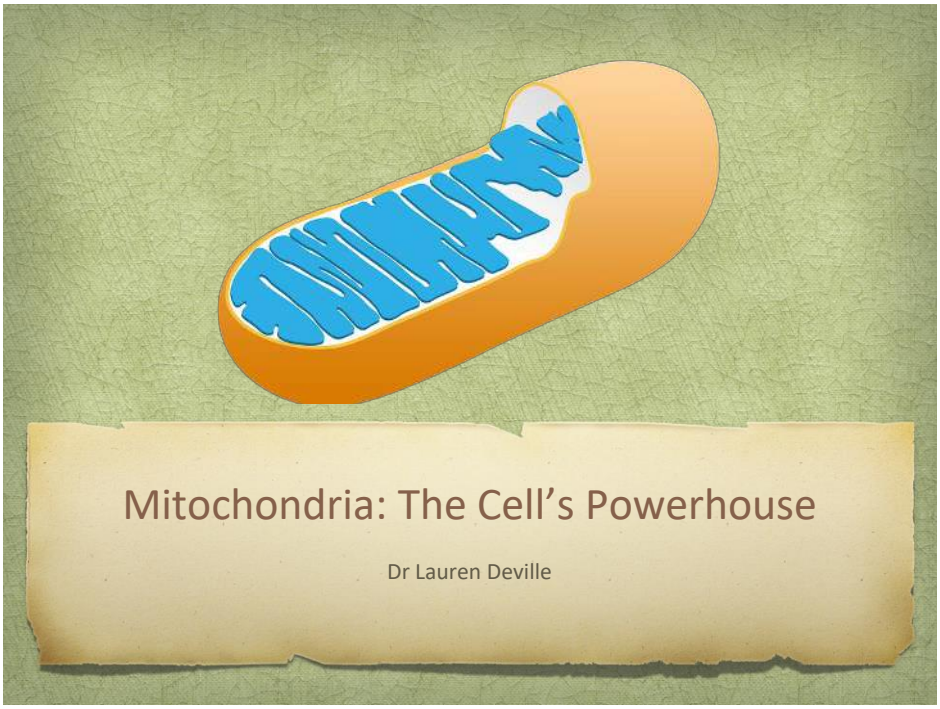
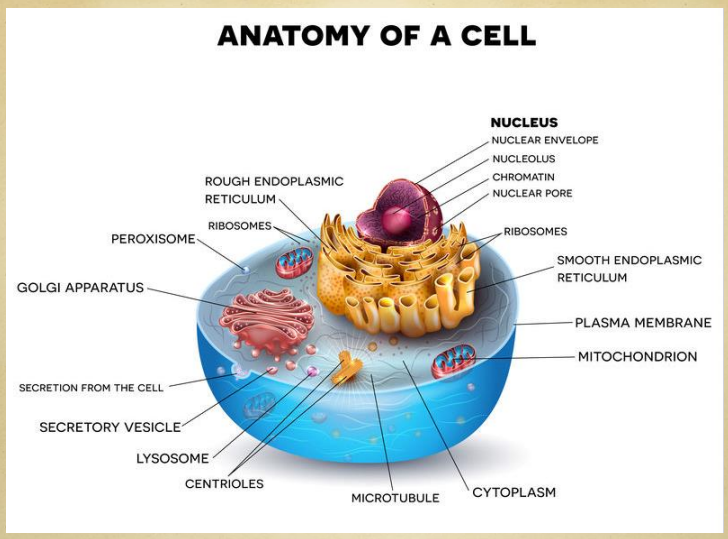


1

Mitochondrial Function

- Organelles that create energy (ATP) via cellular respiration (aerobic)
  - Oxygen in blood —> mitochondria, where it turns glucose, fatty acids, and amino acids into ATP
  - Inner matrix contains enzymes of the TCA or Krebs cycle—> reduced B3, NADH and reduced B2, $FADH_2$
  - **Electron Transport Chain** on cristae (inner membrane folds)
- Each cell (except RBCs) contains hundreds to thousands of mitochondria (depending on the cell's function)
  - Highest in the retina, heart, brain, skeletal muscles
  - Oocytes have 100K mitochondria! (Required for rapid cell division)

2



Notice the double membrane inside the mitochondria, folded to increase surface area.

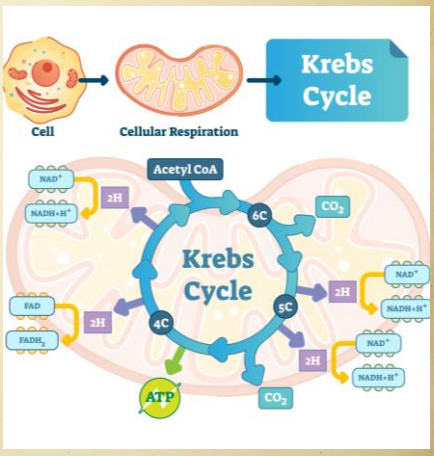
3

Cellular (Aerobic) Respiration

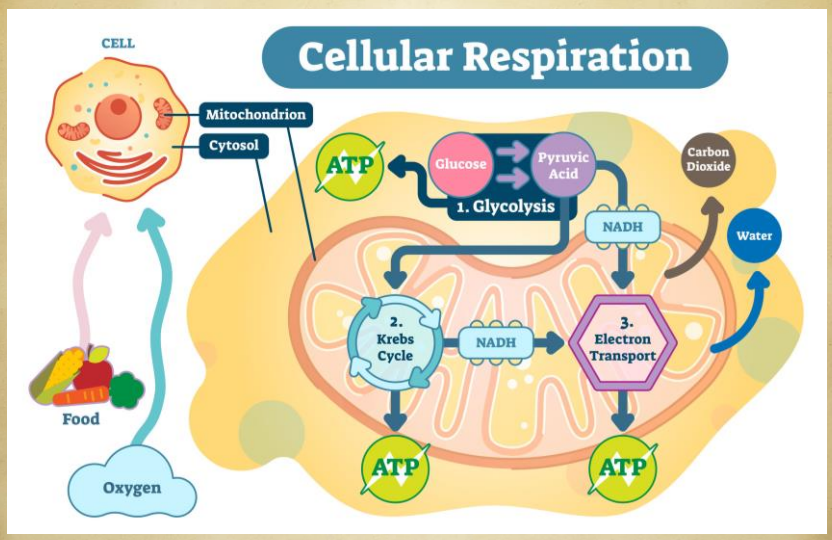
- Food + oxygen = energy (ATP) via mitochondria
  - Glycolysis: glucose —>(10 steps)—> pyruvate (makes two ATP) (or: glycogen —> glucose-6-phosphate—>—> pyruvate: makes three ATP)
  - Alanine transamination (muscle) —> liver —> gluconeogenesis (costs 6 ATP)
  - Pyruvate enters the mitochondria —> acetyl CoA (or: fatty acid breakdown —> acetyl CoA)
  - acetyl CoA —> TCA Cycle —> CO_2, NADH, $FADH_2$
  - NADH and $FADH_2$ —> ETC—> H_2O, ATP
    - Glucose yields 36 ATP from TCA/ETC
    - Fatty acids yield 129 ATP from TCA/ETC

