and ***Borrelia***

Thus the mito could not get back into energy production mode without addressing the hidden 'stressor', no matter how many mito nutrients were given

Analysis	Result Units	Ref

The antibodies indicate humoral immune responses against Borrelia burgdorferi.

The Tickplex Basic ELISA is a screening test for Borrelia pathogen-specific IgG and IgM antibodies and contains a antigen for persisted forms (round bodies) of Borrelia burgdorferi.

Please cross-reference this with the results of EliSpots/i-Spots tests and the CD57+ NK cell test that you may have done.

validated by
Dr.Armin Schwarzbach

Analysis		Result Units	Reference Range	
We recommend to look at the current cellular activity by the Mycoplasma pneumoniae-EliSpot.				
Coxsackie IgG-/IgA-antibodies				
7 Coxsackie-IgG Typ A7 (IFT)	+	1:100	< 1:100	[.....
7 Coxsackie-IgG Typ B1 (IFT)	+	1:1000	< 1:100	[.....
7 Coxsackie-IgA Typ A7 (IFT)	+	1:100	< 1:10	[.....
7 Coxsackie-IgA Typ B1 (IFT)	+	1:100	< 1:10	[.....
The specific positive Coxsackie-Virus Type A7/B1-IgG-/IgA-antibodies indicate current humoral immune responses against Coxsackie-Virus Type A7 and Coxsackie-Virus Type B1 (recent infection with Coxsackie-Virus Type A7/B1?). The test system is highly specific for Coxsackie Virus antibodies. Other Enterovirus antibodies (for example Echovirus IgG/IgA-antibodies) are not detectable.				
Basic Test/Tickplex Plus				
7 Basic Test (new)				
7 B.burg.+afz.+gar.IgG	positive	1,629 Ratio	negative	
Ratio 0,01 - 0,89 = negative Ratio 0,90 - 0,99 = weak Ratio >= 1,00 = positive				
7 B.burg.+afz.+gar.IgM	positive	1,070 Ratio	negative	
Ratio 0,01 - 0,89 = negative Ratio 0,90 - 0,99 = weak Ratio >= 1,00 = positive				
7 B.burg.+afz.+gar+round bod.IgG	positive	2,287 Ratio	negative	
Ratio 0,01 - 0,89 = negative Ratio 0,90 - 0,99 = weak Ratio >= 1,00 = positive				
7 B.burg.+afz.+gar+round bod.IgM	positive	1,121 Ratio	negative	
Ratio 0,01 - 0,89 = negative Ratio 0,90 - 0,99 = weak Ratio >= 1,00 = positive				

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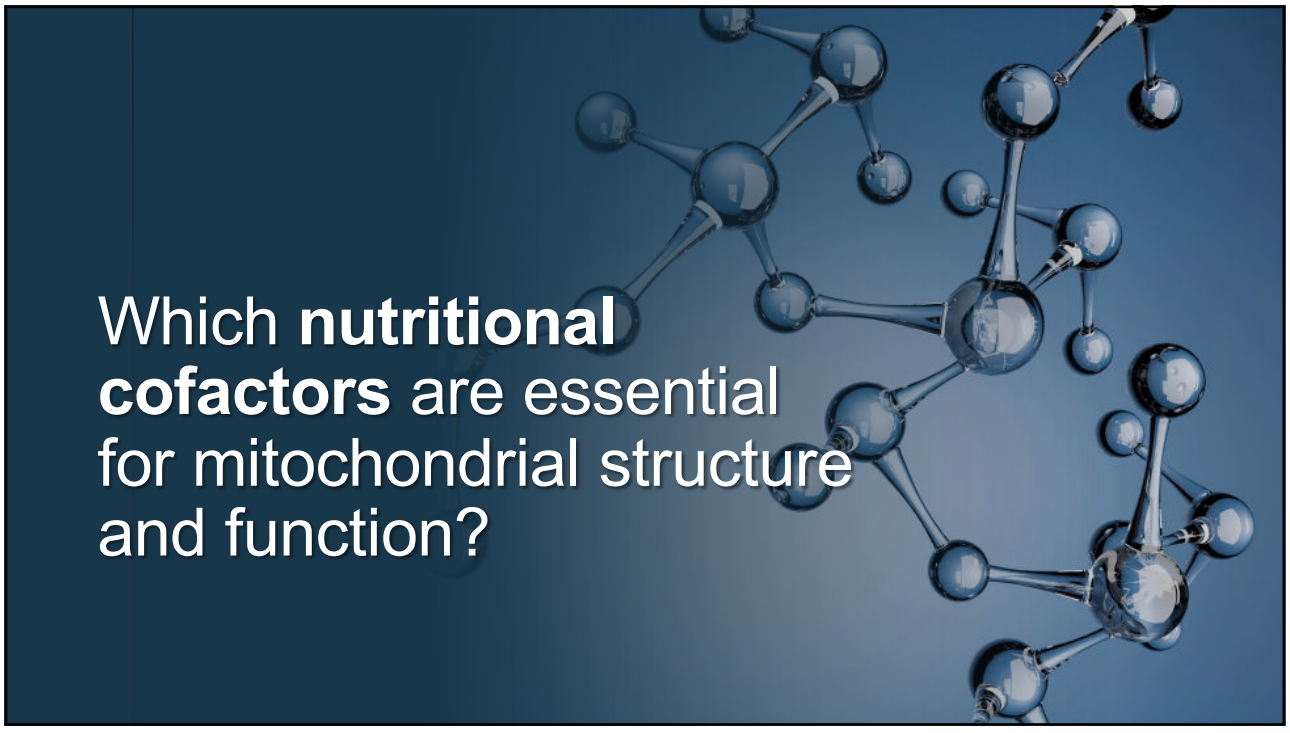

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EPA + DHA: RCT examples in mito function

- In human intervention trials, skeletal muscle function is commonly used to gauge changes in mitochondrial function (see the urolithin A trials later)
- 8 weeks of exercise training with DHA (1.14g) in 'sportsmen' induced mitochondrial adaptations (improved mito proteins) which may contribute to improved mito function
- 4 weeks supplementation EPA + DHA (5g total) prior to 2 weeks single limb immobilisation in healthy young women (N = 20)
  - *Supplementation with dietary ω-3 mitigates immobilization-induced reductions in skeletal muscle mitochondrial respiration in young women*
  - *These data highlight the rapidity of mitochondrial adaptations in response to muscle disuse…and establish that ω-3 supplementation preserves oxidative phosphorylation function and content during immobilization.*

Busquets-Cortés C, Capó X, Martorell M, Tur JA, Sureda A, Pons A. Training Enhances Immune Cells Mitochondrial Biosynthesis, Fission, Fusion, and Their Antioxidant Capabilities Synergistically with Dietary Docosahexaenoic Supplementation. Oxid Med Cell Longev. 2016;2016:8950384, Miotto PM, McGlory C, Bahniwal R, Kamal M, Phillips SM, Holloway GP. Supplementation with dietary ω-3 mitigates immobilization-induced reductions in skeletal muscle mitochondrial respiration in young women. FASEB J. 2019 Jul;33(7):8232-8240.

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EPA + DHA: RCT examples in mito function

- A case-control study found that mitochondrial function was significantly lower (and inflammation was significantly higher) in peripheral blood mononuclear cells (PBMCs) in obese women (N = 19) compared to the lean group (N = 12)
  - Mitochondrial dysfunction was measured via ATP-production, proton leakage, and nonmitochondrial respiration (all higher in the obese group)
- 12 of the obese group were then given EPA (3.5g) and DHA (1.75g) for a month
- The omega-3 FA intervention improved both the inflammatory profile and the mitochondrial function
  - Decreased *non*-mitochondrial respiration and increased the reserve respiratory capacity and BHI (bioenergetics health index – a marker of mito function)

Borja-Magno AI, Furuzawa-Carballeda J, Guevara-Cruz M, Arias C, Granados J, Bourges H, Tovar AR, Sears B, Noriega LG, Gómez FE. Supplementation with EPA and DHA omega-3 fatty acids improves peripheral immune cell mitochondrial dysfunction and inflammation in subjects with obesity. J Nutr Biochem. 2023 Oct;120:109415.

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Mechanisms of EPA + DHA in mito function

- Mitochondrial membrane composition: EPA + DHA increase mito cardiolipin phospholipid content → reducing excessive apoptosis in neurons
  - May this be a reason that EPA + DHA support cognition in ageing?
- Mito-biogenesis: one of the mechanisms by which EPA/DHA may support muscle strength
- Mitochondrial redox status (reducing oxidative effects of ROS)
- Mitochondrial fatty acid β-oxidation with subsequent decrease in lipid accumulation (and → ↓ IR)
- Lessening the inflammatory burden on mitochondria

Stulczewski D, Zgorzynska E, Dziedzic B, et al. EPA stronger than DHA increases the mitochondrial membrane potential and cardiolipin levels but does not change the ATP level in astrocytes. Exp Cell Res. 2023 Mar 1;424(1):113491, Therdyothin A, Phiphopthatsanee N, Isanejad M. The Effect of Omega-3 Fatty Acids on Sarcopenia: Mechanism of Action and Potential Efficacy. Mar Drugs. 2023 Jul 13;21(7):399, Herbst EA, Paglialunga S, Gerling C, et al. Omega-3 supplementation alters mitochondrial membrane composition and respiration kinetics in human skeletal muscle. J Physiol. 2014 Mar 15;592(6):1341-52, Lepretti M, Martucciello S, Burgos Aceves MA, Putti R, Lionetti L. Omega-3 Fatty Acids and Insulin Resistance: Focus on the Regulation of Mitochondria and Endoplasmic Reticulum Stress. Nutrients. 2018 Mar 14;10(3):350.

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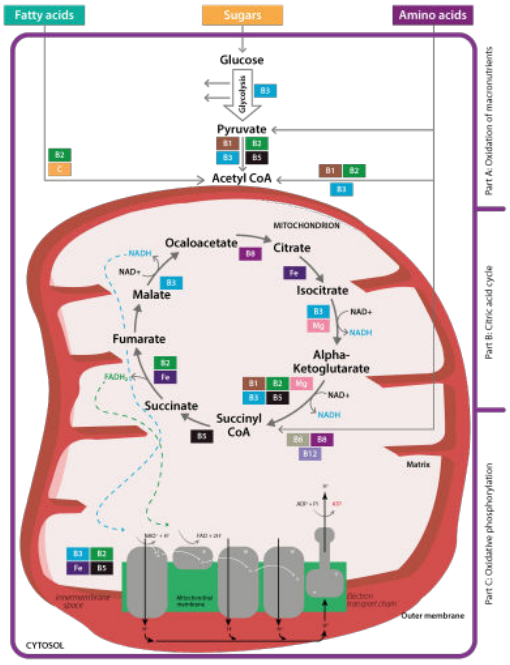
LORRAINE NICOLLE NUTRITION

B vitamins

Used at every stage of the mitochondrial transformation of food into energy:

- Glycolysis
- Krebs cycle
- Electron transport chain (NAD and FAD)
- And speaking of NAD…

Tardy AL, Pouteau E, Marquez D, Yilmaz C, Scholey A. Vitamins and Minerals for Energy, Fatigue and Cognition: A Narrative Review of the Biochemical and Clinical Evidence. *Nutrients*. 2020;12(1):228.



