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An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing

Dr. Deanna Minich, PhD

Mitochondrial Nutrition: Nourishing the Inner Qi

4:15-5:00pm

An event by: Nutritional Medicine Institute

Platinum sponsors: regenerus labs, pure encapsulations

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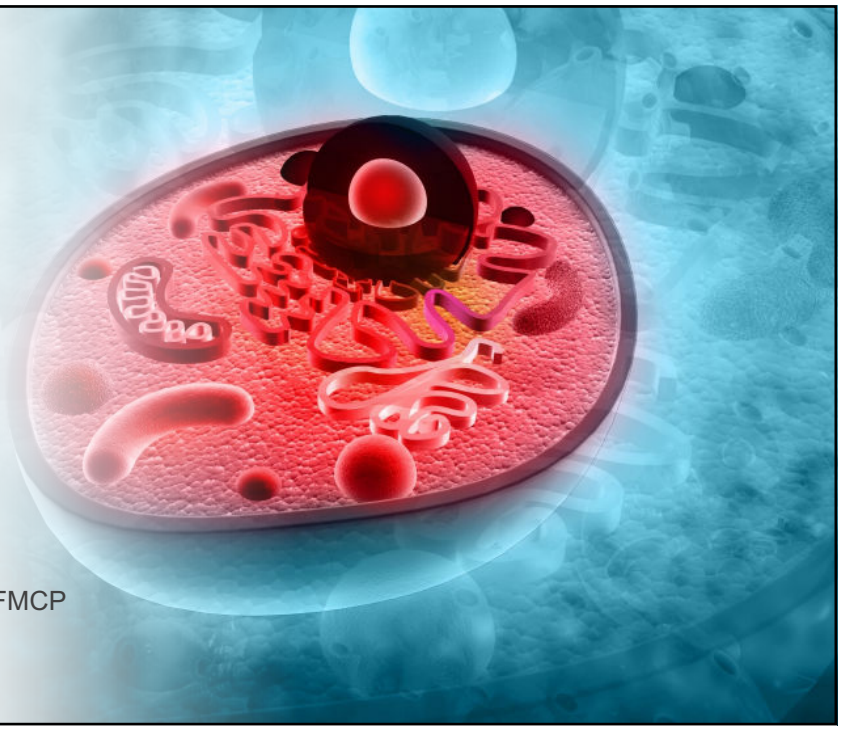
Mitochondrial Nutrition: Nourishing the Inner Qi



Deanna Minich, MS, PhD, CNS, IFMCP
deannaminich.com

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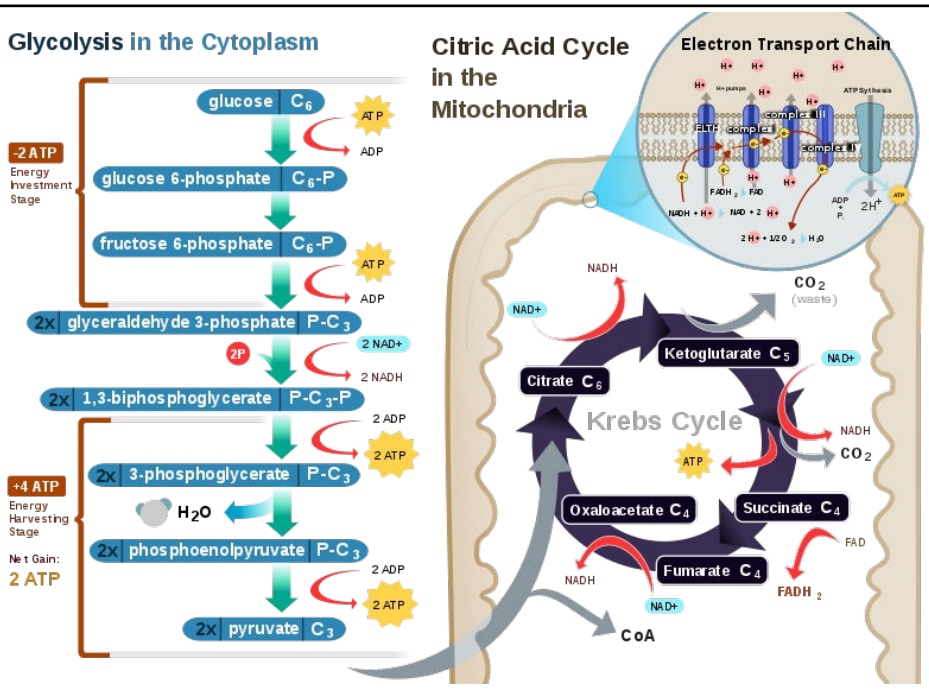
Nutrition for three main metabolic processes



https://commons.wikimedia.org/wiki/File:CellRespiration.svg#file; made by RegisFrey. No changes made. CC-3.0 license.

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How to effectively 'nourish' the mitochondria

- Dietary patterns
- Macronutrients
- Micronutrients
- Phytonutrients
- Summary

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Dietary Patterns

- Ketogenic diet
- Caloric restriction
- Fasting

9

How we create energy is essential: Shifting gears of energy production

Moving into a more ketone-driven metabolic state rather than one fueled by glucose

- Fasting
- Reducing dietary carbohydrates

Branco AF, Ferreira A, Simões RF, et al. Ketogenic diets: From cancer to mitochondrial diseases and beyond. *Eur J Clin Invest*. 2016;46(3):285-298. doi:10.1111/eci.12591 PMID: 26782788.

10

Ketogenic Diet (KD)

- Different variations of the KD
- High fat, moderate protein, low carbohydrates
  - 4:1 (fat: protein/CHO), but 3:1, 2:1, 1:1 have been used.
  - MCTs are more efficiently absorbed, metabolized, and transformed into ketone bodies compared with LCTs.
  - Ketones are produced in the liver from fatty acid oxidation
    - Acetyl Co-A from mitochondrial beta-oxidation either enters the Krebs cycle or converts into KBs, which can then circulate to tissues like the heart and brain for energy.
- Drives mitochondrial respiration rather than glycolysis for energy metabolism
  - Energy from metabolism of ketone bodies vs. glucose

McInnes J. Mitochondrial-associated metabolic disorders: foundations, pathologies and recent progress. *Nutr Metab* (Lond). 2013;10(1):63. Published 2013 Oct 12. doi:10.1186/1743-7075-10-63. PMID: 24499129; Branco AF, Ferreira A, Simões RF, et al. Ketogenic diets: From cancer to mitochondrial diseases and beyond. *Eur J Clin Invest*. 2016;46(3):285-298. doi:10.1111/eci.12591. PMID: 26782788; Huang L, Li H, Zhong J, et al. Efficacy and Safety of the Ketogenic Diet for Mitochondrial Disease With Epilepsy: A Prospective, Open-labeled, Controlled Study. *Front Neurol*. 2022;13:880944. Published 2022 Aug 1. doi:10.3389/fneur.2022.880944. PMID: 35979062

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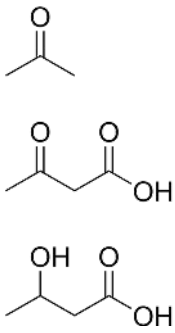
Ketone Bodies:

3- and 4-carbon end-products of fatty acid metabolism

Acetoacetate, β-hydroxybutyrate, acetone
Supplemental ketone salts and esters
Mitoprotective
Decrease oxidative stress
Anti-inflammatory
Transported to other tissues from liver and kidneys to enter TCA cycle
Serve as alternative energy source in situations of glucose dysmetabolism



https://commons.wikimedia.org/wiki/File:Ketone_bodies.png CCBY

McInnes, J. Mitochondrial-associated metabolic disorders: foundations, pathologies and recent progress. *Nutr Metab* (Lond) 10, 63 (2013) doi:10.1186/1743-7075-10-63