4

The job of the TCA cycle: strip electrons from fatty acids and pyruvate, then add them to NADH and FADH2—> ETC



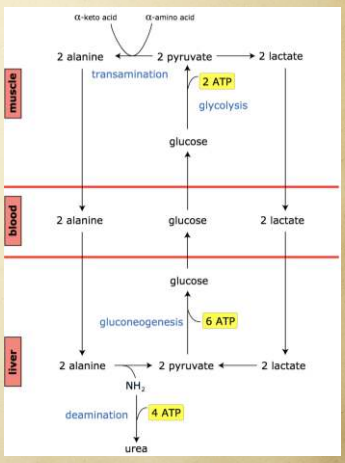
5



6

Pyruvate Transamination

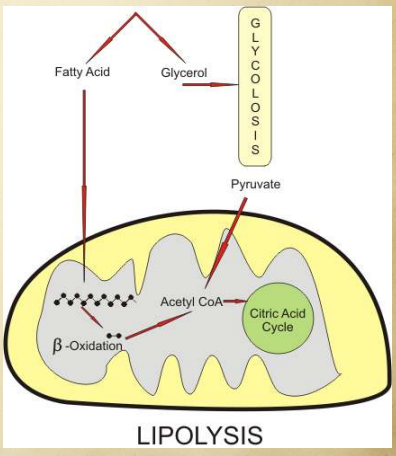
- Muscle recycles pyruvate to alanine
- Sends it to the liver to turn into pyruvate again for gluconeogenesis



7

Carnitine Shuttle

- Fatty acids + Coenzyme A + ATP —> enter outer mitochondrial membrane
- Fatty acyl CoA + carnitine (*from meat, or methionine + lysine in liver and kidneys*) —> fatty acylcarnitine + CoA
- These cross inner mitochondrial membrane, recombining into fatty acyl CoA and carnitine (gets recycled)
- Fatty acyl CoA —> beta oxidation —> Acetyl CoA
- Acetyl CoA —> TCA cycle
- While each glucose makes 38 ATP, each fatty acid (palmitate) makes 129 ATP! (Why people feel more energy on the keto diet)
- Carbs and protein: 4 kCal/gram. Fat: 9 kCal/gram



8

Electron Transport Chain (Oxidative Phosphorylation)

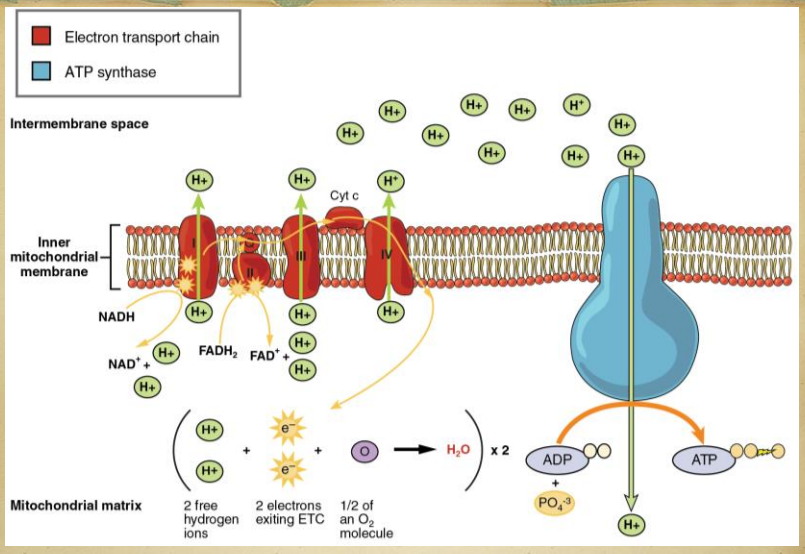
- Five Complexes:
  - Complex 1: removes two electrons from NADH and releases a proton; passes electron to CoQ10. Needs magnesium.
    - ***If electrons leak out of the ETC, it's usually from here, if too much fuel compared to demand or insufficient CoQ10
  - Complex 2: $FADH_2$ enters either from succinate in the TCA or from fatty acids; also donates electrons to CoQ10 (so CoQ10 is reduced from ubiquinone to ubiquinol)
  - Complex 3: contains cytochrome c; gets electrons from CoQ10 (converting it back to ubiquinone)
    - ***second most common place where electrons escape from the ETC, if ATP isn't being used up fast enough

9

Electron Transport Chain (Oxidative Phosphorylation)

- Complex 4: Gets electrons from cytochrome C, adds them to O_2, which turns them into $2H_2O + 4\ H^+$. Requires copper, iron, sulfur.
  - Most often affected by toxins (more later!) Inhibited by H_2S, CO, cyanide (binds to the iron)
- Complex 5: ATPase: One ATP and two H2O for every pair of protons (puts the "phosphorylation" in "oxidative phosphorylation")
  - Coupling: whenever two protons go through
  - Uncoupling: whenever protons are diverted away from here

10



11

Uncoupling the Proton Gradient

- Proton gradient can —> ATP or can —> heat
- For heat: protons pass through uncoupling proteins (UCP)
- This is what makes mammals warm-blooded: happens in internal organs, not just from use of skeletal muscle
- Brown fat has higher amounts of mitochondria and UCPs (high in polar animals to keep warm)
- Uncoupling can happen during times of low energy demand (protecting against runaway oxidative damage)