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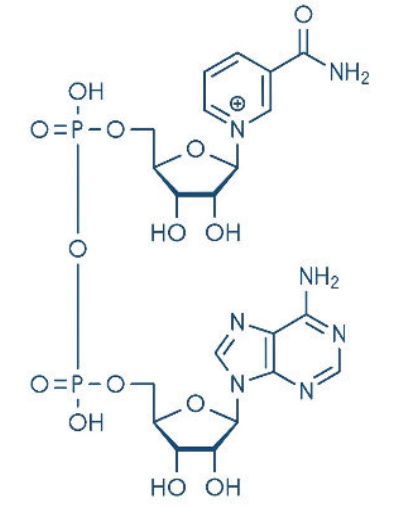
NAD+ (nicotinamide adenine dinucleotide)

- Synthesised from vitamin B3
- Has important roles in the metabolism of macronutrients into ATP (see next →)
- But *also* is crucial as part of the NAD-sirtuin-mitochondrial axis that keeps mitochondria healthy (we'll come back to this later)



nicotinamide adenine dinucleotide

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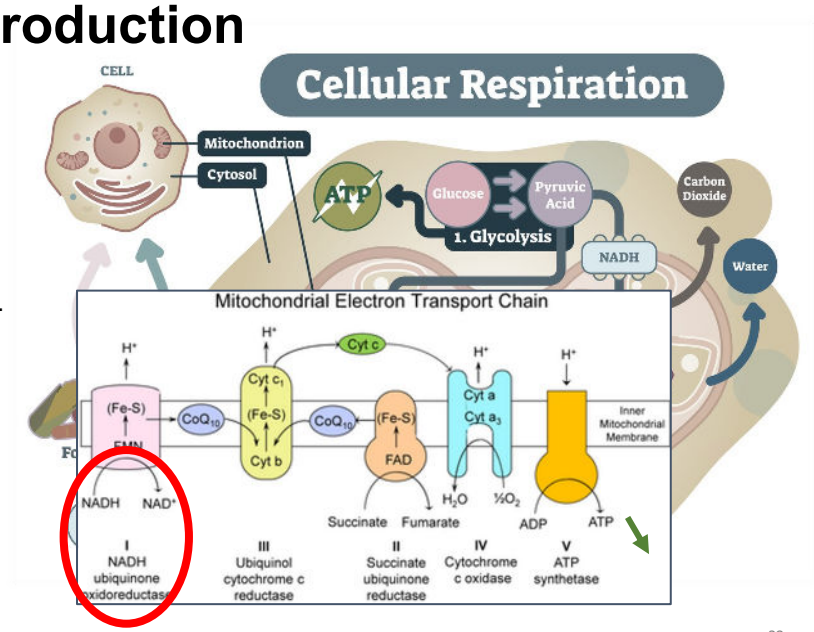
NAD+ in ATP production

1. Cofactor in glucose and fat breakdown – it steals electrons from glucose (C6 H12 O6), as glucose turns into 2 X pyruvate (C3 H4 O3), turning NAD+ into NADH

2. NADH is then used in the ETC: it passes the electrons to ubiquinone in Complex I of the ETC



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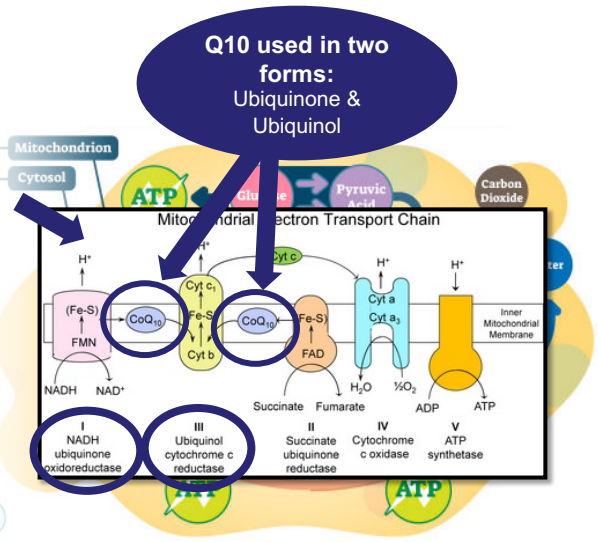
CoQ10: vital for the Electron Transport Chain to work

An electron carrier

Both ubiquinol and ubiquinone

In the first complex of the Electron Transport Chain, NADH donates an electron to ubiquinone

In so doing, ubiquinone becomes ubiquinol



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Other Q10 roles

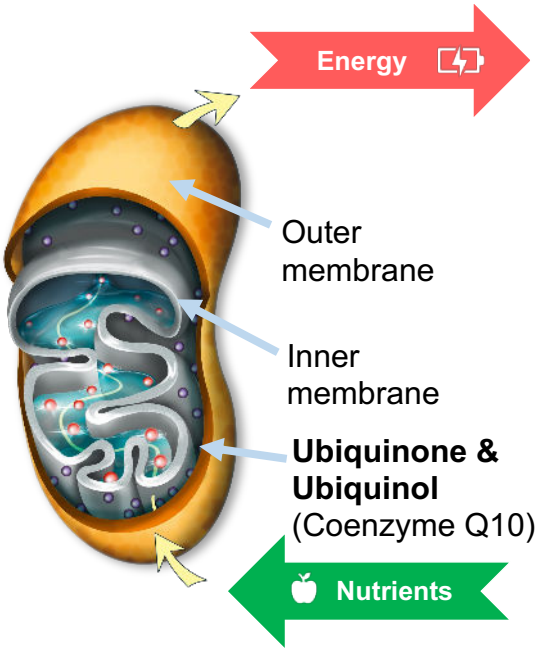
Fat-soluble antioxidant

Anti-inflammatory

Protects **mitochondrial DNA and membranes**, cell membranes, LDL-c

Protects all vital 'busy' organs (those with the most mitochondria)

Co Q10



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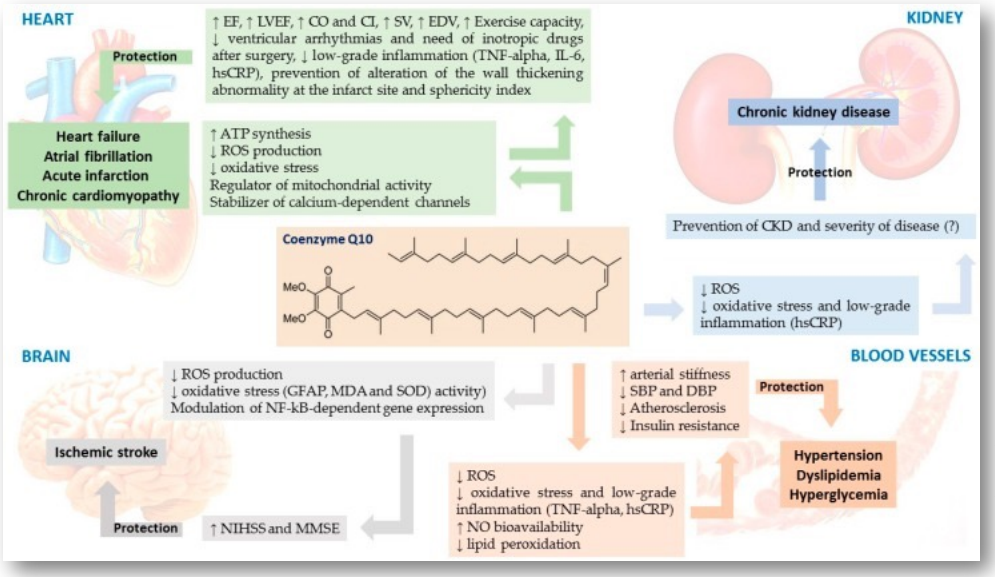
Example of Q10 Mechanisms: CV health



Martelli A, Testai L, Colletti A, Cicero AFG. Coenzyme Q10: Clinical Applications in Cardiovascular Diseases. Antioxidants (Basel). 2020 Apr 22;9(4):341.

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Robust data for Q10 + Se reducing CVD risk

- DBRCT (N = 443, aged 70-88 years)
- Group 1: 200 mg CoQ10 & 200 µg selenium-yeast/day for 4 years
- Group 2 Placebo

Alehagen U, Johansson P, Björnstedt M, et al Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. Int J Cardiol. 2013 Sep 1;167(5):1860-6.

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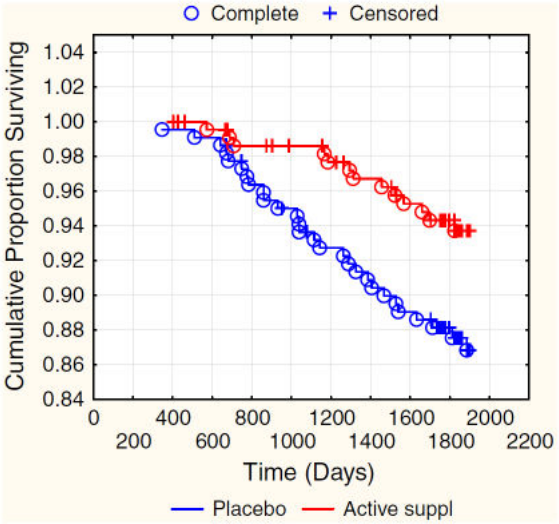
Results: 54% reduction in CV mortality

As well as:

- Stable levels of **NT-ProBNP**
  - A blood biomarker of heart wall stress (the heart is having to work too hard to pump the blood)
- Improved **cardiac function** (via echocardiography)



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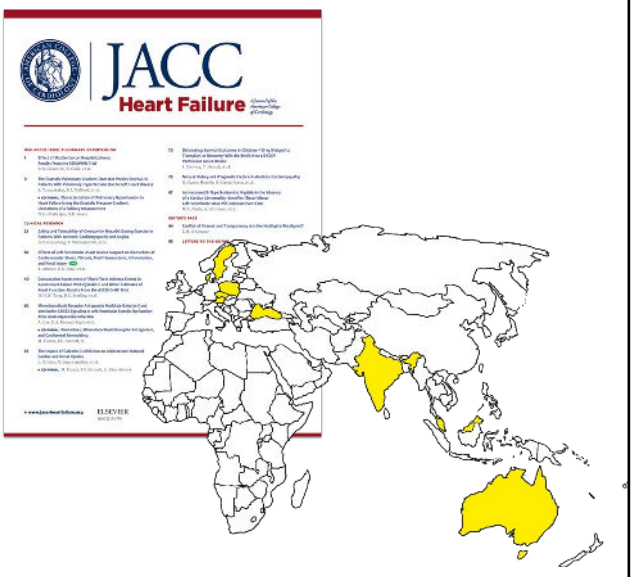
Q10 in heart failure

- 420 heart failure patients from 17 clinics around the world
- Q10 (300mg) vs. placebo daily for 2 years



Mortensen S, Rosenfeldt F, Kumar A, Dolliner P, Filipiak K, Pella D et al. The Effect of Coenzyme Q 10 on Morbidity and Mortality in Chronic Heart Failure. JACC: Heart Failure. 2014;2(6):641-649.