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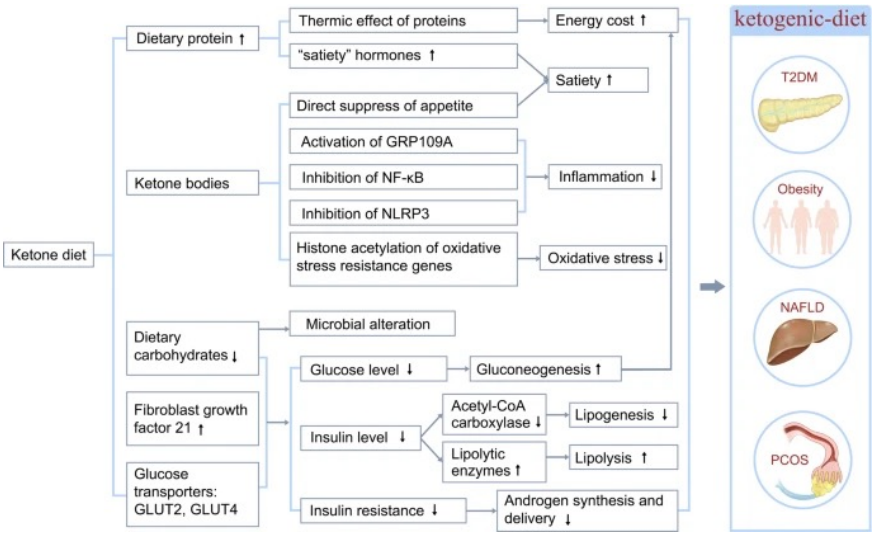
The connection between a KD and metabolism



Zhu, H., Bi, D., Zhang, Y. *et al.* Ketogenic diet for human diseases: The underlying mechanisms and potential for clinical implementations. *Sig Transduct Target Ther* **7**, 11 (2022). https://doi.org/10.1038/s41392-021-00831-w. CCBY 4.0

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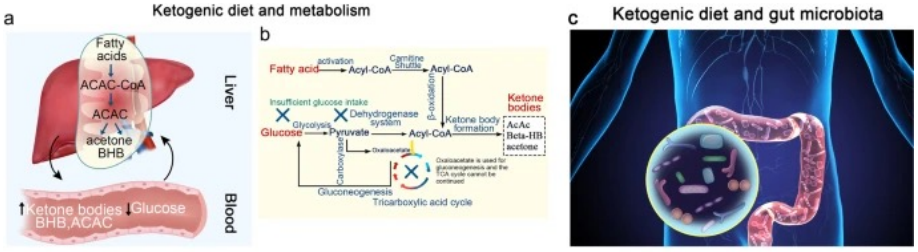
KD-induced changes in metabolism & gut microbiota



FA,and Ketone bodies ↑
- Cholesterol ↓
- TGs ↓
- HDL ↑
- Size and volume of LDL ↑
- Fibroblast growth factor 1 ↓
- HMG-CoA reductase ↑
- PPARα ↑
- Whole-body fatty acid oxidation ↑
- Liver ketogenesis ↑

Glucose ↓
- β-HB,AcAc ↑
- Insulin sensitivity ↑
- Mitochondrial oxidation ATP ↑
- The ratio of insulin to glucagon ↓
- Risk of type 2 diabetes ↓

Composition and diversity
- Bifidobacteria ↓
- Desulfovibrio ↓
- Turicibacter ↓
- Escherichia ↓
- Salmonella ↓
- Vibrio ↓
- Overall diversity ↓
- Akkermansia muciniphila ↑
- Parabacteriodes ↑
- Lactobacillus ↑
- Ruminococcaceae ↑
- Bacteroidetes ↑
- Roseburia ↑

Zhu, H., Bi, D., Zhang, Y. *et al.* Ketogenic diet for human diseases: The underlying mechanisms and potential for clinical implementations. *Sig Transduct Target Ther* **7**, 11 (2022). https://doi.org/10.1038/s41392-021-00831-w. CCBY 4.0

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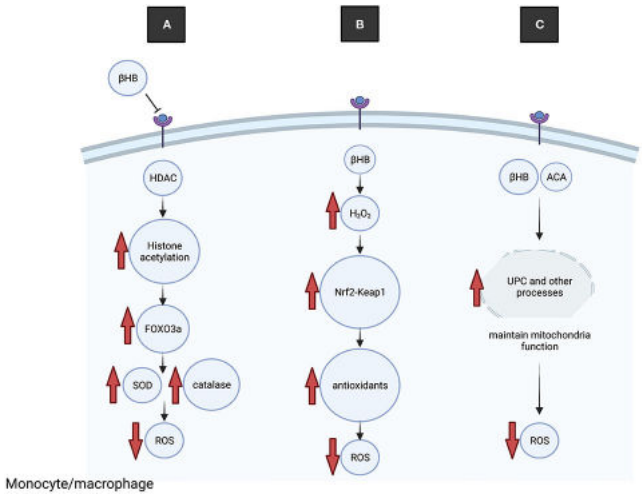
The mechanisms of the ketogenic diet are most likely more extensive than we realize.

- Increase in ROS production and electrophilic stress
- Activation of Nrf2
- Upregulation of ARE to manufacture more endogenous enzymes



Gough SM, Casella A, Ortega KJ, Hackam AS. Neuroprotection by the Ketogenic Diet: Evidence and Controversies. *Front Nutr*. 2021;8:782657. Published 2021 Nov 23. doi:10.3389/fnut.2021.782657. CCBY

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General Principles of a Healthy Ketogenic Diet

- Nutritional adequacy
- Balanced net dietary acid load
- Ensure awareness of cooking methods (reduce AGEs)
- Healthy gut to start (increased need for bile with high-fat, increased risk of metabolic endotoxemia)
- Low toxin load (toxins are lipophilic)
- Moderate and not too low CHO (60-80 g)
- Adequate phytonutrients and green, alkaline-forming vegetables
- Animal products need to be high-quality

References can be found at: https://www.deannaminich.com/what-to-eat-to-fuel-a-healthy-mitochondria/

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Ketogenic Diet (KD)

PROs:

- Improves in mitochondrial activity and mitoprotection with clinical improvements seen in mitochondrial disease
- Lower oxidative stress and inflammation
- May help modify the gut microbiome to have favorable microorganisms
- Reduces glucose availability for cancer cells
- Emerging research is indicating its use in bipolar disorder
- Can help with neurological disorders
  - Successful in treating epilepsy (mitochondrial defects in hippocampal neurons)
  - Betahydroxybutyrate (BHB) as a fuel source for neurons

PMID: 26782788; PMID: 38542723; PMID: 34888340; PMID: 39053576; PMID: 35979062; PMID: 38895313

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Ketogenic Diet (KD)

CONS/FURTHER RESEARCH:

- **Side effects**:
  - Gastrointestinal issues:
    - Gastroesophageal reflux, vomiting, constipation
  - Metabolic issues:
    - Hypoglycemia, hyperlipidemia, acidosis
  - Other:
    - Dehydration, lethargy, nutrient deficiencies

PMID: 26782788; PMID: 34888340; PMID: 35979062

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Ketogenic Diet (KD)

CONS/FURTHER RESEARCH:

- High levels of BHB may, in a dose-dependent manner, upregulate inflammation.
- Studies with animals do not always translate to human clinical outcomes.
- Potentially high toxin load due to lipophilic agents in dietary fats
- Constant oversight and monitoring to ensure adherence with a more traditional ketogenic diet comprised of 80–90% of total calories from fats, 4% from carbohydrates and 6% from proteins.
- Still some mixed results in the literature about its effects; more data needed for different conditions.
- Questions remain as to how long someone should follow it for general mitochondrial health vs. mitochondrial disease indications.