12

Potential ETC Problems

- If e^- don't make it to their destination (combine with O2 anywhere but at Complex 4)—> superoxide (O^-)
  - Should happen with no more than 4% O2 consumed, which should —> H_2O_2 by superoxide dismutase —> H_2O by glutathione peroxidase
- The ETC is the primary site of endogenous free radical formation
- This leads to oxidative stress in surrounding tissues, subsequent dysfunction, cell death and atrophy
- Worse in cases of hypoxia (such as a stroke): no O2—> bottleneck of e- at Complex 4—> e- leak out and lead to tissue damage
- If insufficient CoQ10, e- leaks out at Complex 1.
- If overeating, e- leaks out at Complex 1
- If not enough exercise, e- leaks out at Complex 3

13

Free Radical Feedback

- Excess superoxide signals the mitochondria: something's broken
- Transcription factors in mtDNA are "redox sensitive": oxidation tells it to make more of whichever complex might be broken
- Supplemented antioxidants would quench this signal, and mitochondria would continue to be inefficient.
  - May be why antioxidant supplementation has not been shown to lengthen life span. Moderate amounts of free radicals might be useful!
- Free radicals primarily damage the mitochondria (membranes and mtDNA) themselves—> lower energy production
- Enough mitochondrial damage and death can initiate apoptosis of the cell.
- As we age, this means atrophy, and degenerative disease

14

Anaerobic Respiration

- Glycolysis: glucose —>(10 steps)—> pyruvate
  - Or: glycogen —> glucose-6-phosphate—>—> pyruvate
- Pyruvate —> lactate (cofactor: NADH, or Vit B3)
- Lactate: low pH—> feedback that more energy is needed, causes burning pain

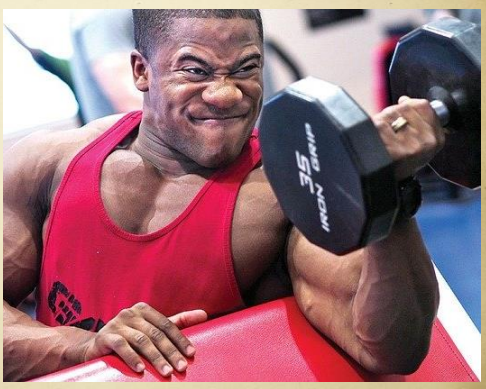


Image by 272447 from Pixabay

15

Diet (Overeating) and Mitochondria

- Excess glucose or fatty acids —> —> high amt of electrons entering the TCA —> ETC
- Electrons leak out mostly at Complex 1 —> superoxide buildup (beyond the hydrogen peroxide compensatory ability) —> oxidative damage, esp to mitochondrial membrane (local)
- One way overeating leads to faster aging.
- As low as 10% caloric restriction has been shown to extend lifespan across species.

Image by Shutterbug75 from Pixabay

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The Ketogenic Diet

- Most common keto dieter claims: more energy, more mental clarity, weight loss
- Brain can use glucose or ketones for energy; 25% ketones usually. When in ketosis >4 days: 70% from ketones
- If glucose usage is inefficient (Alzheimer's: Type 3 DM!), ketones are a good alternative source
- Good for excitotoxicity (seizures, ADD/ADHD): glutamate stimulates glycolysis in astrocytes—> perpetual ATP generation and —> apoptosis. Ketosis bypasses the process.

Image by Steve Buissinne from Pixabay

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Exercise Effects on Mitochondria

- Low energy demand: ATP builds up bc it's not being used; dissociates into ADP and phosphate —> ADP + ADP —> AMP + ATP; AMP gets recycled
- Can lead to e- leakage at Complex 3, superoxide formation, oxidative damage
- Use ATP and you'll make more: ATPase turns back on!
- One way in which exercise is "anti-aging"
- Aerobic exercise 15-20 min, 3-4 times per week increases mitochondria in muscle cells by 50% in 6 wks!

Image by StockSnap from Pixabay

18

Environmental Effects on Mitochondria: Find and Remove Obstacle to Cure!!!

- Heavy metals: Belyaeva EA, Sokolova TV, Emelyanova LV, Zakharova IO. Mitochondrial electron transport chain in heavy metal-induced neurotoxicity: effects of cadmium, mercury, and copper. *ScientificWorldJournal*. 2012;2012:136063. doi:10.1100/2012/136063
- Pesticides and solvents: Zolkipli-Cunningham Z, Falk MJ. Clinical effects of chemical exposures on mitochondrial function. *Toxicology*. 2017;391:90-99. doi:10.1016/j.tox.2017.07.009
- Phthalates and plasticizers: Melnick RL, Schiller CM. Mitochondrial toxicity of phthalate esters. *Environ Health Perspect*. 1982;45:51-56. doi:10.1289/ehp.824551
- Combustion byproducts:"combustion pollutants comprise four main classes: particulate matter (PM), heavy metals, organic pollutants (e.g., dioxins and polycyclic aromatic hydrocarbons or PAHs) and, the more recently realized pollutant-particle systems known as environmentally persistent free radicals (EPFRs)." Lomnicki S, Gullett B, Stöger T, et al. Combustion By-Products and their Health Effects--combustion engineering and global health in the 21st century: issues and challenges. *Int J Toxicol*. 2014;33(1):3-13. doi:10.1177/1091581813519686
- Lyme Disease: Peacock BN, Gherezghiher TB, Hilario JD, Kellermann GH. New insights into Lyme disease. *Redox Biol*. 2015;5:66-70. doi:10.1016/j.redox.2015.03.002
- Toxic mold (mostly clinical) Lieberman A, Curtis L. Mold Exposure and Mitochondrial Antibodies [published online ahead of print, 2020 Feb 21]. *Altern Ther Health Med*. 2020;AT5799.

Image by MonikaP from Pixabay

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Side Note: H_2S SIBO and Complex 4 Toxicity

- H_2S is produced by normal flora: Escherichia coli, Salmonella enterica, Clostridia and Enterobacter aerogenes
- Compensatory mechanism due to low sulfur from diet? (Required for sulfation and glutathione transferase Phase 2 pathways)
- H_2S: Toxic to Complex 4; also means poor detoxification
- For those with SIBO sxs + chemical sensitivity/toxicity + fatigue: think this
- (No testing available yet: sulfite strips on Amazon, Pepto Bismol: bismuth binds to H_2S. If symptomatic relief: diagnostic.)