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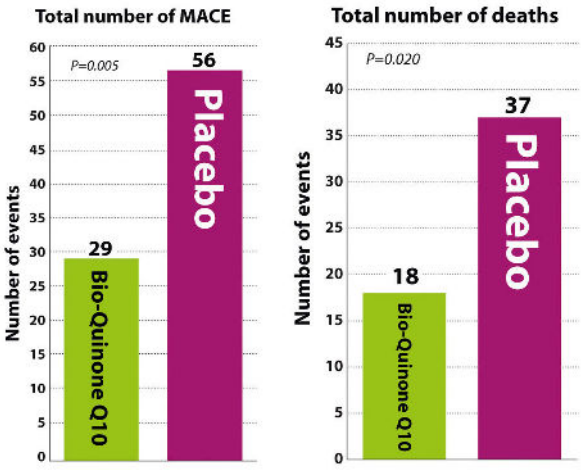
Results

- 42% decrease in cardiovascular death
- 43% decrease in Major Adverse Cardiac Events (MACE)
- Heart stress peptide (NT-proBNP) remained stable



Mortensen S, Rosenfeldt F, Kumar A, Dolliner P, Filipiak K, Pella D et al. The Effect of Coenzyme Q 10 on Morbidity and Mortality in Chronic Heart Failure. JACC: Heart Failure. 2014;2(6):641-649

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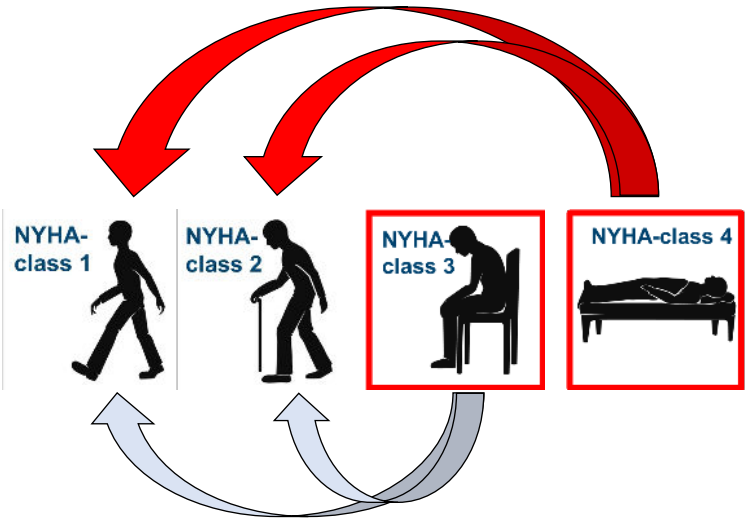
Results

- ✓ Improvement in heart function (ejection fraction)
- ✓ Decreased hospitalizations
- ✓ Improvements in New York Heart Association (NYHA) Class



Mortensen S, Rosenfeldt F, Kumar A, Dolliner P, Filipiak K, Pella D et al. The Effect of Coenzyme Q 10 on Morbidity and Mortality in Chronic Heart Failure. JACC: Heart Failure. 2014;2(6):641-649

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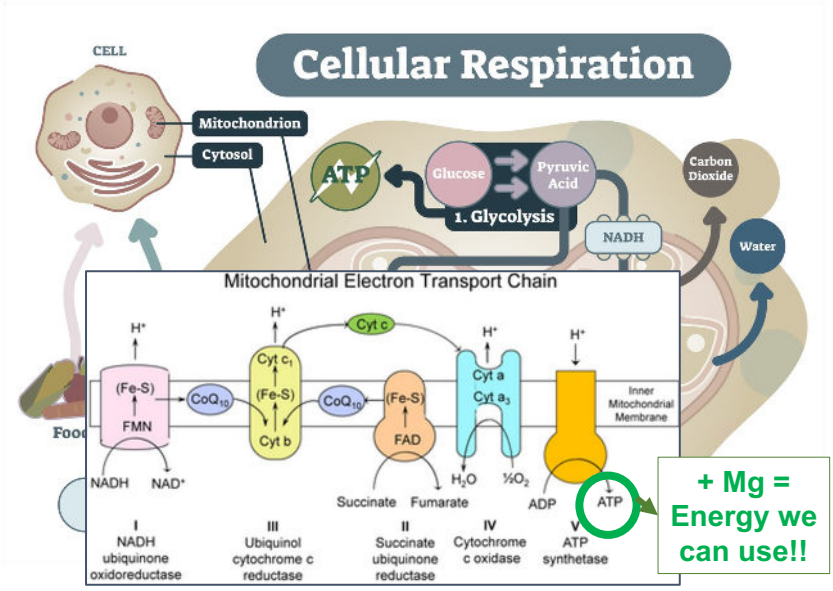
Magnesium

- Co-factor for the ATP synthase enzyme – last step in ATP synthesis
- Mg is also a co-factor in glycolysis and Krebs cycle enzymes



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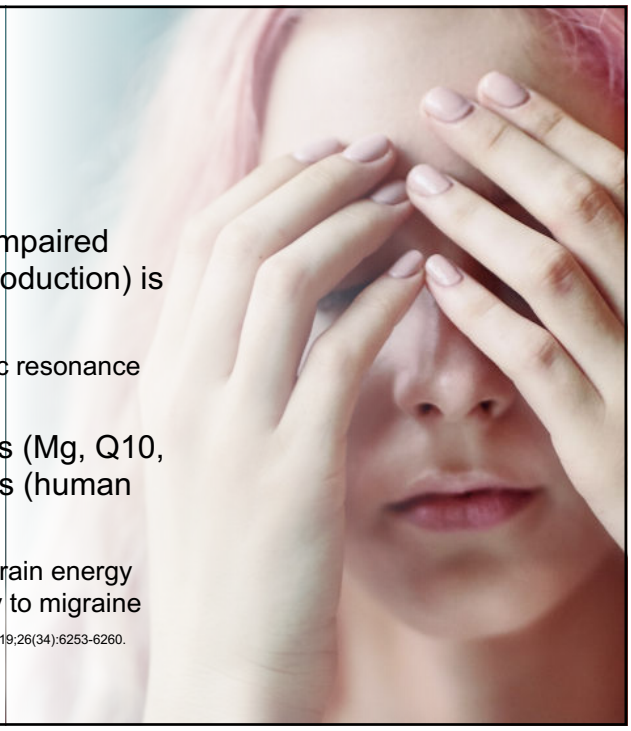
Migraine as an example in humans

- Several studies have confirmed that impaired mitochondrial OXPHOS (→ energy production) is associated with migraine
  - Biochemical, morphological and magnetic resonance spectroscopy studies
- Supplementing mitochondrial nutrients (Mg, Q10, B2) is effective in migraine prophylaxis (human studies)
  - Supports the hypothesis that improving brain energy metabolism may reduce the susceptibility to migraine



Cevoli S, Favoni V, Cortelli P. Energy Metabolism Impairment in Migraine. Curr Med Chem. 2019;26(34):6253-6260.

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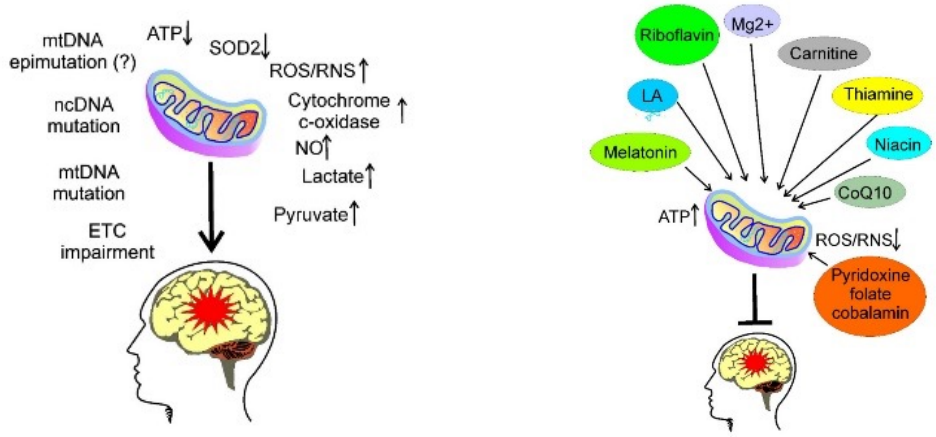
Other nutrients studied in migraine because of their effects on **mitochondrial function**



Fila M, Chojnacki C, Chojnacki J, Blasiak J. Nutrients to Improve Mitochondrial Function to Reduce Brain Energy Deficit and Oxidative Stress in Migraine. Nutrients. 2021 Dec 10;13(12):4433.

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L-carnitine in mitochondrial health

- An amino acid made from lysine within the liver and kidneys
- Transports long chain fatty acids into the mitochondria so they can be beta-oxidised to produce ATP
- Thus supports health of organs high in mitochondria, especially the heart, skeletal muscle and liver

- Levels can become **depleted** in:
  - Intense physical activity
  - High fat diets
  - Certain antibiotics
  - Metabolic stress
- Best food source = red meats, such as beef or lamb
  - Little / none in white meat, fish and vegetables

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L-carnitine

- Can be attached to an acetyl group (ALCAR) to cross the BBB
- Positive effects in human trials of several conditions typically associated with an underlying mitochondrial imbalance. E.g.:
- Exercise-induce muscle soreness and damage
- Exercise capacity in intermittent claudication
- Elevated liver enzymes in NAFLD
- Elevated blood glucose, blood lipids, blood pressure, oxidative stress and inflammation in metabolic syndrome
- Typically dosed at 500-2000mg/day elemental

All refs cited at Frank K, Patel K, Lopez G, Willis B. L-Carnitine Research Analysis. examinecom [Internet]. 2021 May 26; Available from: https://examine.com/supplements/carnitine/

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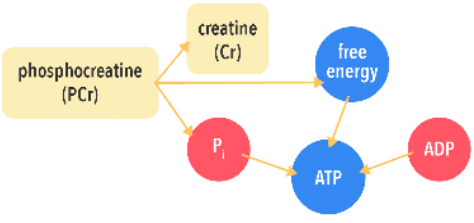
Creatine (formed from methionine, arginine and glycine)

- Phosphocreatine (created from creatine ingestion) donates inorganic phosphate (Pi) to ADP to recycle it back to form ATP
- In a stressed cell, this process can step in to provide ATP quickly until the ETC can produce sufficient ATP again
- Thus it can provide a source of energy to cells with impaired OXPHOS due to mitochondrial dysfunction
  - And consequently can protect these cells from excess mtROS and hypoxia-induced cell death



Marshall RP, Droste JN, Giessing J, Kreider RB. Role of Creatine Supplementation in Conditions Involving Mitochondrial Dysfunction: A Narrative Review. Nutrients. 2022 Jan 26;14(3):529.