PMID: 26782788; PMID: 34888340; PMID: 35979062

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Overnutrition leads to mitochondrial aging

- Increased insulin/IGF-1
- Decreased sirtuins
- Increased reactive metabolites and mitochondrial dysfunction
- Increase in shortened telomeres
- Increase in cellular senescence
- Impaired stem cell renewal
- Decreased B cell and T cell proliferation resulting in reduced immune response
- Increased inflammation
- Reduced beta-cell regeneration

Newgard CB, Sharpless NE. Coming of age: molecular drivers of aging and therapeutic opportunities. *J Clin Invest*. 2013;123(3):946-950. doi:10.1172/JCI68833; López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217. doi:10.1016/j.cell.2013.05.039. Yuliyanasari N, Rejeki PS, Hidayati HB, Subsomwong P, Miftahussurur M. The effect of intermittent fasting on preventing obesity-related early aging from a molecular and cellular perspective. *J Med Life*. 2024;17(3):261-272. doi:10.25122/jml-2023-0370

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Types of Intermittent Fasting

Types of IF	Definitions
TRF	Ad libitum food intake is allowed only during specified hours, creating prolonged intervals without food.
eTRE	Limits the eating window to 4–10 h (most commonly 8 h), with food consumed in the earlier part of the day, with the remaining 14–20 h in an unfed state.
dTRE	Limits the eating window to 4–10 h (most commonly 8 h), with food consumed in the later part of the day, with the remaining 14–20 h in an unfed state.
ADF	Involves a day of fasting alternated with a day with ad libitum food intake.
ADMF	Involves a day of fasting, with less than 25% of the normal calorie intake, alternated with a day with ad libitum food intake.
PF	Fasting for 2–21 days.
5:2 diet	Eating ad libitum for 5 days per week, with severely restricted calorie intake on the other 2 days, to about 25% of normal levels to maintain energy balance.
Religious fasting	Fasting is essential in many religious and spiritual practices, such as the Ramadan, Greek Orthodox, or the Daniel fast practiced by Jews.

Yuliyanasari N, Rejeki PS, Hidayati HB, Subsomwong P, Miftahussurur M. The effect of intermittent fasting on preventing obesity-related early aging from a molecular and cellular perspective. *J Med Life*. 2024;17(3):261-272. doi:10.25122/jml-2023-0370. CCBY 4.0

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Effects of fasting on organ systems: Overall positive effects

Various organs or system	Function
Brain	Improved cognition, neurotropic factor production, synaptic plasticity, mitochondrial biogenesis, and resistance to injury and disease
Cardiovascular system	Reduced blood pressure, reduced resting heart rate, increased parasympathetic tone, stress resistance, enhanced right ventricular function, upregulated glycemic control, and protected myocardium against ischemia and inflammation-induced cellular damage
Lipolysis	Lipolysis, reduced leptin production, reduced inflammation
Muscles	Increased insulin sensitivity, enhanced efficiency/endurance, and reduced inflammation
Intestines	Enhanced motility, reduced inflammation, and enhanced intestinal stem cell function
Liver	Glycogen depletion, ketone production, increased insulin sensitivity, and reduced lipid accumulation
Blood	Elevated ketone level, reduce glucose, insulin, and leptin levels, elevated adiponectin levels, reduced inflammatory cytokines, and reduced markers of oxidative stress
Endocrine	Increased growth hormone in serum, decreased IGF-I concentration, and improved glucose metabolism
Immune system	Reduced the inflammatory response
Kidney	Boosted renal H_2S production

Yuliyanasari N, Rejeki PS, Hidayati HB, Subsomwong P, Miftahussurur M. The effect of intermittent fasting on preventing obesity-related early aging from a molecular and cellular perspective. *J Med Life*. 2024;17(3):261-272. doi:10.25122/jml-2023-0370. CCBY 4.0

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Contraindications for Fasting

- With type 1 diabetes
- With a history of eating disorders or disordered eating patterns
- Who are pregnant, trying to become pregnant, or are breastfeeding
- Taking certain medications
- With hypoglycemic tendencies
- With adrenal problems
- Who are underweight
- Who are severely ill or otherwise compromised

References found at: https://www.deannaminich.com/the-pros-and-cons-of-different-types-of-fasting/

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Switching between fasting and KD may promote mitochondrial resilience

- Fasting and KD have some similar yet distinct effects on cellular health.
- KD works through ketone bodies to inhibit histone deacetylases (HDACs), reduce oxidative stress and inflammation, and improve mitochondrial efficiency.
- Intermittent short-term fasting improves insulin/leptin sensitivity, stimulates autophagy, activates AMPK, inhibits mTOR, enhances mitochondrial resilience, reducing oxidative stress and inflammation.

Paoli A, Tinsley GM, Mattson MP, De Vivo I, Dhawan R, Moro T. Common and divergent molecular mechanisms of fasting and ketogenic diets. *Trends Endocrinol Metab*. 2024;35(2):125-141. doi:10.1016/j.tem.2023.10.001

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Several dietary patterns can favorably improve mitochondrial health

- Compared with an ad lib habitual diet, individuals on a calorie restricted (CR) diet, intermittent fasting (IF), and a ketogenic diet (KD) improved their maximal respiration oxygen consumption rate as shown in monocytes.
- Gut microbiota diversity was increased.

Guevara-Cruz M, Hernández-Gómez KG, Condado-Huerta C, et al. Intermittent fasting, calorie restriction, and a ketogenic diet improve mitochondrial function by reducing lipopolysaccharide signaling in monocytes during obesity: A randomized clinical trial. *Clin Nutr*. 2024;43(8):1914-1928. doi:10.1016/j.clnu.2024.06.036

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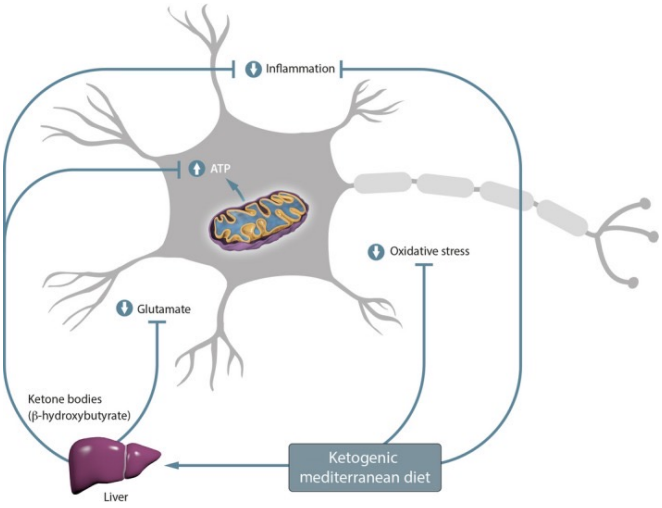
Ketogenic "hybrid" diets may be an easier way to get multiple health features

High polyphenolic and antioxidant potential of a Mediterranean diet + the metabolic benefits of a KD



Caplliure-Llopis J, Peralta-Chamba T, Carrera-Juliá S, et al. Therapeutic alternative of the ketogenic Mediterranean diet to improve mitochondrial activity in Amyotrophic Lateral Sclerosis (ALS): A Comprehensive Review. *Food Sci Nutr*. 2019;8(1):23-35. Published 2019 Dec 16. doi:10.1002/fsn3.1324. CCBY 4.0

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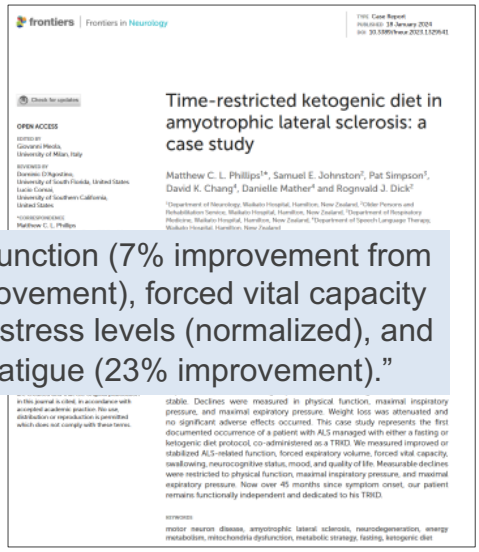
Combining time restriction and the ketogenic diet in an individual with ALS over 18 months


frontiers | Frontiers in Neurology

Time-restricted ketogenic diet in amyotrophic lateral sclerosis: a case study

Matthew C. L. Phillips, Samuel E. Johnston, Pat Simpson, David K. Chang, Danielle Mather and Rognvald J. Dick

"During this time, he improved in ALS-related function (7% improvement from baseline), forced expiratory volume (17% improvement), forced vital capacity (13% improvement), depression (normalized), stress levels (normalized), and quality of life (19% improvement), particularly fatigue (23% improvement)."