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Environmental Effects on Mitochondria: Pharmaceuticals

- Pharmaceuticals (just to name a few!)
  - H2 blockers: cimetidine, ranitidine
  - Statins (inhibits CoQ10 synthesis)
  - Beta blockers: deplete CoQ10
  - Amiodarone: inhibit beta oxidation, the ETC
  - psychotropic medications: antidepressants, benzodiazepines, antipsychotics, lithium
  - Valproic acid: depletes L-carnitine —> less beta oxidation
  - Tylenol (depletes antioxidants, esp glutathione)
  - ASA: sequesters CoA
  - ABx: tetracyclines (inhibit beta oxidation), fluoroquinolones

21

Quinolones and Mitochondria

- "It has been suggested that bactericidal antibiotics induce the formation of toxic reactive oxygen species (ROS) in bacteria. We show that clinically relevant doses of bactericidal antibiotics-quinolones, aminoglycosides, and β-lactams-cause mitochondrial dysfunction and ROS overproduction in mammalian cells."

  Kalghatgi S, Spina CS, Costello JC, et al. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. *Sci Transl Med.* 2013;5(192):192ra85. doi:10.1126/scitranslmed.3006055

- Oxidative stress leads to mitochondrial dysfunction

Image by Steve Buissinne from Pixabay

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Mitochondria and Chronic Disease: Chronic Fatigue Syndrome

- Low ATP levels —> ADP + ADP —> ATP + AMP (which gets recycled)
- —> anaerobic metabolism (glycolysis only): faster, but —> lactic acid (pain), low ATP (glycolysis—> only 2!), low ATP building blocks dt AMP recycling so low D-Ribose
- Perpetuates the problem!

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Mitochondria and Chronic Disease: Autism

- "Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as (a) elevated lactate, pyruvate, and alanine levels in blood, urine and/or cerebrospinal fluid, (b) serum carnitine deficiency, and/or (c) enhanced oxidative stress."

Palmieri L, Persico AM. Mitochondrial dysfunction in autism spectrum disorders: cause or effect?. *Biochim Biophys Acta*. 2010;1797(6-7):1130-1137. doi:10.1016/j.bbabio.2010.04.018

24

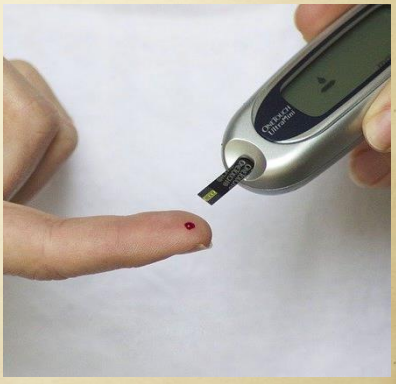
Mitochondria and Chronic Disease: Alzheimer's

- Glutamate hypersensitivity—> mitochondria produce too much ATP —> free radicals leak into cytosol —> mitochondrial damage
- Atrophy due to apoptosis of neurons (secondary to oxidative damage to mitochondria) —> dementia
- *"the link between mitochondrial dysfunction and autophagy in Alzheimer's disease is also discussed. As a result of insufficient digestion of oxidatively damaged macromolecules and organelles by autophagy, neurons progressively accumulate lipofuscin that could exacerbate neuronal dysfunction."*
  - Paula I. Moreira, Cristina Carvalho, Xiongwei Zhu, Mark A. Smith, George Perry, Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology, Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, Volume 1802, Issue 1, 2010, Pages 2-10

25

Mitochondria and Chronic Disease: Insulin Resistance and Diabetes

- Oxidative damage to pancreatic beta cells (say due to toxicity) —> apoptosis —> atrophy —> decreased insulin production
- Hyperglycemia —> superoxide production in endothelial cells —> CVD
- *"One of the defects in metabolic syndrome and its associated diseases is excess cellular oxidative stress… and oxidative damage to mitochondrial components, resulting in reduced efficiency of the electron transport chain."*
  - Garth L. Nicolson. Metabolic Syndrome and Mitochondrial Function: Molecular Replacement and Antioxidant Supplements to Prevent Membrane Peroxidation and Restore Mitochondrial Function. Journal of Cellular Biochemistry 100:1352–1369 (2007)



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Mitochondria and Chronic Disease: Seizures and Excitotoxicity

- In ADD/ADHD, seizures, chemical sensitivity, biotoxin illness, Alzheimer's, etc
- Glutamate—> glycolysis in astrocytes—> eventually apoptosis
- *"Since mitochondrial oxidative phosphorylation provides the major source of ATP in neurons and mitochondria participate in cellular Ca(2+) homeostasis and generation of reactive oxygen species, their dysfunction strongly affects neuronal excitability and synaptic transmission. Therefore, mitochondrial dysfunction is proposed to be highly relevant for seizure generation."*

Folbergrová J, Kunz WS. Mitochondrial dysfunction in epilepsy. *Mitochondrion*. 2012;12(1):35-40. doi:10.1016/j.mito.2011.04.004

27

Mitochondria and Chronic Disease: Heart Disease

- ATP required to maintain gradient for ionic balance in heart
- Atrophy due to apoptosis of cardiac cells —> decreased contractility and diastolic dysfunction —> hypertrophy—> heart failure
- Ischemic events: mitochondria slow down. When O2 is restored, continuing xu of ATP (AMP got removed) means electrons leak out, react with O2—> superoxide radicals (ischemia-reperfusion injury)
- *"Mitochondrial dysfunction is associated with the development of numerous cardiac diseases such as atherosclerosis, ischemia-reperfusion (I/R) injury, hypertension, diabetes, cardiac hypertrophy and heart failure (HF), due to the uncontrolled production of reactive oxygen species (ROS). Therefore, early control of mitochondrial dysfunction is a crucial step in the therapy of cardiac diseases."*

Siasos G, Tsigkou V, Kosmopoulos M, et al. Mitochondria and cardiovascular diseases-from pathophysiology to treatment. *Ann Transl Med*. 2018;6(12):256. doi:10.21037/atm.2018.06.21

Image by Jan Alexander from Pixabay

28

Mitochondria and Chronic Disease: Infertility

- Oocytes have >100K mitochondria per cell
- Age-related infertility: decrease in mitochondrial function, and particularly CoQ10

Xu Y, Nisenblat V, Lu C, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol*. 2018;16(1):29. Published 2018 Mar 27. doi:10.1186/s12958-018-0343-0

- Lower cellular energy —> miscarriage or errors in cell division (such as in Downs Syndrome) or other birth defects

Image by RitaE from Pixabay

29

Mitochondria and Chronic Disease: Cancer

- 1930, Otto Warburg: found higher aerobic glycolysis, gluconeogenesis, and lactic acid production in tumor cells, and reduced fatty acid oxidation dt impaired TCA cycle and oxidative phosphorylation: **i.e. mitochondrial damage**
- Takes 8-10 mutations in a normal cell before it becomes malignant (Some of these can be inherited, so it takes fewer mutations for those people: i.e. cancer predisposition)
- Mitochondria usu trigger apoptosis with cellular damage. But certain mutations prevent this.