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Human trials of creatine

- Best known for improving muscle ATP in athletes
- A systematic review and meta-analysis of 9 RCTs reported creatine to reduce muscle damage post-intensive training and speed recovery
- A systematic review of 6 RCTs reported that creatine improves short term memory and reasoning in healthy individuals
- RCT of 75 Parkinson's disease patients with mild cognitive decline reported a combination of creatine (5g) and CoQ10 (100mg) to delay the cognitive decline at 12 and 18 months
- Most studies of biomarkers of mitochondrial function are still animal and cell studies

Jiaming Y, Rahimi MH. Creatine supplementation effect on recovery following exercise-induced muscle damage: A systematic review and meta-analysis of randomized controlled trials. J Food Biochem. 2021 Oct;45(10):e13916, Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. *Exp Gerontol.* 2018;108:166-173, Li Z, Wang P, Yu Z, et al. The effect of creatine and coenzyme q10 combination therapy on mild cognitive impairment in Parkinson's disease. *Eur Neurol.* 2015;73(3-4):205-211.

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Clinical Action Plan:
Are more mito cofactor nutrients required?

1. Assess nutrient status

…via dietary history, urinary organic and amino acids, erythrocyte membrane fatty acids testing, blood testing (e.g. Q10)

2. Create a personalised supplement plan for these nutrients

Aim for O3I of 8-12% to guide omega-3 dosing

3. Is there a need for creatine?

How is cognitive function / is the client very physically active / are they eating animal proteins?

4. Is there a need for L-carnitine?

Animal protein consumption / suberic/adipic organic acids?

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Which **nutrition and lifestyle interventions** may support healthy ageing by stimulating **mitogenesis and mitophagy**?

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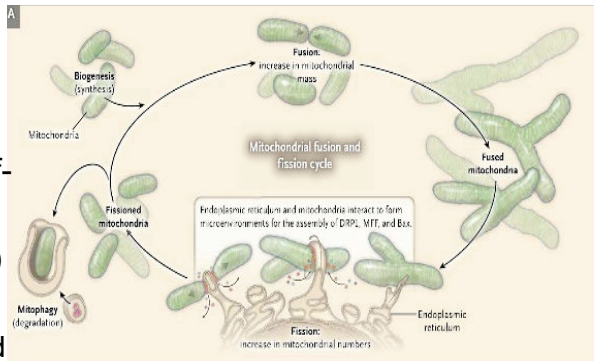
Mitophagy and **biogenesis**

- Mito are constantly shape-shifting through fusion and fission
  - Can be ball-shaped or thread-like
- Worn-out mito are identified and self-digested (mitophagy) and/or…
- …new mito are created (biogenesis) from:
  - Recycled parts from mitophagy; and new parts coded for by mtDNA and nDNA



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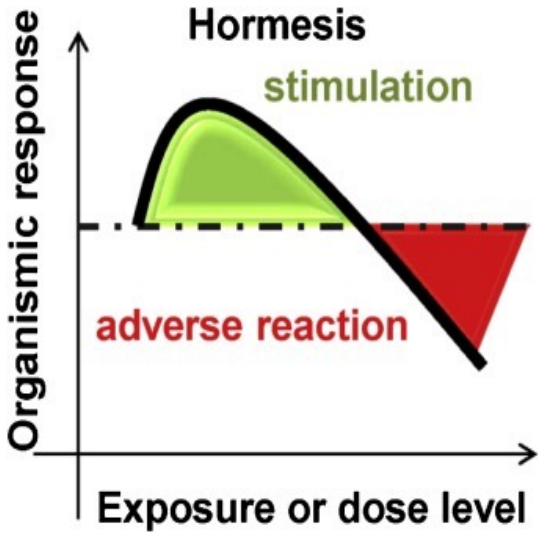
Stimulated by hormesis

- A dose response phenomenon characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect.
- Hormesis mildly *increases* mito ROS, which → an adaptive response that → ↑ stress resistance that → a long-term *reduction* of oxidative stress and stimulation of autophagy and mitophagy



Da W, Chen Q, Shen B. The current insights of mitochondrial hormesis in the occurrence and treatment of bone and cartilage degeneration. Biol Res. 2024 Jun 1;57(1):37.

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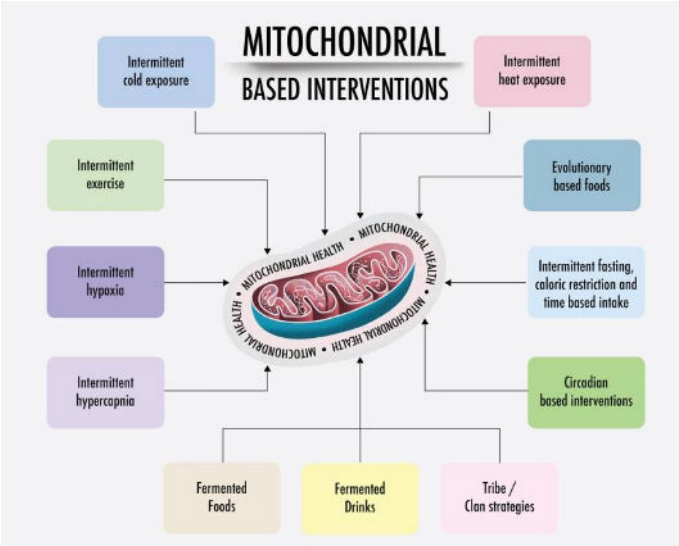
Hormetic strategies

Mild stress and/or energy deficit:

- Exercise (see later): very powerful!
- Calorie restriction, fasting, IF, FMD
- Cold exposure (cold showers, outdoor swimming)
- ? Supplemental ketones (early studies: may have mito anti-ageing benefits even while eating carbs)
- Caffeine during energy deficit (releases FAs from adipocytes into blood stream → ↑ hepatic acetyl CoA → ketones)



Casanova A, Pruimboom L.et al., Mitochondria: It is all about energy. Front Physiol. 2023 Apr 25;14:1114231, Murray AJ, Knight NS, Cole MA, et al (2016). Novel ketone diet enhances physical and cognitive performance. *FASEB J.* 30(12):4021-4032, Vandenberghe C, St-Pierre V, Courchesne-Loyer A, et al (2017). Caffeine intake increases plasma ketones: an acute metabolic study in humans. *Can J Physiol Pharmacol.* 95(4):455-458, Veech RL, Bradshaw PC, Clarke K, et al (2017). Ketone bodies mimic the life span extending properties of caloric restriction. *IUBMB Life.* 69(5):305-314

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The **mitochondrial paradox**

To make energy, we need to eat food

But to get ***more*** **energy**, we need to…

- … **Eat less food** (to make mito *function* better)
- … And **exercise more** (to increase mito *number*)

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Fasting → mitophagy → healthy ageing

- *'Because… humans evolved in environments where food was relatively scarce, they developed numerous adaptations that enabled them to function at a high level, both physically and cognitively, when in a food-deprived/fasted state.'*
- *'Studies of IF (e.g., 60% energy restriction on 2 days per week or every other day), PF (e.g., a 5 day diet providing 750-1100kcal) and time-restricted feeding (TRF; limiting the daily period of food intake to 8h or less) in normal and overweight human subjects have demonstrated… weight loss and improvements in… insulin resistance and… risk factors for CVD.*

'The cellular and molecular mechanisms by which IF improves health and counteracts disease processes involve activation of adaptive cellular stress response signaling pathways that *enhance mitochondrial health, DNA repair and autophagy*.'

Mattson MP, Longo VD, Harvie M (2017). Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 39:46-58

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Exercise → mitophagy → healthy ageing

- *'One procedure that is well-known to improve physical and psychological well-being, decrease mortality, and decrease the risk of age-related disease, is exercise…*
- ***The increase in autophagy and remodeling of the mitochondrial network**, leading to adaptive improvements in quality control and increased reserve capacity, may play key roles…*
- *A deeper understanding of the role of natural… molecules regulated by exercise—exerkines and exosomes… holds promise for preventing, slowing, and perhaps reversing some of the effects of aging'*
- Also found to increase mitochondrial *number a*s well as mitophagy and biogenesis

Naviaux RK. Incomplete Healing as a Cause of Aging: The Role of Mitochondria and the Cell Danger Response. Biology (Basel). 2019 May 11;8(2):27

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What **type and dose of exercise** for mitochondrial health?

- For general health, a combination of zone 2 + HIIT + weight training
- Research by Inigo San-Millan et al (Tour de France coach and professor at the University Medicine, Colorado) reports zone 2 an effective exercise strategy for mitochondrial health
- During zone 2 training, mitochondria generate energy aerobically, using fat as the primary fuel
  - This improves **mito function** and the ability to **burn fat** (and **clear lactate)**
- The 'talk test' can help you roughly determine when you're in zone 2 (you can talk but you sound slightly out of breath)

San-Millán I, Stefanoni D, Martinez JL, Hansen KC, D'Alessandro A, Nemkov T. Metabolomics of Endurance Capacity in World Tour Professional Cyclists. Front Physiol. 2020 Jun 5;11:578.