Phillips MCL, Johnston SE, Simpson P, Chang DK, Mather D, Dick RJ. Time-restricted ketogenic diet in amyotrophic lateral sclerosis: A case study. *Front Neurol*. 2024;14:1329541. Published 2024 Jan 18. doi:10.3389/fneur.2023.1329541

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Nordic Diet and Mitochondria Function

- A healthy vs. average Nordic diet were compared in 68 people in a randomized intervention study
- The individuals on the healthy Nordic diet had differentially expressed pathways related to mitochondrial function and inflammation.

Myhrstad MCW, et al. Healthy Nordic Diet Modulates the Expression of Genes Related to Mitochondrial Function and Immune Response in Peripheral Blood Mononuclear Cells from Subjects with Metabolic Syndrome-A SYSDIET Sub-Study. *Mol Nutr Food Res*. 2019 Apr 9:e1801405. doi: 10.1002/mnfr.201801405. [Epub ahead of print]

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Summary: Dietary Patterns

- The ketogenic diet, fasting, and caloric restriction all benefit mitochondrial health in their unique ways.
- It may be best to switch between them for added mitochondrial resilience.

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Macronutrients

- Protein
- Fat
- Carbohydrate

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Dietary Protein:
Mixed results for mitochondrial health

- Dietary protein restriction impairs mitochondrial health. PMID 38064763
- Some studies indicate that a high protein/low CHO diet results in mitochondrial biogenesis or would be helpful for mitochondrial health; however, there are many variables that aren't consistent. PMID: 18697911, 28911136, 32652799, 23880314
- Type of protein may not vary in response. PMID: 30698812

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High-Protein Diet and Mitochondrial Biogenesis

- N=45 healthy male participants assigned to eucaloric high protein/low carb, hypocaloric high protein/low carb, eucaloric high carb, or hypocaloric high carb diet for 7 days.
- A hypocaloric, high-protein diet resulted in favorable markers related to mitochondrial biogenesis: increased AMPk, SIRT1, PGC-1α.

Furber, M., Anton-Solanas, A., Koppe, E., Ashby, C., Roberts, M., & Roberts, J. (2017). A 7-day high protein hypocaloric diet promotes cellular metabolic adaptations and attenuates lean mass loss in healthy males. *Clinical Nutrition Experimental*, *14*, 13-25.https://doi.org/10.1016/j.yclnex.2017.05.002

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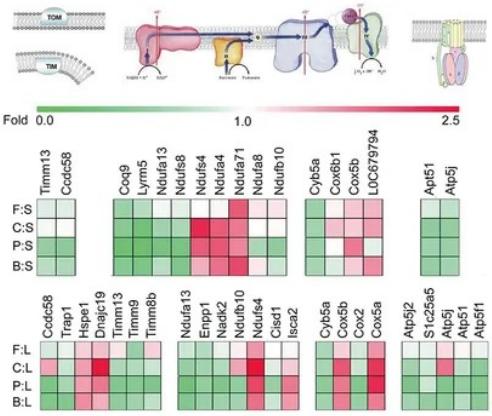
Dietary Protein Sources Have Differential Effects on Mitochondrial Oxidative Phosphorylation

- Rats randomly assigned to a high-protein diet (n=11 for each) for 90 days
  - Pork
  - Beef
  - Chicken
  - Fish
  - Soy
  - Casein



Chicken, pork, and beef diets had upregulated PGC-1a and decreased triglycerides most

Shi X, Huang Z, Zhou G, Li C. Dietary Protein From Different Sources Exerted a Great Impact on Lipid Metabolism and Mitochondrial Oxidative Phosphorylation in Rat Liver. *Front Nutr.* 2021;8:719144. Published 2021 Aug 26. doi:10.3389/fnut.2021.719144. CCBY

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High-Protein and Legume Hypocaloric Diets Increase Mitochondrial Oxidation by 25%

- 4 hypocaloric diets with high protein content for 8 weeks
  - Control diet
  - Legume diet
  - Fatty fish diet
  - High-protein diet
- N=35 obese men

Mitochondrial oxidation was activated by the high-protein diet and the legume diet.

Abete I, Parra D, Martinez JA. Legume-, fish-, or high-protein-based hypocaloric diets: Effects on weight loss and mitochondrial oxidation in obese men. *J Med Food.* 2009 Feb;12(1):100-8. doi: 10.1089/jmf.2007.0700.

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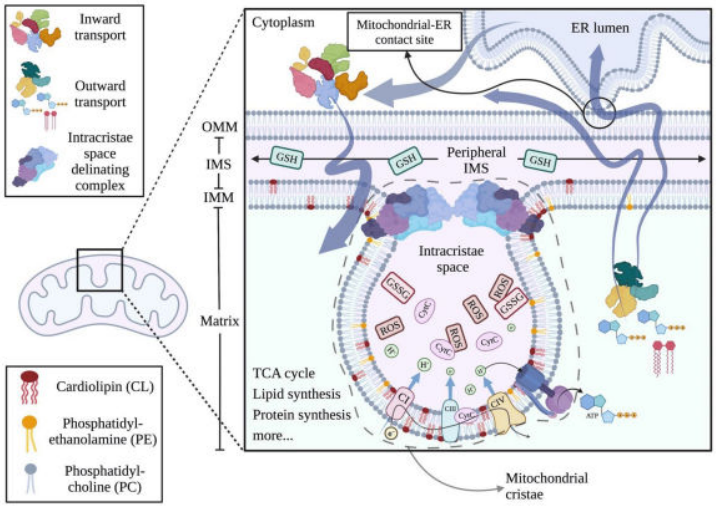
Fatty Acids

- Mitochondrial membrane as a lipid bilayer
- Many phospholipids and omega-3 fats
- Fat-soluble antioxidants as protecting the bilayer membrane



Poulaki, A.; Giannouli, S. Mitochondrial Lipids: From Membrane Organization to Apoptotic Facilitation. *Int. J. Mol. Sci.* 2022, *23*, 3738. https://doi.org/10.3390/ijms23073738. CCBY 4.0

PMID: 24121995, 22710344

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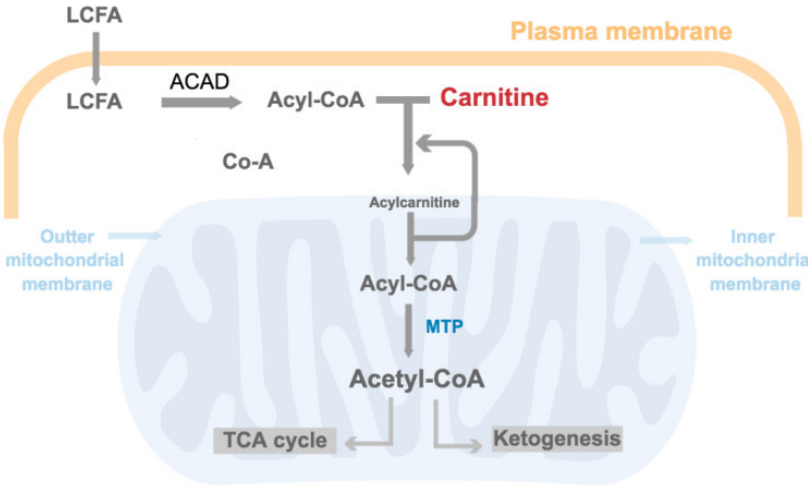
Carnitine is required for fatty acid oxidation