Księżakowska-Łakoma K, Żyła M, Wilczyński JR. Mitochondrial dysfunction in cancer. *Prz Menopauzalny*. 2014;13(2):136-144. doi:10.5114/pm.2014.42717

30

Identifying Mitochondrial Dysfunction

- Other symptoms include:
  - muscle weakness, rhabdomyolysis, and loss of muscle coordination
  - Learning disabilities or spectrum disorders
  - Neuropathy and autonomic nervous system dysfunction
  - Parkinson's or Alzheimer's Disease
  - Migraines
  - Visual and hearing problems
  - Chronic Fatigue and Fibromyalgia
  - Schizophrenia and Bipolar Disorder
  - **Can be almost any chronic symptoms!**

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Testing for Mitochondrial Dysfunction

- For inherited dysfunction: DNA testing or muscle biopsy
- Test for suspected toxic offender, if relevant: Solvent urine testing, mycotoxin urine testing and/or biotoxin markers (TGFb1, complement c3a/c4a), heavy metal testing (hair or urine with provoked chelator), Lyme and coinfection testing (Lyme WB — not Abs!, CD57, HLA DR)
- For acquired:
  - lactic acid
  - uric acid (breakdown product of AMP)
  - pyruvate
  - amino acid profile (looking for alanine: lysine under 2.5)
  - carnitine (free and total) and acylcarnitine
  - CoQ10

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Once you've removed the obstacle to cure, then: Optimizing Mitochondrial function

- *TCA Cycle requires: Vitamin B1, B2, B3, B5, B6, iron, magnesium, manganese, cysteine, ALA, zinc, copper*
- *Beta-oxidation: L-carnitine, Vitamin C*
- *Pyruvate dehydrogenase (pyruvate —> Acetyl CoA): B1, B2, B3, B5, ALA*
- *ETC: B2, B6, iron, sulfur, zinc, copper, CoQ10, magnesium*
- **ESSENTIAL COFACTORS**: A B-complex, a multivitamin (with iron if they're low), ALA, NAC, L-carnitine, CoQ10

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Optimizing Mitochondrial Function: CoQ10

- **Found in: beef, herring, chicken, soybean oil, peanuts** (negligible amounts; our bodies must make it from tyrosine + vitamins and trace minerals)
- Both Complexes 1 and 2 feed into CoQ10, which then passes electrons to Complex 3.
- Without CoQ10, no ATP gets made from the mitochondria. Just 2 ATP from glycolysis! (or 3 from glycogen breakdown)
- Serves as an antioxidant in its own right
- I recommend the water soluble ubiquinol form, as it is far more absorbable than ubiquinone.
- Dose: 100-3000 mg (higher doses divided)

Image by Couleur from Pixabay

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Optimizing Mitochondrial Function: L-Carnitine

- Found in: meat, dairy, fish, poultry; synthesized from lysine and methionine (and also requiring iron, Vit C, B6, and B3).
- Remember: 38 ATP from glucose, 129 from fatty acids. Without carnitine: no fatty acids can enter the mitochondria
- Clears lactic acid buildup: restores pyruvate
- Therapeutic range: 500-2000 mg/d

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Optimizing Mitochondrial Function: Magnesium

- Found in: whole grains, almonds and nuts, beans, green leafies, fish, meat
- Necessary cofactor at Complex 1
- Stored in mitochondria; binds to ATP to make it usable (ATP is usually Mg-ATP)
- VERY frequently deficient: lost in urine with dehydration, decreased absorption from PPIs and antacids
- Therapeutic dose: 200-900 mg/d

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Optimizing Mitochondrial Function: D-Ribose

- Building block for ATP (5-carbon backbone)
- In high ATP demand but poor mitochondrial function (or no oxygen), 2 ATP from glycolysis —> ADP + P
  - Eventually via adenylate kinase reaction: ADP + ADP —> ATP + AMP; then the body gets rid of AMP
    - If AMP leaks into cell—> uric acid
  - This depletes D-Ribose; it's slow to make.
  - Taking it speeds things up considerably.
  - Dose: 3-15 grams per day (I usually start with 5 grams)

37

Optimizing Mitochondrial Function: NAC

- Found in: poultry, wheat, dairy, eggs, garlic, onions, meat
- N-Acetyl Cysteine (NAC), the precursor for the powerful antioxidant glutathione, has also been effective in treating mitochondrial dysfunction.
  - Frantz, M.-C. and Wipf, P. (2010), Mitochondria as a target in treatment. Environ. Mol. Mutagen., 51: 462-475. doi:10.1002/em.20554
- Dose: 600-1800 mg/d

Image by Couleur from Pixabay

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Optimizing Mitochondrial Function: Lipid Replacement Therapy

- "Lipid Replacement Therapy (LRT) administered as a nutritional supplement with antioxidants can prevent oxidative membrane damage, and LRT can be used to restore mitochondrial and other cellular membrane functions via delivery of undamaged replacement lipids to cellular organelles."
  - Garth L. Nicolson, PhD. Lipid Replacement as an Adjunct to Therapy for Chronic Fatigue, Anti-Aging and Restoration of Mitochondrial Function. *Journal of the American Nutraceutical Association.* Vol. 6 No. 3, 2003, 22-28
- "Important lipids that require constant replacement are phospholipids, glycophospholipids and other lipids that make up cellular and organelle membranes, especially mitochondrial membranes."
  - Garth L. Nicolson, PhD. Lipid Replacement as an Adjunct to Therapy for Chronic Fatigue, Anti-Aging and Restoration of Mitochondrial Function. *Journal of the American Nutraceutical Association.* Vol. 6 No. 3, 2003, 22-28
- Lipid dosing: EPA 1000-3000 mg, phosphatidylcholine 9 grams