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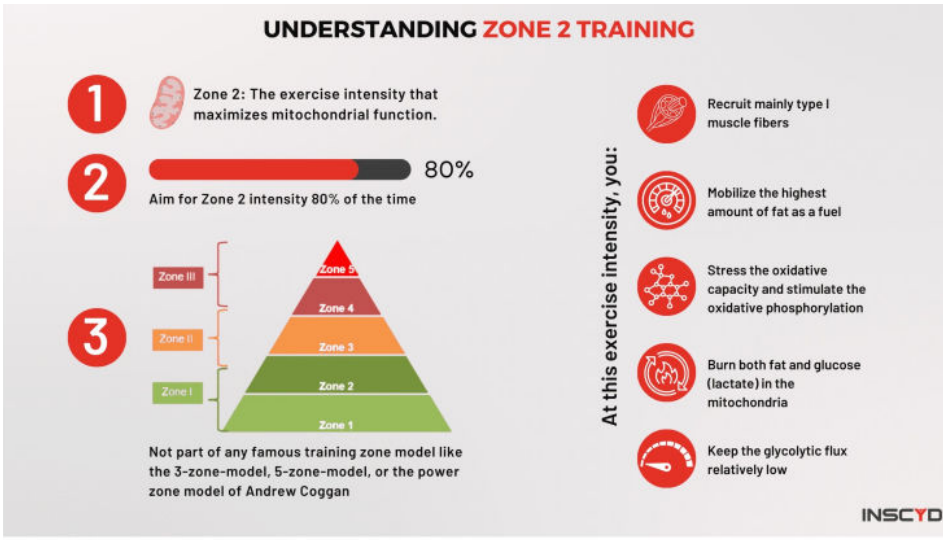
This great for us as practitioners, as most people can cope with Zone 2 training without danger of injury or burnout



Vossen L. Zone 2 Training: Benefits, Science, and How-To Guide [Internet]. INSCYD. 2023. Available from: https://inscyd.com/article/zone2-training/

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Duration and frequency for mito health

- 1 – 1.5 hours duration for mito effect
  - Untrained individuals start at 30 mins and work up
  - Athletes may need a lot longer duration (up to 4-5 hours)
- 3 - 4 times a week
- Zone 2 = low intensity = recruitment of type I muscle fibres (that have many mitochondria) → produce energy by using fat as fuel
  - **Increasing fat combustion helps our mitochondria to be more metabolically flexible – able to easily switch fuel source**
- But: more intense training (e.g. HIIT) = recruitment of type II muscle fibres → use carbs as fuel and **produce lactate**
  - Thus mixing low + high intensity means you don't get the zone 2 benefit, as you produce lactate; and the type I muscle fibres will use the lactate for energy rather than fat (i.e. lactate inhibits lipolysis)

Vossen L. Zone 2 Training: Benefits, Science, and How-To Guide [Internet]. INSCYD. 2023. Available from: https://inscyd.com/article/zone2-training/

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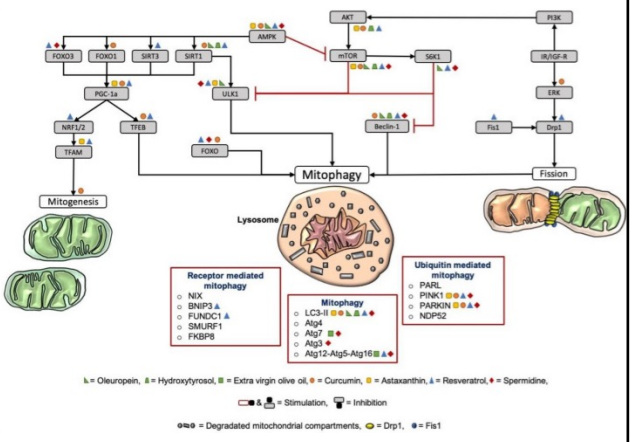
The *mechanism:* **fasting/CR/exercise → mitophagy + biogenesis via AMPK**

- **AMPK** is a central regulator of mitophagy (via ULK1) and mitogenesis (via **PGC-1α and Nrf1/2)** – both activated in energy deficit
- Oxidative / hormetic stress activates the AMPK pathway and inhibits **mTOR**
  - mTOR blocks mitophagy
- The main upstream mediators of PGC-1α are FOXO1/3 and **SIRT1/3**
- The upstream modulator of mTOR is the **IR/IGF-R** (insulin receptor/insulin growth factor receptor)



Varghese N, Werner S, Grimm A, Eckert A. Dietary Mitophagy Enhancer: A Strategy for Healthy Brain Aging? Antioxidants (Basel). 2020 Sep 29;9(10):932

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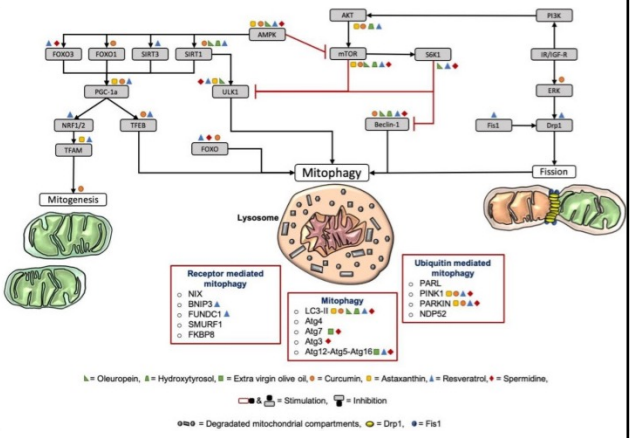
So scientific research is focusing on **compounds that stimulate or inhibit these**, as exercise and fasting are thought to be inaccessible by many. For example:

Resveratrol, urolithin A, quercetin, olive oil phenols, curcumin and astaxanthin:

- May stimulate AMPK for both mitogenesis and mitophagy
- May stimulate mitogenesis through the Nrf2 factor

(we will return to these molecules)



Varghese N, Werner S, Grimm A, Eckert A. Dietary Mitophagy Enhancer: A Strategy for Healthy Brain Aging? Antioxidants (Basel). 2020 Sep 29;9(10):932, Makarov M, Korkotian E. Differential Role of Active Compounds in Mitophagy and Related Neurodegenerative Diseases. Toxins (Basel). 2023 Mar 6;15(3):202.

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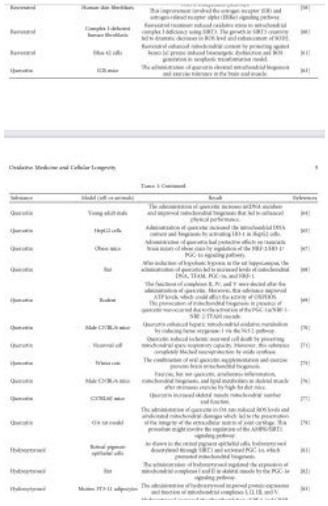
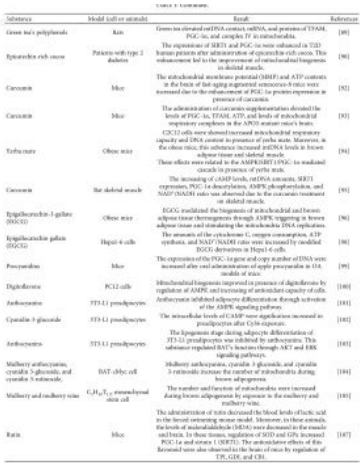
Most polyphenols and glucosylinates are 'good for you' toxins

Cell and animal studies show they stimulate mitophagy and/or mitogenesis and inhibit mTOR

Human studies show improvement in dxs related to mitochondrial dysfunction

But more human studies are needed to *link* the dxs with the mito mechanisms, i.e., measurement of improved mito function





Chandrasekaran V, Hediyal TA, Anand N, et al. Polyphenols, Autophagy and Neurodegenerative Diseases: A Review. Biomolecules. 2023 Jul 31;13(8):1196, Chodari L, Dilsiz Aytemir M, Vahedi P, Alipour M, Vahed SZ, et al. Targeting Mitochondrial Biogenesis with Polyphenol Compounds. Oxid Med Cell Longev. 2021 Jul 12;2021:4946711.

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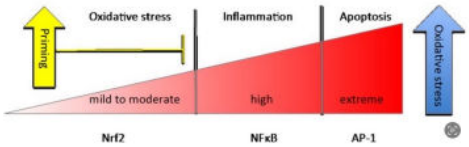
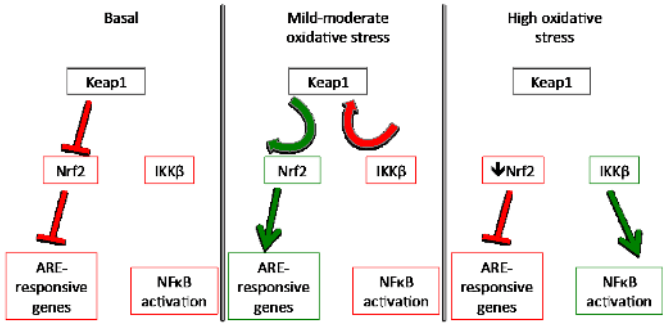
LORRAINE NICOLLE NUTRITION

Nrf2 and NFkB: walking the line





Stefanson AL, Bakovic M. Dietary regulation of Keap1/Nrf2/ARE pathway: focus on plant-derived compounds and trace minerals. Nutrients. 2014 Sep 19;6(9):3777-801.

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Some practitioners are translating this into real world practice via '***intermittent metabolic switching***'

Mattson MP, Moehl K, Ghena N, et al (2018). Intermittent metabolic switching, neuroplasticity and brain health. *Nat Rev Neurosci*. 19(2):63-80

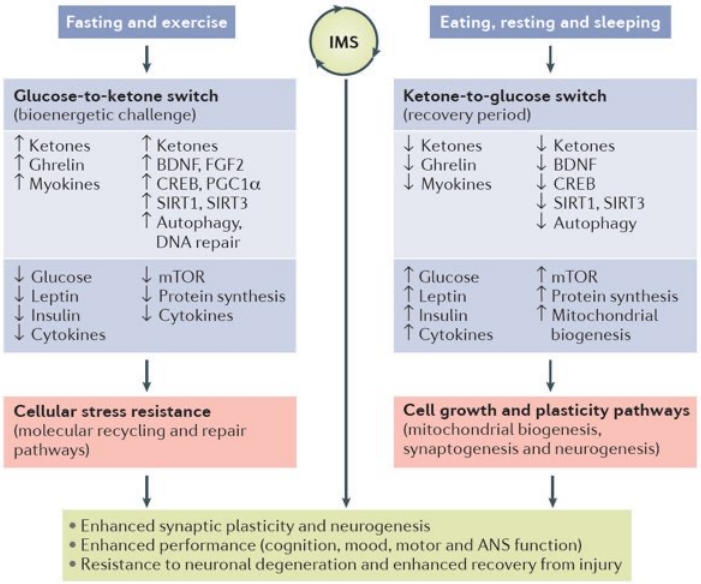

Figure 3 | **Model for how intermittent metabolic switching may optimize brain performance and increase resistance to injury and disease.**