Watson KS, Boukhloufi I, Bowerman M, Parson SH. The Relationship between Body Composition, Fatty Acid Metabolism and Diet in Spinal Muscular Atrophy. *Brain Sci.* 2021;11(2):131. Published 2021 Jan 20. doi:10.3390/brainsci11020131. CCBY 4.0

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Fats:
Most essential mitochondria-related nutrients

Omega-3 fatty acids:

Comprise the mitochondrial membrane, regenerate the membrane and assist with fluidity, and may alter cell signaling which could impact mitochondrial function

Product	Effect	Mechanism	Type of Study
Fish oil	Improvement in mitochondrial efficiency	Increased content or enhanced kinetics of ETC	Animal model
Fish oil	Reduced body fat mass	Stimulation of lipid oxidation	Human study
Fish oil	Decrease in insulinemia	Increased lipid oxidation	Human study
DHA + EPA	Improve in mitochondrial ADP kinetics	Incorporation in mitochondrial membranes, displacing ω-6 species in several phospholipids population	Human study
DHA + EPA	Decrease in H_2O_2 production	Increased tolerance to Ca^{2+}-induced MPTP opening	Isolated mitochondria
Fish oil	Improvement in ATP production in brain	Improvement in membrane fluidity	Animal model
EPA and DHA	Increase in ATP and reduction in ROS levels in hepatocytes	Increase in the length of mitochondrial tubes by an increase in Mfn2 mRNA levels	Cell culture
EPA	Restoration of skeletal muscle mitochondrial capacity	Increase in coupling efficiency of the ETC	Animal model

Serrano JCE, Cassanye A, Martín-Gari M, Granado-Serrano AB, Portero-Otín M. Effect of Dietary Bioactive Compounds on Mitochondrial and Metabolic Flexibility. *Diseases*. 2016;4(1):14. Published 2016 Mar 10. doi:10.3390/diseases4010014. CCBY 4.0

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Fats:
Most essential mitochondria-related nutrients

- **Omega-3 fatty acids**:
  - 1-month supplementation with 5.25 g omega-3s (3.5 g EPA and 1.75 DHA) improved mitochondrial function and increased respiratory capacity and bioenergetic health in obese women. **PMID: 37437746**
- **MCTs:** Increase fat oxidation, enhance mitochondrial biogenesis, reduce food intake, and help with body composition **PMID: 29420554**
- **Excessive saturated fat** is discouraged as it may decrease the efficiency of the respiratory transport chain and lead to greater ROS and damage to the mitochondria. **PMID: 32574416**

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Carbohydrates: Most essential mitochondria-related nutrients

- **Dietary fiber:** Helps reduce energy intake and provides SCFAs that could serve as energy substrates. **PMID: 28933394**
- **Low glycemic impact**: Enhances cellular metabolic and mitochondrial function; helps increase mitochondrial oxidation **PMID: 24847102**

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Lower GI diet activates mitochondrial oxidation and helps with energy adaptation

- N=32, overweight/obese BMI
- Follow two higher GI or lower GI energy-restricted diets (-30%)
- Mitochondrial oxidation was activated after the lower GI diet.
- Weight regain was only seen in the high GI diet one year later.

Abete I, Parra D, Martinez JA. Energy-restricted diets based on a distinct food selection affecting the glycemic index induce different weight loss and oxidative response. *Clin Nutr*. 2008;27(4):545-551. doi:10.1016/j.clnu.2008.01.005

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A high-carbohydrate diet lowers the rate of adipose tissue mitochondrial respiration

- N=27 individuals assigned low (20%), moderate (40%), or high (60%) carbohydrate diets for 20 weeks
- High-carbohydrate diet resulted in lower mitochondrial respiration.

Bikman BT, Shimy KJ, Apovian CM, Yu S, Saito ER, Walton CM, Ebbeling CB, Ludwig DS. A high-carbohydrate diet lowers the rate of adipose tissue mitochondrial respiration. *Eur J Clin Nutr*. 2022 Sep;76(9):1339-1342. doi: 10.1038/s41430-022-01097-3.

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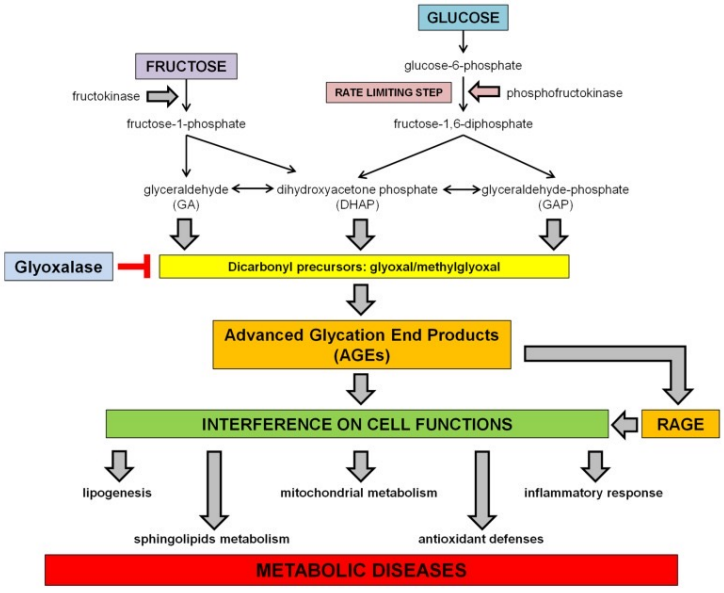

Aragno M, Mastrocola R. Dietary Sugars and Endogenous Formation of Advanced Glycation Endproducts: Emerging Mechanisms of Disease. *Nutrients*. 2017;9(4):385. Published 2017 Apr 14. doi:10.3390/nu9040385; This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

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Micronutrients:
Vitamins & Minerals

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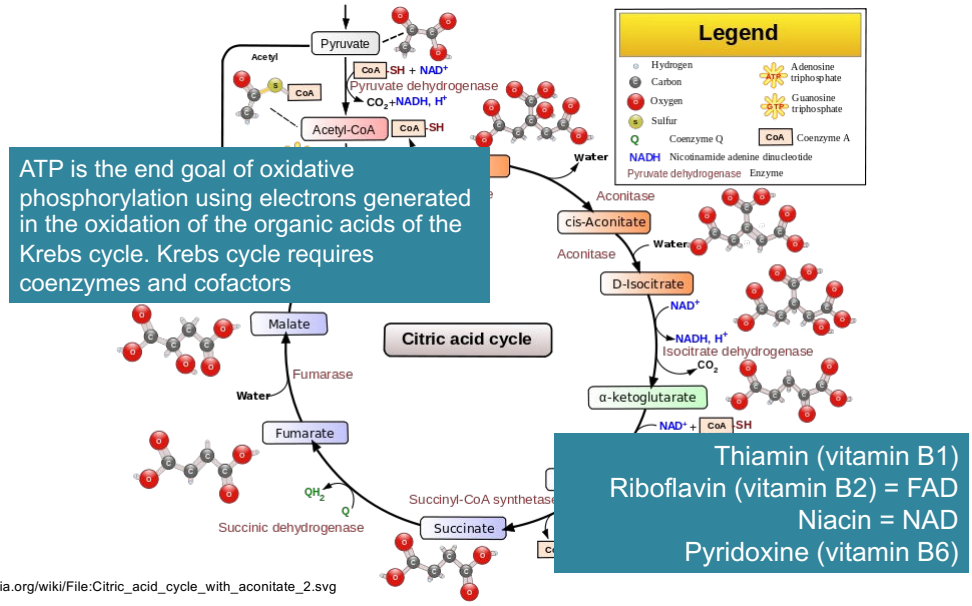
Genomic instability and damage increase with age

Fenech M. Genomic stability: A new paradigm for recommended dietary allowances (RDAs). *Forum Nutr.* 2003;56:97-100.