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Optimizing Mitochondrial Function: Thiamin (B1)

- Found in: Brewer's yeast, brown rice, soy, beef, sunflower seeds, whole grains
- Cofactor for pyruvate —> acetyl CoA
- "A recent study found significantly lower lactate levels in patients with thiamine deficiencies after supplementation with thiamine (200 mg)."
  - Donnino, Michael W. M.D.1,2; Andersen, Lars W. M.D.1,3; Chase, Maureen M.D. M.P.H.1; Berg, Katherine M. M.D.2; Tidswell, Mark M.D.4; Giberson, Tyler B.S.1; Wolfe, Richard M.D.1; Moskowitz, Ari M.D.5; Smithline, Howard M.D.6; Ngo, Long Ph.D.5; Cocchi, Michael N. M.D.1,7 for the Center of Resuscitation Science Research Group Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock, Critical Care Medicine: February 2016 - Volume 44 - Issue 2 - p 360-367 doi: 10.1097/CCM.0000000000001572
- Therapeutic dose: 25-200 mg/d

Image by Casey Pilley from Pixabay

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Optimizing Mitochondrial Function: Riboflavin (B2)

- Found in: molasses, green leafies, almonds, whole milk, meats, whole grains
- Needed to make $FADH_2$ from the TCA for Complex 2.
- Therapeutic dose: 25-100 mg/d

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Optimizing Mitochondrial Function: Niacin (B3)

- Found in: peanuts, liver, chicken, fish, brown rice.
- Aka niacinamide, niacin, nicotinic acid, nicotinamide riboside in supplements.
- "NADH is synthesized from niacin (B3) and is required to supply protons for oxidative phosphorylation."

Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem Biol Interact*. 2006;163(1-2):94-112. doi:10.1016/j.cbi.2006.04.014

- Long-term high doses can lead to elevated liver enzymes and liver damage
- Therapeutic dosing: 20-2000 mg/d of nicotinamide riboside (not niacin due to flushing)

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Optimizing Mitochondrial Function: Pantothenic Acid (B5)

- Found in: liver, mushrooms, whole grains, dairy, veggies. Pantothenic acid or pantethine in supplements.
- "Pantothenic acid (B5) is required for coenzyme A formation and is also essential for alpha-ketoglutarate and pyruvate dehydrogenase complexes as well as fatty acid oxidation."
  - Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem Biol Interact*. 2006;163(1-2):94-112. doi:10.1016/j.cbi.2006.04.014
- Without CoA: no pyruvate could get in to the ETC
- Also a necessary component of heme (carrier of O2, required for the ETC)
- Therapeutic dosing: 25-100 mg/d

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Optimizing Mitochondrial Function: Pyridoxine (B6)

- Found in: trout, blueberries, organ meats, molasses, green leafies, whole grains
- Necessary for multiple enzymes in TCA, ETC, heme
- Therapeutic dosages: 25-500 mg/d of pyridoxal-5-phosphate (active form)

Image by Heidelbergerin from Pixabay

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Optimizing Mitochondrial Function: Biotin (B7)

- Found in: egg yolk, organ meats, milk, barley, brewer's yeast, royal jelly
- "Biotin (B7) is the coenzyme of decarboxylases required for gluconeogenesis and fatty acid oxidation."

  Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem Biol Interact*. 2006;163(1-2):94-112. doi:10.1016/j.cbi.2006.04.014

- Therapeutic dose: 10-30 mg/d

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45

Optimizing Mitochondrial Function: Folate (B9)

- Found in: green leafies, berries, citrus fruits, legumes, salmon, eggs, dairy
- B6, folate, and B12: contribute to the methylation cycle, responsible for forming 80% of the body's phosphatidylcholine, necessary for lipid replacement
- Necessary for "initiation of mitochondrial protein synthesis"

  E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence, Clinical Nutrition, Volume 38, Issue 3, 2019, Pages 982-995.

- Necessary for synthesis of purines
- Therapeutic dose: 400 mcg-20 mg/d
- Side note: folate, 5-MTHF, folate, folinic acid; NOT folic acid

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Optimizing Mitochondrial Function: Cobalamin (B12)

- Found in: trout, liver, beef, eggs, salmon
- B6, folate, and B12: contribute to the methylation cycle, responsible for forming 80% of the body's phosphatidylcholine, necessary for lipid replacement
- Methylation —> SAMe—> formation of creatine
- Daily dose: 500-5000 mcg/d of methylcobalamin, adenosylcobalamin, or hydroxycobalamin (NOT cyanocobalamin: toxic to Complex 4)

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Optimizing Mitochondrial Function: Iron

- Found in: meat, poultry, raisins, prunes, whole grains
- Necessary for heme formation, TCA cycle, ETC
- Therapeutic dosing: 18-60 mg/d
- Don't dose unless you've tested and they are anemic or iron saturation is below 22%; can otherwise —> free radicals.
- If ferritin is low and iron saturation is fine, check homocysteine and support methylation if over 7.

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Optimizing Mitochondrial Function: Vitamin C

- Found in: citrus fruits, broccoli, bell peppers
- "Involved in the biosynthesis of carnitine, the key factor in beta-oxidation"

  E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence, Clinical Nutrition, Volume 38, Issue 3, 2019, Pages 982-995
- Therapeutic dose: 500-8000 mg/d (buffered if you get that high!)