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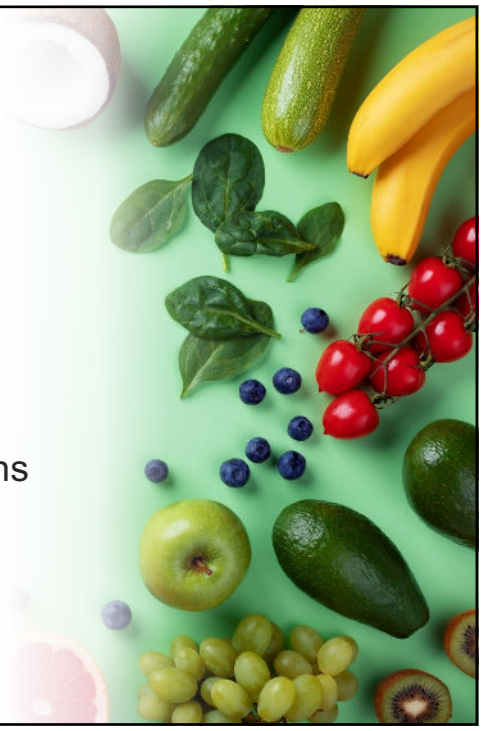
Summary list of **phytochemicals** that come up repeatedly in mitochondrial health studies

- Resveratrol
- Quercetin
- EGCG
- Curcumin
- Sulphoraphane
- Olive oil phenols
- Proanthocyanidins
- Urolithin A (a *metabolite* of a phytochemical)



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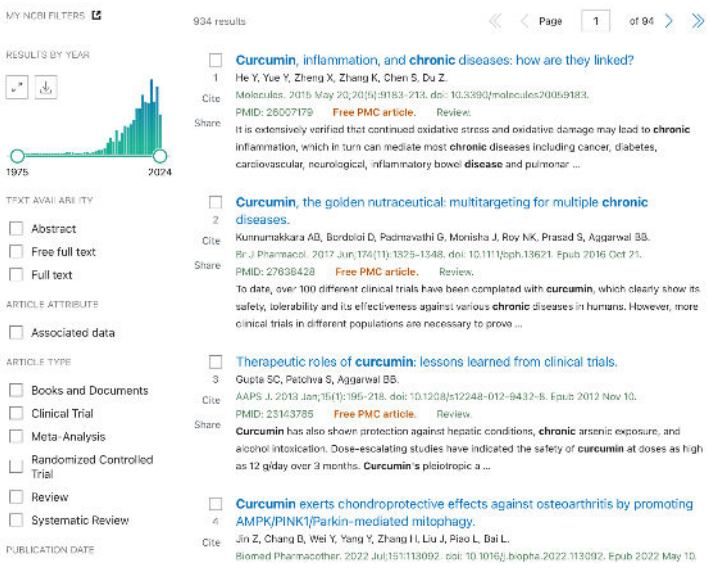
Huge body of human trial evidence for curcumin in chronic illness

934 peer reviewed papers published on curcumin therapy in chronic illness (September 2024)



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Two examples of relevant studies: curcumin's effect on…

Mito dysfunction in neurodegenerative dxs

Mito dysfunction in osteoarthritis

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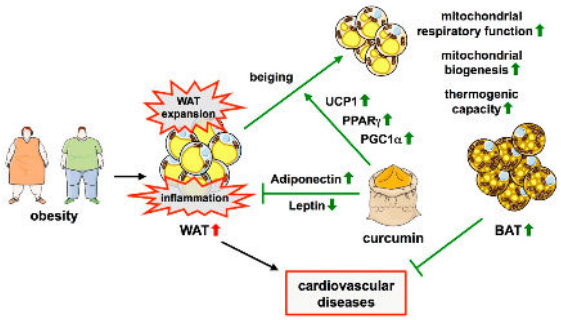
Protective effects of curcumin in obesity-induced VAT inflammation

- Curcumin can inhibit obesity-induced adipose tissue inflammation via mitochondrial support
- It also drives the formation of beige adipocytes in WAT, which results in BAT-like characteristics of these cells
- Underlying mito mechanisms: the upregulation of PPARγ, PGC1α, and UCP1, resulting in increased mitochondrial biogenesis, improved respiratory chain function, and thermogenesis



Cox FF, Misiou A, Vierkant A, et al. Protective Effects of Curcumin in Cardiovascular Diseases-Impact on Oxidative Stress and Mitochondria. Cells. 2022 Jan 20;11(3):342

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Urolithin A

- Not found in the diet as it is a post-biotic made from polyphenols called ellagitannins
  - Pomegranates, raspberries, strawberries, walnuts, almonds
- Cell and animal studies demonstrate that it stimulates mitophagy
- Recent study (100 healthy adults) reported **only 40% of participants** produced detectable amounts after drinking pomegranate juice
- Compared to the low- and non-producers, the higher producers had:
  - A higher ratio of *firmicutes-to-bacteroidetes*
  - Increased abundance of *Akkermansia muciniphilia*
  - A high abundance of species belonging to the *Clostridiales* and *Ruminococcaceae* families

Singh A, D'Amico D, Andreux PA, et al. Direct supplementation with Urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. Eur J Clin Nutr. 2022 Feb;76(2):297-308.

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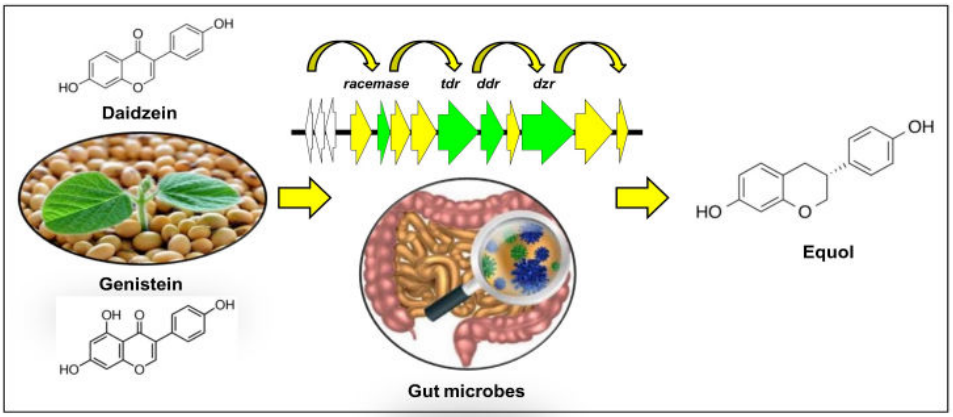
This may be the case with many phytochemicals, as they all depend on metabolism by gut bacteria. E.g. equol for the benefits of soy isoflavones

Equol synthesis is well established as highly variable between populations and also between individuals



Vázquez L, Flórez AB, Redruello B, Mayo B. Metabolism of Soy Isoflavones by Intestinal Bacteria: Genome Analysis of an *Adlercreutzia Equolifaciens* Strain That Does Not Produce Equol. Biomolecules. 2020 Jun 23;10(6):950. Soukup ST, Engelbert AK, Watzl B, Bub A, Kulling SE. Microbial Metabolism of the Soy Isoflavones Daidzein and Genistein in Postmenopausal Women: Human Intervention Study Reveals New Metabotypes. Nutrients. 2023 May 17;15(10):2352.

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Human trials on Urolithin A

- 4 weeks of UA (500 and 1000mg) in sedentary elderly individuals improved mito gene expression, compared to placebo, similar to aerobic exercise (N = 100)
- 1000mg UA for 4 months vs. placebo reduced muscle fatigue and improved endurance in 66 healthy adults (+65 years) (N = 66)
  - Significant improvements in leg (17%) and hand (16%) endurance and significant reductions in CRP
- 4 months of UA (500 and 1000mg) in middle-aged adults (ages 45-65 years) vs. placebo statistically improved aerobic endurance and physical performance, as well as a 12% increase in muscle strength and a reduction in CRP levels

Andreux PA, Blanco-Bose W, Ryu D, et al. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. Nat Metab. 2019 Jun;1(6):595-603, Liu S, D'Amico D, Shankland E, et al. Effect of Urolithin A Supplementation on Muscle Endurance and Mitochondrial Health in Older Adults: A Randomized Clinical Trial. JAMA Netw Open. 2022 Jan 4;5(1):e2144279, Singh A, D'Amico D, Andreux PA, et al. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. Cell Rep Med. 2022 May 17;3(5):100633.

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Issues to consider with new categories of supplements like this

- Might this be a game-changer in preserving muscle function during times of little/no physical exercise (e.g. during injury or illness)?
- Or: is it truly any better for mitophagy than existing tools, i.e., other polyphenol postbiotics? (Those that we make in the gut from ECGC, OPCs, curcumin, quercetin, etc).
  - No RCTs as yet that compare them
- All UA trials to-date are sponsored by the manufacturer of the supplement
- Taking the supplement provides a great deal more of the postbiotic than it is possible get from food – how do we know how much is too much over what period of time, whether it needs to be cycled, and whether it is equally good for everyone?

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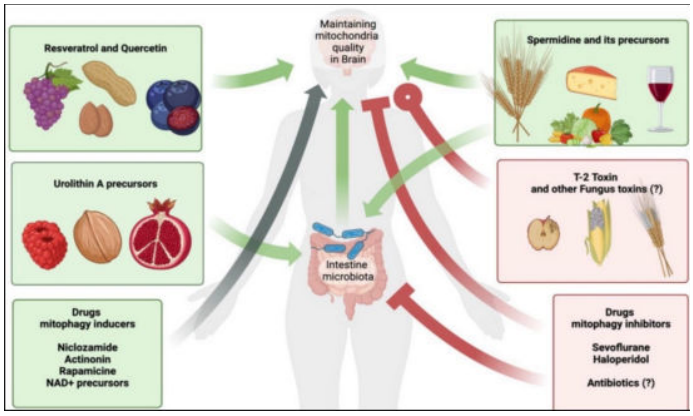
2023 review

Dietary compounds in mitophagy

- **Urolithin A, resveratrol, quercetin, and spermidine** have cell, animal (and nascent human) evidence in mitochondrial health conditions like cognitive function and memory
- ***'Their influence on mitophagy can be considered proven both in vitro and in vivo.'***
- Among toxins and drugs that inhibit mitophagy, this review hypothesizes that long-term antibiotic use (via gut dysbiosis) may disrupt mitophagy, including in the brain with subsequent effects on neural function



Makarov M, Korkotian E. Differential Role of Active Compounds in Mitophagy and Related Neurodegenerative Diseases. Toxins (Basel). 2023 Mar 6;15(3):202.