48

Krebs Cycle & Cofactors



ATP is the end goal of oxidative phosphorylation using electrons generated in the oxidation of the organic acids of the Krebs cycle. Krebs cycle requires coenzymes and cofactors

Thiamin (vitamin B1)
Riboflavin (vitamin B2) = FAD
Niacin = NAD
Pyridoxine (vitamin B6)

https://en.wikipedia.org/wiki/File:Citric_acid_cycle_with_aconitate_2.svg

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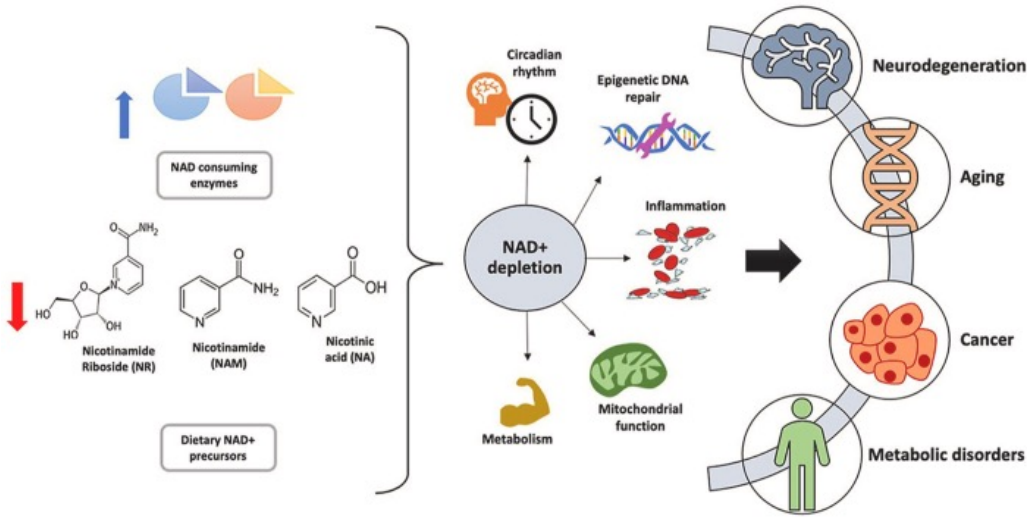
NAD+

- Low NAD^+ can lead to reduced mitochondrial homeostasis
- NAD^+ levels are decreased by ~30% in sarcopenic adults.



Amjad S, Nisar S, Bhat AA, et al. Role of NAD^+ in regulating cellular and metabolic signaling pathways. *Mol Metab.* 2021;49:101195. doi:10.1016/j.molmet.2021.101195. CCBY 4.0

50

Vitamin C

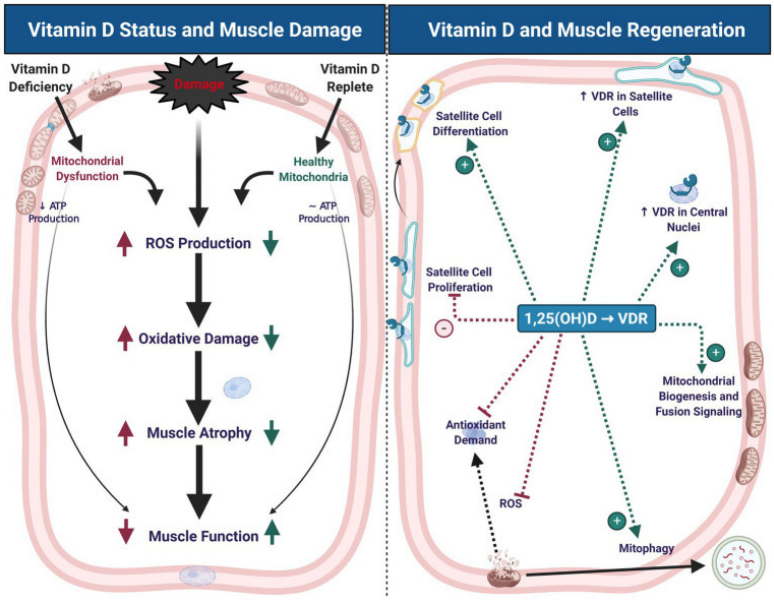
- Essential antioxidant and anti-inflammatory
- However, it may blunt some of the mitochondrial adaptations to exercise.

Bruns DR, Ehrlicher SE, Khademi S, et al. Differential effects of vitamin C or protandim on skeletal muscle adaptation to exercise. *J Appl Physiol (1985)*. 2018;125(2):661-671. doi:10.1152/japplphysiol.00277.2018.

Gomez-Cabrera MC, Domenech E, Romagnoli M, et al. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. *Am J Clin Nutr*. 2008;87(1):142-149. doi:10.1093/ajcn/87.1.142

51

Vitamin D deficiency leads to mitochondrial dysfunction, decreased ATP, and increased ROS.



Latham CM, Brightwell CR, Keeble AR, et al. Vitamin D Promotes Skeletal Muscle Regeneration and Mitochondrial Health. *Front Physiol*. 2021;12:660498. Published 2021 Apr 14. doi:10.3389/fphys.2021.660498. CCBY

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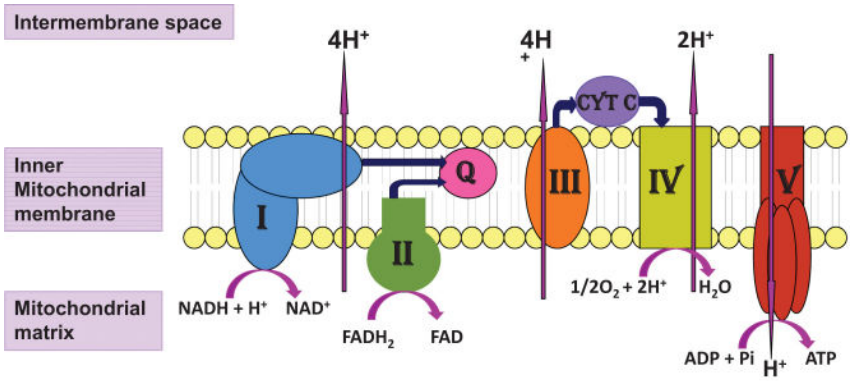
Coenzyme Q10

Coenzyme Q_{10} serves many roles in mitochondrial health, including a pivotal role as electron carrier within the respiratory complex, assisting in the transfer and continuous passage of electrons derived from complexes I and II to complex III.



Graphic Source: Neergheen, V., Chalasani, A., Wainwright, L., Yubero, D., Montero, R., Artuch, R., & Hargreaves, I. (2017). Coenzyme Q10 in the Treatment of Mitochondrial Disease. *Journal of Inborn Errors of Metabolism and Screening*. https://doi.org/10.1177/2326409817707771; https://creativecommons.org/licenses/by/3.0/. No changes made.

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Minerals and the Mitochondria

- The mitochondria are rich in minerals.
- 11 of 12 essential minerals for human health are involved with the mitochondria.
  - "The mitochondrial metallome"
  - Ca, Co, Cu, Fe, K, Mg, Mn, Mo, Na, Se, Zn
  - K, Fe, Mg, and Na are in the highest concentration in mitochondria.
  - Some others considered possibly beneficial
- Deficiencies in these minerals can result in increased ROS, redox imbalance, and mitochondrial decline.
- They act as central processing units for minerals.