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Optimizing Mitochondrial Function: Selenium

- Found in: brazil nuts, walnuts, fish, whole grains, meat, eggs
- This is necessary for mitochondrial biogenesis

  E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence, Clinical Nutrition, Volume 38, Issue 3, 2019, Pages 982-995
- Therapeutic dosing: 200-600 mcg. Toxicity > 1000 mcg/d
- 4 Brazil Nuts daily = about 200 mcg

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Optimizing Mitochondrial Function: Caffeine

- "Increases cAMP resulting in increased effectiveness of complexes I and IV… caffeine may stimulate oxidative phosphorylation."
  - E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence, Clinical Nutrition, Volume 38, Issue 3, 2019, Pages 982-995

Image by Christoph from Pixabay

51

Optimizing Mitochondrial Function: Melatonin

- "Stimulates complexes I and IV, probably by scavenging of ROS, especially peroxynitrite and nitric oxide"
  - E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence, Clinical Nutrition, Volume 38, Issue 3, 2019, Pages 982-995
- "melatonin rescued mitochondria from oxidative stress-induced mitochondrial dysfunction and may prevent subsequent cell death of muscle cells"
  - Hibaoui, Y., Roulet, E. and Ruegg, U.T. (2009), Melatonin prevents oxidative stress-mediated mitochondrial permeability transition and death in skeletal muscle cells. Journal of Pineal Research, 47: 238-252. doi: 10.1111/j.1600-079X.2009.00707.x
- "melatonin affects mitochondria by increasing the activity of the electron transfer system and ATP production, increasing mitochondrial membrane potential and membrane fluidity and by closing the mitochondrial permeability pore."
  - León, J., Acuña-Castroviejo, D., Escames, G., Tan, D.-X. and Reiter, R.J. (2005), Melatonin mitigates mitochondrial malfunction. Journal of Pineal Research, 38: 1-9. doi: 10.1111/j.1600-079X.2004.00181.x
- Dosing: if inadequate sleep, up to 5 mg nightly.

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Optimizing Mitochondrial Function: Lipoic Acid (ALA)

- Found in: spinach, broccoli, yams, potatoes, yeast, tomatoes, Brussels sprouts, carrots, beets, rice bran, red meat
- Necessary for enzymes in the TCA as well as for pyruvate dehydrogenase
- "Involved in energy production as it is an essential cofactor in mitochondrial dehydrogenase complexes"
  - E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence, Clinical Nutrition, Volume 38, Issue 3, 2019, Pages 982-995
- Therapeutic dose: 600-1200 mg

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Optimizing Mitochondrial Function: Creatine

- Found in meat and fish
- Made from methionine, glycine, and arginine
- Stored as creatine phosphate (so can donate a phosphate to ADP). Great for anaerobic activity: why weight lifters and sprinters take it.
- Also protective against ischemic damage for the same reason?
- Dose: 2-10 grams (some do loading doses of 20 grams for the first week)

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Optimizing Mitochondrial Function: PQQ

- Diet sources: cocoa powder (far and away the highest!), kiwis, green peppers, and parsley
- Involved in mitochondrial biogenesis
- Protects against chemical toxicity in the mitochondria
- Antioxidant
- Dose: 10-20 mg

Image by Alexander Stein from Pixabay

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Optimizing Mitochondrial Function: Massage

- "when administered to skeletal muscle that has been acutely damaged through exercise, massage therapy appears to be clinically beneficial by reducing inflammation and promoting mitochondrial biogenesis."
  - Buck Institute for Research on Aging. "Massage reduces inflammation and promotes growth of new mitochondria following strenuous exercise, study finds." ScienceDaily. ScienceDaily, 1 February 2012.

Image by Mariolh from Pixabay

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Optimizing Mitochondrial Function: Cryotherapy and Hydrotherapy

- Cold—> "browns" white adipose tissue (beige fat): higher mitochondria and uncoupling potential
  - Philip A. Kern, Brian S. Finlin, Beibei Zhu, Neda Rasouli, Robert E. McGehee, Jr, Philip M. Westgate, Esther E. Dupont-Versteegden, The Effects of Temperature and Seasons on Subcutaneous White Adipose Tissue in Humans: Evidence for Thermogenic Gene Induction, *The Journal of Clinical Endocrinology & Metabolism*, Volume 99, Issue 12, 1 December 2014, Pages E2772–E2779
- The Wim Hof method?

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Therapeutic Approach

- Identify and remove the obstacle to cure. THEN:
- Soothe and heal tissue
- Give body building blocks it needs to repair

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Case Studies

- SV, 14 yo F
- Tremors with hard running (pt is on cross country team); worse with dairy
  - Labs: low MPV (7.0), high monocytes (8.1) and high basophils (1.6). Wondered about early myeloproliferative disorder; hematologist ruled this out
  - Tx: CoQ10 for CBC abnormalities; Allergy Elimination Protocol
  - Tremors gone x 1.5 yrs, until school schedule changed. Fatigue + increased tremors, controlled with higher CoQ10 dose
    - Labs: cortisol high midday and bedtime
  - Tx: with phosphatidylserine midday and bedtime, fatigue resolved. Had to stay on higher CoQ10: presumed stress on ETC from high ATP demand of running

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Case Studies

- WW, 58 yo M, Chronic Fatigue, Fibromyalgia, insomnia x 6 yrs. On four sleep meds, laundry list of supplements. Poor diet due to no energy to prepare food.
  - alanine: lysine ratio 3.94 (>2.5 suggestive of mitochondrial dysfunction)
  - Tx: niacinamide, L-Carnitine, D-Ribose, glycine for deeper sleep, higher fat diet (pt can't do keto: too much effort)
    - A few weeks later: more good days than before
    - Pt went to Belize for all-inclusive 6 wks: food prepared fresh, no stress. Sleep normalized within a week! No need for naps, energy all day, no pain.
    - Cause here: poor diet? Stress at home (disability paperwork, pressure from his wife that he wasn't working)?

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Case Studies

- DB, 66 yo F
- PTC with muscle weakness and atrophy and anxiety after starting *atorvastatin*. Tx anxiety with *citalopram* which made both worse. Currently managed anxiety with *Xanax*. Walks with a cane. Migratory pain.
- Was already on many mitochondrial supplements
- Statin seemed to trigger *Lyme*: + WB
- Tx: Cowden herbs for Lyme, homeopathic of atorvastatin
  - Able to taper off of Xanax
  - 2 mo later: able to ride a recumbent bike for exercise
  - Muscle strength improved, energy improved, migratory pain mostly gone. Usually does not need a cane.