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A note in spermidine (mentioned in the 2023 review)

- A polyamine present in many plant foods (as diverse as grapefruit, wheatgerm and soy)
- Evidenced to support mitophagy/autophagy in cell studies, flies and mice, as well as to block mTOR
- Appears to support memory/cognition/heart in cell and animal studies
- 6 human trials on Pubmed
  - Most have equivocal or null effect
  - 2 report benefits in mild cognitive decline, but whether this is via autophagy is hypothetical as the evidence for this mechanism is still only in cells/animals
- 3-month trial: 30 people with subjective CD were given 1.2 mg of spermidine vs placebo. Spermidine improved mnemonic memory but not recognition memory
- 3-month trial: 92 subjects (with and without dementia) eating bread rolls containing either 3.2mg or 1.9mg spermidine. Reported improvement in cognitive performance in subjects with mild and moderate dementia for the higher spermidine dosage

Wirth M, Benson G, Schwarz C, et al. The effect of spermidine on memory performance in older adults at risk for dementia: A randomized controlled trial. Cortex. 2018 Dec;109:181-188. Pekar T, Bruckner K, Pauschenwein-Frantsich S, et al. The positive effect of spermidine in older adults suffering from dementia : First results of a 3-month trial. Wien Klin Wochenschr. 2021 May;133(9-10):484-491.

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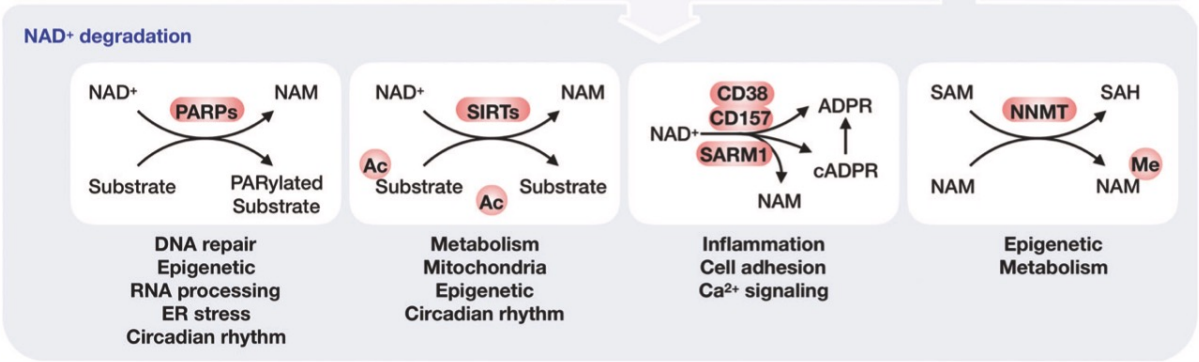
Back to NAD+. We've seen that NADH donates electrons in the ETC to produce ATP. But NAD+ also has other roles, including stimulating mitophagy (as it is a cofactor for sirtuins – see next →)



A critical cofactor for approx. 300 enzymes

Including sirtuins that trigger mitophagy (sirtuins catalyse deacetylation of proteins and histones)

Xie, N., Zhang, L., Gao, W. *et al.* NAD+ metabolism: pathophysiologic mechanisms and therapeutic potential. Sig Transduct Target Ther 5, 227 (2020).

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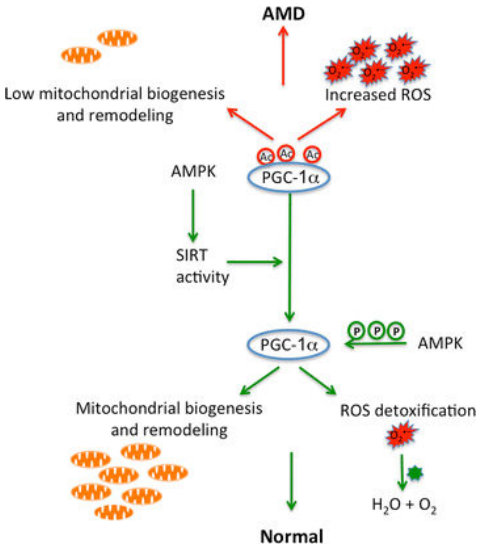
SIRT1 uses NAD+ to activate PGC-1α (via deacetylation). The acetyl groups are transferred from PGC1a to NAD+ (see next slide for detail of SIRT1 deacetylation)

- We've already seen that AMPK (stimulated via fasting/CR/exercise) increases SIRT1 activity
- AMPK can also *directly* activate PGC-1α via phosphorylation

This increases mito numbers + energy production, and reduces ROS production



Ac acetylation, *p* phosphorylation

Golestaneh N, Chu Y, Cheng SK, et al. Repressed SIRT1/PGC-1α pathway and mitochondrial disintegration in iPSC-derived RPE disease model of age-related macular degeneration. J Transl Med. 2016 Dec 20;14(1):344.

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Sirtuins remove acetyl groups from histones and other proteins (like PGC1-a)

- HDACs (like SIRT1) allow histones to wrap the DNA more tightly – they condense the DNA, making less of it available for expression – hence **sirtuins can silence genes that can drive cell dysfunction and premature ageing**
- This is an 'epigenetic' change to a gene, as it changes the *function* but not the *structure* of the DNA
- SIRT1 needs NAD+ as its cofactor

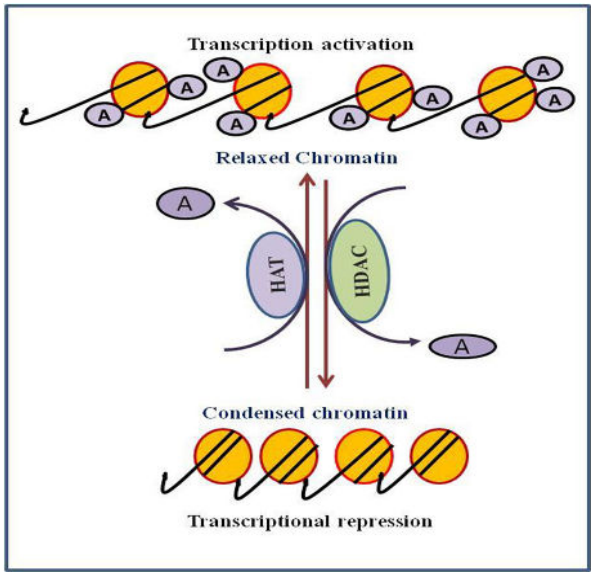

Image: Shukla S, Tekwani BL. Histone Deacetylases Inhibitors in Neurodegenerative Diseases, Neuroprotection and Neuronal Differentiation. Front Pharmacol. 2020 Apr 24;11:537.

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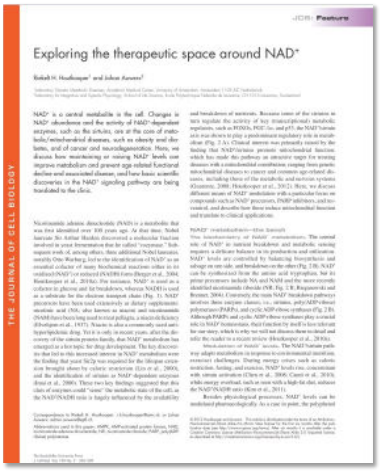
NAD+ and/or precursor human trials

Efficacy in mitochondrial-related health conditions:

- Hyperlipidaemia
- Parkinson's disease
- Retinal function in glaucoma
- Insulin sensitivity in prediabetes
- Muscle function in ageing individuals
- Physical performance in T2DM
- Fatigue and biomarkers in CFS


Exploring the therapeutic space around NAD+

THE JOURNAL OF CELL BIOLOGY

Houtkooper RH, Auwerx J. Exploring the therapeutic space around NAD+. J Cell Biol. 2012 Oct 15;199(2):205-9.

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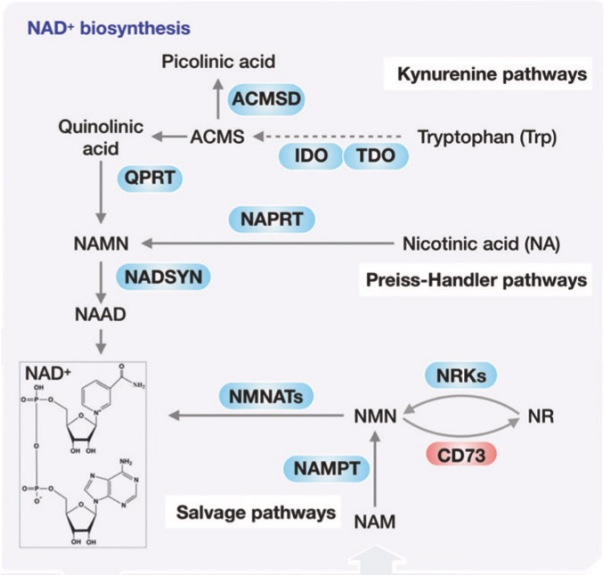
NAD+ Biosynthesis

3 different pathways:

1. Kynurenine pathway (tryptophan)
2. Preiss-Handler pathway (nicotinic acid)
3. Salvage pathways



Xie, N., Zhang, L., Gao, W. *et al.* NAD$^+$ metabolism: pathophysiologic mechanisms and therapeutic potential. *Sig Transduct Target Ther* **5**, 227 (2020). https://doi.org/10.1038/s41392-020-00311-7

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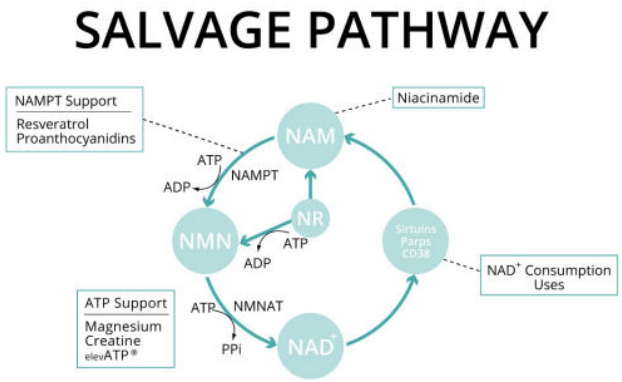
NAD+ seems to decline as we age (?less efficient salvaging enzymes; ?more used up by PARPs to repair DNA damage)

Might it be healthier to support the salvage enzymes rather than give high doses of NAD+ precursors over the longer term, to avoid taxing methylation?