Killilea DW, Killilea AN. Mineral requirements for mitochondrial function: A connection to redox balance and cellular differentiation. *Free Radic Biol Med*. 2022;182:182-191. doi:10.1016/j.freeradbiomed.2022.02.022

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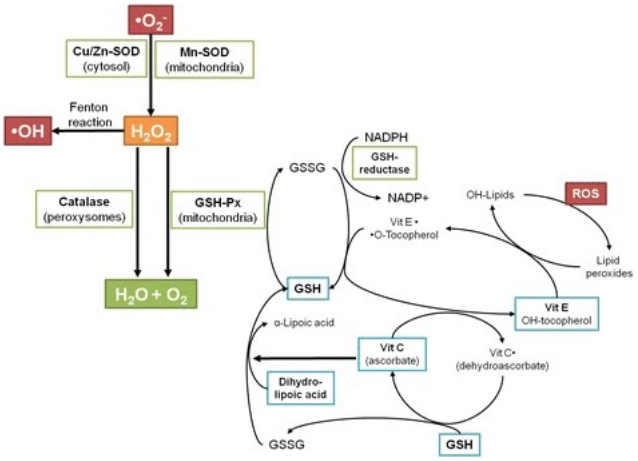
Antioxidant Defense Support for the Mitochondria

Nutritional support needed for:

- Superoxide dismutase
- Catalase
- Glutathione peroxidase



Kurutas, E.B. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. *Nutr J* 15, 71 (2015). https://doi.org/10.1186/s12937-016-0186-5. CCBY 4.0.

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Mitochondrial Support: The Spectrum of Other Nutrient Compounds

- Acetyl-L-carnitine
- Alpha-lipoic acid
- Creatine
- D-ribose
- L-carnitine
- N-acetylcysteine
- Taurine

56

Summary

Nutrient insufficiencies and deficiencies, particularly in vitamins and minerals, can accelerate the aging process related to mitochondrial decay.

Ames BN, Atamna H, Killilea DW. Mineral and vitamin deficiencies can accelerate the mitochondrial decay of aging. *Mol Aspects Med*. 2005;26(4-5):363-378. doi:10.1016/j.mam.2005.07.007

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Phytonutrients

- Beiging phytonutrients
- Antioxidant phytonutrients
- Polyphenols
- Phytomelatonin

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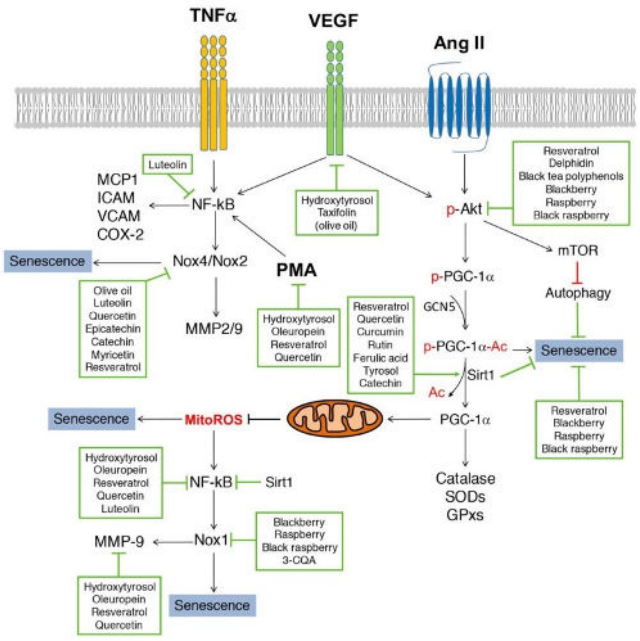
Phytochemicals serve as the intracellular network of mitochondrial support

Serino A, Salazar G. Protective Role of Polyphenols against Vascular Inflammation, Aging and Cardiovascular Disease. *Nutrients*. 2018 Dec 28;11(1):53. doi: 10.3390/nu11010053. PMID: 30597847; PMCID: PMC6357531. CCBY 4.0.



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Mitochondria-Adipose Axis:
Beiging

"There is increasing evidence that the global rise in temperature is contributing to the onset of diabetes, which could be mediated by a concomitant reduction in brown fat activity.

Brown (and beige) fat are characterised as possessing a unique mitochondrial protein uncoupling protein (UCP)1 that when activated can rapidly generate large amounts of heat."

Symonds ME1,2, Farhat G3, Aldiss P1, Pope M1, Budge H1. Brown adipose tissue and glucose homeostasis - the link between climate change and the global rise in obesity and diabetes. Adipocyte. 2019 Dec;8(1):46-50. doi: 10.1080/21623945.2018.1551689. Epub 2018 Dec 3.

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Food-derived compounds, especially those containing flavonoids, shown to activate brown fat and browning of adipose tissue

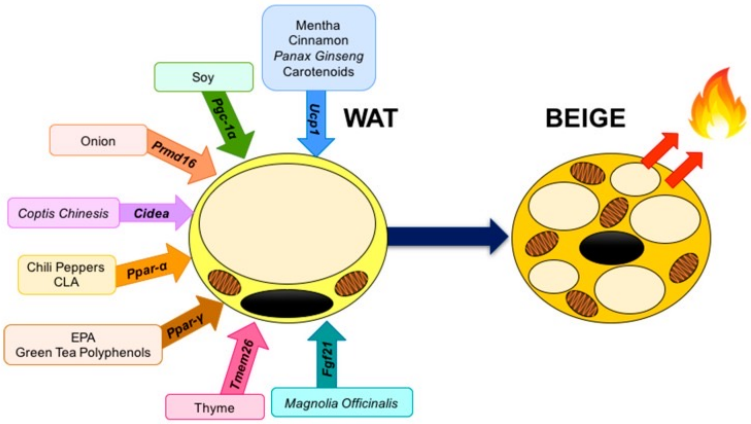

Image Credit: Lorente-Cebrián S, Herrera K, I Milagro F, Sánchez J, de la Garza AL, Castro H. miRNAs and Novel Food Compounds Related to the Browning Process. *Int J Mol Sci.* 2019;20(23):5998. Published 2019 Nov 28. doi:10.3390/ijms20235998

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Phytochemicals and Microorganisms to Promote Mitophagy and Regulate Intestinal Oxidative Damage

- **Targeting ROS production, oxidative damage, and mitophagy is a potential mechanism for managing oxidative damage to intestinal cells.**
- Phytonutrients and mitophagy:
  - Urolithin A (PMID: 30742114)
  - Resveratrol (PMID: 28770830)
  - Panax notoginseng saponins (PMID: 30531436)
- Gut bacteria and antioxidant properties:
  - *Bifidobacterium longum infantis* (PMID: 33225894)
  - *Lactobacillus plantarum* FC255 (PMID: 23681127)

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Phytoprotection through the endogenous antioxidant defense system

Lee SE, Park YS. The Emerging Roles of Antioxidant Enzymes by Dietary Phytochemicals in Vascular Diseases. *Life (Basel)*. 2021;11(3):199. Published 2021 Mar 4. doi:10.3390/life11030199. CCBY 4.0

- Anthocyanin
- Baicalein
- Berberine
- Curcumin
- EGCG
- Fisetin
- Myricetin
- Quercetin
- Resveratrol

Summary of phytochemicals with modulating Nrf2 activity and antioxidant enzymes.

Phytochemical	Effects	Altered Antioxidant enzyme
Anthocyanin	Prevent eye disease	SOD, CAT, GPx [71]
	Anti-diabetic effect	CAT, SOD [72]
	Hypotensive effect	HO-1, SOD [73]
Baicalein	Anti-ischemic effect	HO-1 [74]
	Cardiopulmonary protective effect	GPx, SOD [75]
Berberine	Anti-inflammation effect	NQO-1, HO-1 [76]
	Anti-atherosclerotic effect	HO-1 [77]
	Anti-diabetic effect	GR [78]
Curcumin	Anti-atherosclerotic effect	HO-1 [79]
	Cardio protective effect	SOD [80]
	Anti inflammation effect	HO 1 [81]
	Vasculoprotective effect	CAT [82]
	Cardio-protective effect	GPx, GR [83]
	Cardio-protective effect	GR, SOD [84]
	Anti-diabetic effect	PON1 [85]
EGCG	Neuroprotective effect	SOD, GPx [86]
	Anti inflammation effect	HO 1 [87]
Fisetin	Anti-inflammation effect	HO-1 [88]
	Neuroprotective effect	SOD, CAT [89]
	Anti-hypertrophic effect	SOD, CAT, HO-1 [90]
Myricetin	Anti-inflammation effect	HO-1 [91]
	Anti-oxidative effect	SOD, GPx [92]
Quercetin	Anti diabetic effect	SOD, CAT [93]
	Vasculoprotective effect	HO 1 [94]
Resveratrol	Vasculoprotective effect	SOD, GPx [95]
	Neuroprotective effect	SOD, HO-1 [96]
	Vasculoprotective effect	HO-1 [97]

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SIRT-inducing bioactives: SIRTfoods

Sirtuins are NAD-dependent deacetylases involved in regulation of lifespan and metabolism.