- B3 is detoxified via methylation (NNMT – nicotinamide-N-methyltransferase)
- Thus if supplementing NAD/NADH/NMN, also put in methyl donors and cofactors



Key: NAM= nicotinamide; NA= nicotinic acid; NR=nicotinamide riboside; NMN= nicotinamide mononucleotide; NAMPT = nicotinamide phosphoribosyltransferase

Image: How is NAD+ Made? Salvage Pathway [Internet]. Neurohacker Collective. Available from: https://neurohacker.com/how-is-nad-made-salvage-pathway

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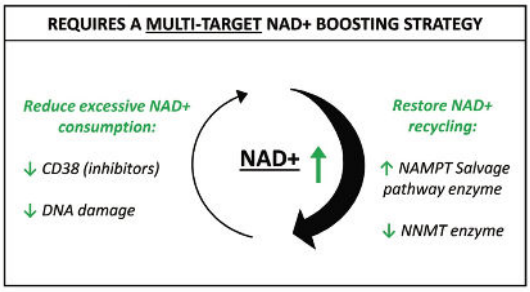
Supporting the NAD+ salvage enzymes

NAD+ recycling is via NAMPT, which reduces with age/inflammation:

- **Supporting AMPK (CR/exercise)** may increase NAMPT (and thus NAD$^+$, sirtuins, and mitochondrial efficiency)
- **Resveratrol, proanthocyandins** (early studies) – may support NAMPT and AMPK

Also address the *causes* of NAD+ decline:

- Reduce excessive *consumption* of NAD+ (inflammation that requires CD38 and DNA damage that draws on PARP)



Key: NAMPT = nicotinamide phosphoribosyltransferase; NNMT: Nicotinamide N-methyltransferase

Conlon NJ. The Role of NAD+ in Regenerative Medicine. *Plast Reconstr Surg*. 2022;150(4 Suppl):41S-48S, How is NAD+ Made? Salvage Pathway [Internet]. Qualia. [cited 2024 Jul 22]. Available from: https://www.qualialife.com/how-is-nad-made-salvage-pathway#:~:text=Whether%20the%20source%20of%20the; Poljsak B, Kovač V, Milisav I. Healthy Lifestyle Recommendations: Do the Beneficial Effects Originate from NAD⁺ Amount at the Cellular Level? Oxidative Medicine and Cellular Longevity. 2020:8819627

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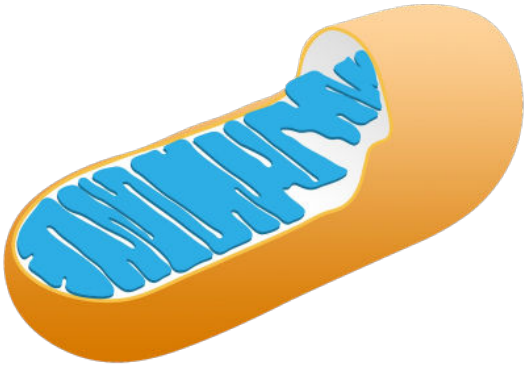
Back briefly to CoQ10

- Like NAD+, Q10 has more than one role in mitochondrial health:
  - Used in the ETC for ATP synthesis
  - Used as an antioxidant in the mitochondria (membranes and mtDNA)
  - Also stimulates SIRT1 for mitophagy and mitogenesis (via PGC1-a)



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A 2023 evaluation of blood markers from a human trial reported…

- …**Selenium** yeast (200mcg) and **coenzyme Q10** (200mg)/day for 4 years
- … increased **SIRT1** levels **in humans**…
- …protecting against **vascular ageing** and atherosclerosis

antioxidants

MDPI

Article

Increased SIRT1 Concentration Following Four Years of Selenium and Q_{10} Intervention Associated with Reduced Cardiovascular Mortality at 10-Year Follow-Up—Sub-Study of a Previous Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial

Tone Raar Opstad, Jan Alexander, Jan Aaseth, Anders Larsson, Ingebjørg Seljeflot and Urban Alehagen

Abstract: Background: Selenium and coenzyme Q_{10} (SeQ_{10}) possess antioxidant and anti-inflammatory properties, potentially mediated via Sirtuin1 (SIRT1). We aimed to investigate the influence of a SeQ_{10} intervention on SIRT1 concentration, with potential interactions with microRNAs. Methods: In this sub-study of a prospective double-blind placebo-controlled clinical trial, healthy subjects (mean age 79 years) were randomized to receive an active treatment (n = 305, combined 200 µg/day of Se and 200 mg/day of Q_{10}) or a placebo (n = 306). SIRT1 concentration and microRNAs were measured with ELISA and PCR, respectively. Results: After four years, SIRT1 concentration was increased in the active treatment group, with means (SD) ng/mL of 669 (436) vs. 292 (362), p < 0.001, and decreased in the placebo group, 198 (306) vs. 269 (372), p = 0.002, and the difference between the groups were significant (p = 0.036, adjusted). Those who suffered CV death during a 10-year follow-up (n = 25 and n = 52 in the active treatment and placebo groups, respectively) had significantly lower baseline SIRT1 concentrations compared to the survivors (p = 0.011). MiR-130a-3p was significantly downregulated during the intervention and correlated inversely with SIRT1 at baseline (r = −0.466, p = 0.007). Conclusion: The increased SIRT1 concentration after the SeQ_{10} intervention associated with reduced CV mortality, partly mediated via miR-130a-3p, suggests that SIRT1 is an additional mediator of the intervention's preventing vascular ageing.

Keywords: sirtuin1; selenium; coenzyme Q_{10}; intervention; cardiovascular mortality

1. Introduction

It is now well accepted that an optimal supply of the essential trace element selenium (Se) has multiple health-promoting benefits, and supplementation may be beneficial in subjects with low Se levels [1–6]. With its anti-oxidative and anti-inflammatory effects afforded by a number of selenoproteins, Se has been shown to reduce the harm mediated by reactive oxygen species and to reduce inflammation [7,8]. Coenzyme Q_{10} (ubiquinone) is another known regulator of oxidative stress. Coenzyme Q_{10} is primarily present in the mitochondria and is a component of the electron transport chain but also acts as a

Antioxidants 2023, 12, 759. https://doi.org/10.3390/antiox12030759 https://www.mdpi.com/journal/antioxidants

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Opstad TB, Alexander J, Aaseth J, et al. Increased SIRT1 Concentration Following Four Years of Selenium and Q10 Intervention Associated with Reduced Cardiovascular Mortality at 10-Year Follow-Up-Sub-Study of a Previous Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial. Antioxidants (Basel). 2023 Mar 21;12(3):759

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Clinical Action Plan:
How to optimise mitogenesis and mitophagy?

Devise a personalised plan of fasting and exercise (incl. zone 2)

How energy-depleted is the client?

Does their exhaustion warrant a short-term trial of NAD+ or precursors?

Does the client have a history of metabolic issues and/or is in mid-life or beyond –

Consider trialling CoQ10

Increase phytochemicals:

- ALWAYS increase **brightly coloured plants abundantly** in the diet: 8-10 veg + herbs and spices + nuts and seeds + wholegrains + seaweed + broccoli sprouts
- **Which to supplement?** Consider their **pleiotropic effects** and trial those that hit many of the goals simultaneously for that particular client

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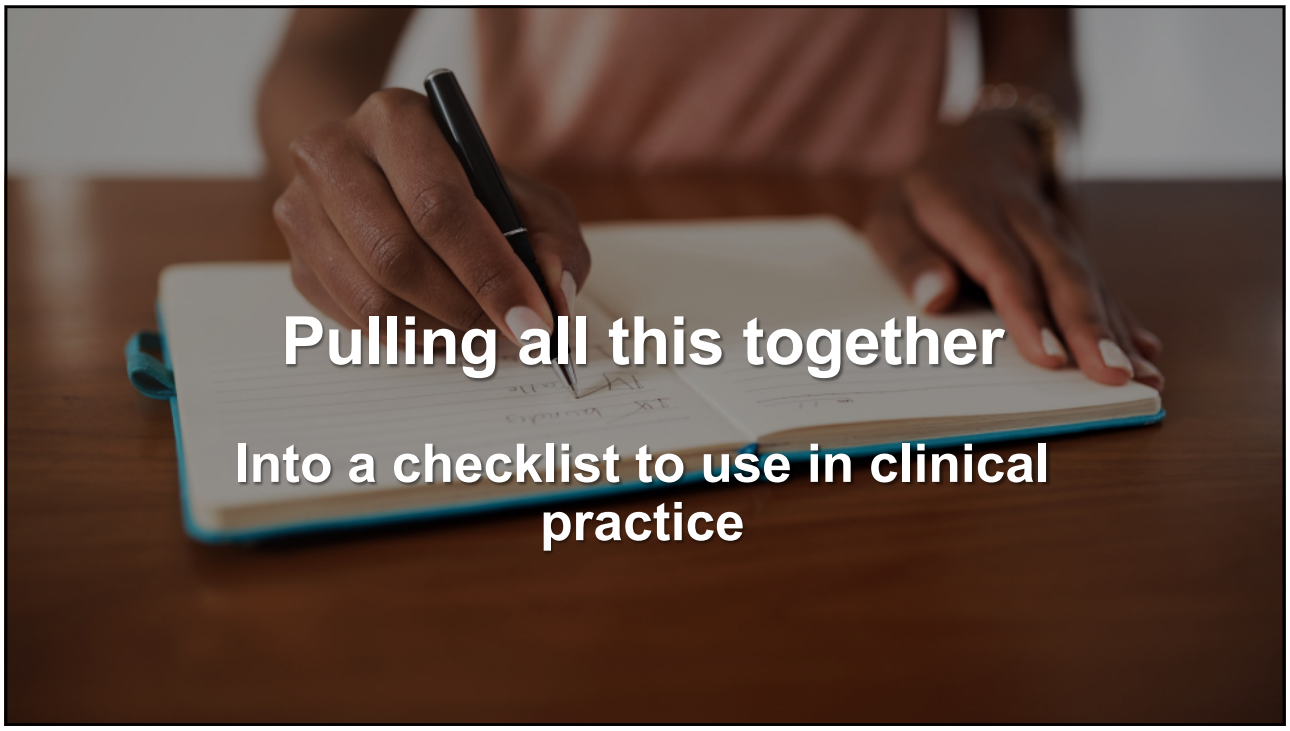

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1. Is mito dysfunction present?

Chronic illness? Are there mito-damaging inputs in the case history? Lab biomarkers?

2. What underlying biochemical imbalances could be contributing to mito dysfunction?

Complete a systems matrix

3. Work on the systems that need support

?Inflammation, ?oxidation, ?methylation, ?dysbiosis, ?compromised barriers, ?dyslipidaemia, ?HPA imbalance, and more…

Clinical practice checklist: investigations

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Clinical practice checklist: interventions

4. Avoid or reduce

Damaging inputs/toxins/overeating/sedentary

5. Supply nutrients that support mito bioenergetic processes

CoQ10, NAD+, L-carnitine, magnesium, B vitamins, creatine, EPA+DHA

6. Stimulate mitophagy and mitogenesis

Diet (keto/CR,TRF), physical exercise, NAD+, Q10, phytochemicals and their metabolites

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NMI
SUMMIT
2024
An Energetic View:
Mitochondrial Nutrition
for Fatigue, the Brain,
& Healthy Ageing
Saturday 12th October
Featuring Dr. Joseph Pizzorno, Lorraine Nicolle, Claire Sehinson,
Professor Robert Thomas, Dr. Deanna Minich
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