Table adapted from: Pallauf K, Giller K, Huebbe P, Rimbach G, Nutrition and Healthy Ageing: Calorie Restriction or Polyphenol-Rich "MediterrAsian" Diet?, *Oxidative Medicine and Cellular Longevity*, 2013, Article ID 707421, 14 pages, 2013. https://doi.org/10.1155/2013/707421. CCBY.

Sirtfoods	
Name of compound	"Sirtfoods" found in
Daidzein	Soybean, tofu, and other soy product
Fisetin	Strawberries, apples, persimmons, grapes
Formononetin	Soybean
Isoliquiritigenin	Soybean, shallots, and licorice
Hydroxytyrosol	Olive oil
Kaempferol	Cabbage, kale, parsley, different types of beans, Corchorus olitorius*, and cruciferous vegetable
Piceatannol	Red wine, grapes, and Rhodomyrtus tomentosa #
Quercetin	Onions, apples, white wine, capers, and Corchorus olitorius
Resveratrol	Red wine, red grapes

*consumed in Japan as "Molokheka"; #edible plant native to Asia; and ◊possibly other phenolic compounds found in olive oil.

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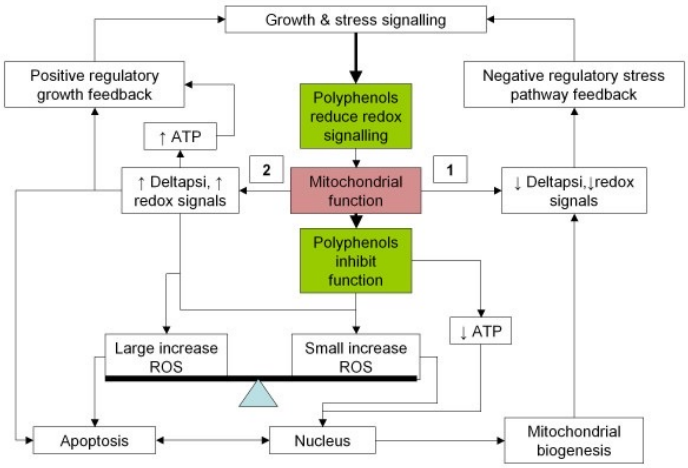
Mitochondria and Polyphenols



Nunn AV, Bell JD, Guy GW. Lifestyle-induced metabolic inflexibility and accelerated ageing syndrome: insulin resistance, friend or foe?. *Nutr Metab (Lond)*. 2009;6:16. Published 2009 Apr 16. doi:10.1186/1743-7075-6-16. (http://creativecommons.org/licenses/by/2.0),

65

Dietary apple polyphenols enhance mitochondrial turnover and respiratory chain enzymes in rats

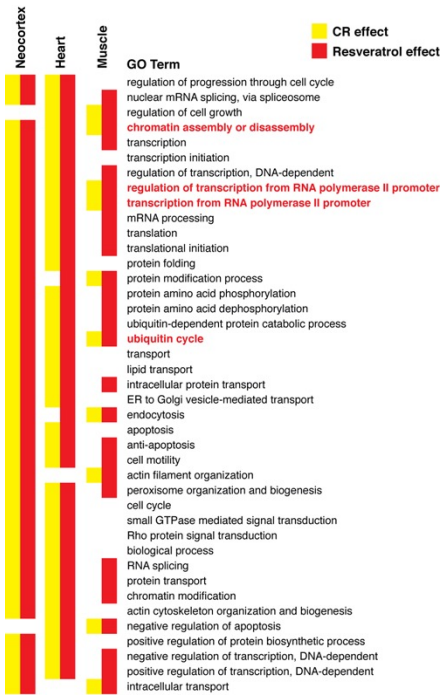
- Animals fed dietary apple polyphenols (0.5-5%) had
  - increased respiratory chain complex enzyme activity in skeletal muscle → may result in ATP synthesis efficiency and improved muscle endurance
  - increased mitochondrial biosynthesis and turnover (mitophagy)

Yoshida Y, Tamura Y, Kouzaki K, Nakazato K. Dietary apple polyphenols enhance mitochondrial turnover and respiratory chain enzymes. *Exp Physiol*. 2023 Oct;108(10):1295-1307. doi: 10.1113/EP091154. Epub 2023 Sep 1. PMID: 37658608; PMCID: PMC10988434.

66

Resveratrol acts as a caloric restriction mimetic

Barger JL, et al. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. *PLoS One*. 2008 Jun 4;3(6):e2264. CCBY.



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Calorie restriction-like effects of 30 days of resveratrol supplementation

- Resveratrol resulted in the following:
  - Reduced sleeping and resting metabolic rate
  - Activated AMPK
  - Increased SIRT1 and PGC-1α protein levels
  - increased citrate synthase activity without change in mitochondrial content
  - improved muscle mitochondrial respiration on a fatty acid-derived substrate

N=11 healthy, obese men
150 mg/day resveratrol vs. placebo

Timmers S, Konings E, Bilet L, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab*. 2011;14(5):612-622. doi:10.1016/j.cmet.2011.10.002. PMID: 22055504

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Giving resveratrol at different times of day resulted in altered antioxidant activity

In an animal study:

- Giving resveratrol (i.p.) during the **active (dark) period** acts as a **strong antioxidant** in the heart, liver, and kidney of male rats in a dose-dependent manner
- During the **inactive (light) period**, it acted as a **pro-oxidant**, increasing oxidative stress (TBARS) in increasing doses

Gadacha W, Ben-Attia M, Bonnefont-Rousselot D, Aouani E, Ghanem-Boughanmi N, Touitou Y. Resveratrol opposite effects on rat tissue lipoperoxidation: pro-oxidant during day-time and antioxidant at night. *Redox Rep*. 2009;14(4):154-158. doi:10.1179/135100009X466131. PMID: 19695122

69

Melatonin is a mitochondria-targeted antioxidant

- Chronobiotic phytoantioxidant taken up and produced by mitochondria
- Believed to have evolved alongside mitochondria as a protective mechanism against oxidative stress

Reiter RJ, Rosales-Corral S, Tan DX, Jou MJ, Galano A, Xu B. Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. *Cell Mol Life Sci.* 2017 Nov;74(21):3863-3881. doi: 10.1007/s00018-017-2609-7. Epub 2017 Sep 1.

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Clinical Application: Mitochondria-Focused Eating

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Features of a Mitochondria-Focused Way of Eating

1. Low toxin load
2. Low glycemic index
3. Low carbohydrate/higher short- and medium-chain fats
4. Anti-inflammatory
5. High phytonutrient density and antioxidant potential
6. Enhanced levels of mitochondrial cofactors
7. Reduced AGEs
8. Intermittent fasting

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Summary & Takeaways

- The mitochondria need specific **nutrients** to function, particularly to allow for proper metabolism of substances to energy.
- The amount and timing **of food intake** influences mitochondrial function.
- There is science to support recommendations for the role of **macronutrients, micronutrients, and phytonutrients** in bioenergetics.

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An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing

Please join us in the Conservatory for

the NMI Gala Evening

An event by: Nutritional Medicine Institute

Platinum sponsors: regenerus labs powered by ONNOS pure encapsulations

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