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Case Studies

- BR, 52 yo F
- PTC with laryngopharyngeal reflux. Pt took an herbal sleep combo —> racing heart —> *atenolol*—> anxiety —> *Xanax + Zoloft* —> GERD, gas, bloating, tingling and numbness
- GERD poorly treated with *Prilosec* —> Nissen fundoplication. On max dose of Dexilant. No relief.
- Pt able to eat only a small handful of foods
- Labs: Comprehensive Stool culture: +4/4 klebsiella, +1 alpha hemolytic strep, +2 beta strep, +4 hemolytic E coli, +2 lactobacillus, microscopic yeast present
- Tx: gut healing (glutamine, NAG, zinc carnosine, probiotics, aloe juice, Grapefruit seed extract, CandidaStat), reverse food elimination (try adding back hypoallergenic foods). Homeopathic phosphorus for burning pain and reflux
  - 3 mo later: gas, bloating, tingling and numbness resolved, GERD much improved, able to reintroduce starchy veggies.
  - 6 mo later: GERD mostly gone; able to reintroduce grains, started Dexilant taper. Repeat stool culture much improved.
    - Then she mentioned fibroids beginning when moving into a new house. Started solvent detox protocol.
  - 1 yr later: Periods much lighter and pain-free. Completely off Dexilant (and all medications). Eating normally.

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Case Studies

- YM, 44 yo F
- PTC with fatigue, persistent rash beginning when she moved into a new house a few years earlier
- On 20 mg hydrocortisone, 3 grains NatureThroid (= to 300 mcg Synthroid)
- Tx: solvent detox protocol x 3 mo; tested for and eliminate food allergies
  - Rash cleared up in 6 wks
  - able to taper her off of hydrocortisone, replaced with 6 mo adrenal support (B vitamins, Vitamin C)
  - Lowered NatureThroid all the way to 1/4 grain (25 mcg)

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Case Studies

- CR, 36 yo F
- PTC mostly bedridden with daily migraines, beginning after moving into a moldy home. Liver pain, chemical sensitivities, bloating, brain fog. Wore sunglasses indoors dt light sensitivity.
- Tried a wide variety of medications, some of which took the edge off and some of which did nothing
- Tested for mold (TGFb1 = 8732), candida Abs (IgG 33, IgA 28)
  - HLA DR: 4-3-53 (multi-susceptible to Lyme and mold)
- Tx: candida protocol (diet, anti fungal, probiotics), activated charcoal, castor oil packs
  - 3 mo later: migraines from daily to 17 per month, liver pain gone, brain fog and bloating gone, sunglasses indoors no longer required
  - 6 mo later: migraines only 1-3 times per month, except when re-exposed to mold. Looked for continued obstacle to cure: CD57 was 32
  - Now: desensitizing her to mold (homeopathic mold nosode), treating presumed Lyme with AL Complex (Byron White)

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Case Studies

- EM, 64 yo F
- Severe asthma, allergies, and chemical sensitivities x 6 yrs since putting in laminate flooring (formaldehyde). Cannot afford to redo floors. Had to stop allergy shots dt aggravation.
- Labs: MARCoNS nasal swab (+), HLA DR (4-3-53: multisusceptible), candida Abs (IgG 111, IgM 11, IgA 19), complement c4a (1079.7), MSH (<8)
- Tx: solvent detox protocol, activated charcoal, BEG spray + Xlear for MARCoNS, Low Dose Immunotherapy (homeopathic) for Yeast
  - 1.5 mo later: asthma significantly better; has not needed an inhaler. Began Toxic Mold Nosode
  - 2 mo later: able to go into stores and browse, nebulizer no longer needed. Able to start allergy shots again. Recommended DNRS protocol

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Thank you!

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Example of Mitochondria Testing

- Metabolic Analysis Profile (Organic Acids): A first morning void (FMV) urine collection

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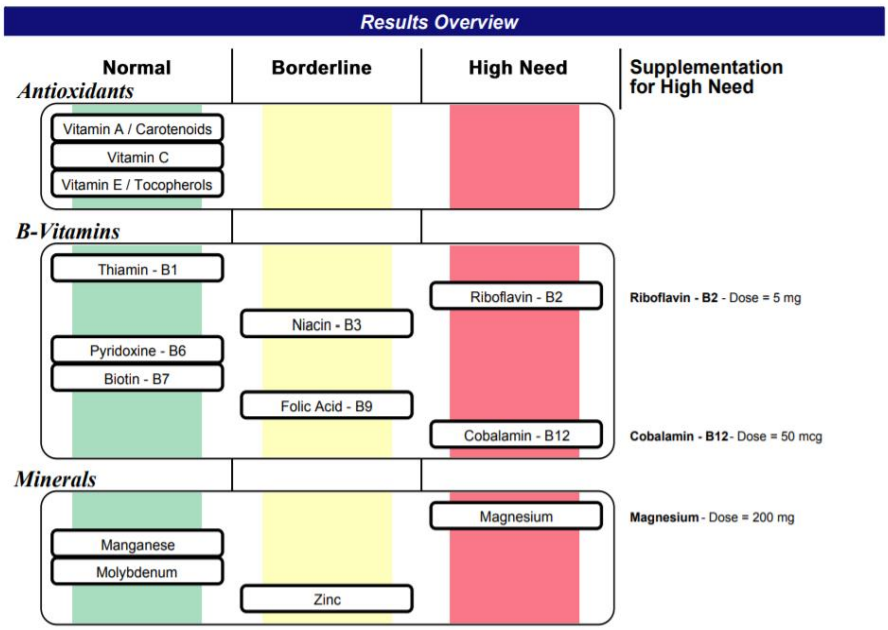

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SUGGESTED SUPPLEMENT SCHEDULE

Supplements	Daily Recommended Intake (DRI)	Patient's Daily Recommendations	Provider Daily Recommendations
Antioxidants			
Vitamin A / Carotenoids	1,000 IU	1,000 IU	
Vitamin C	15 mg	50 mg	
Vitamin E / Tocopherols	9 IU	25 IU	
B-Vitamins			
Thiamin - B1	0.5 mg	1 mg	
Riboflavin - B2	0.5 mg	5 mg	
Niacin - B3	6 mg	20 mg	
Pyridoxine - B6	0.5 mg	1 mg	
Biotin - B7	8 mcg	50 mcg	
Folic Acid - B9	150 mcg	300 mcg	
Cobalamin - B12	0.9 mcg	50 mcg	
Minerals			
Magnesium	80 mg	200 mg	
Manganese	1.2 mg	1 mg	
Molybdenum	17 mcg	25 mcg	
Zinc	3 mg	5 mg	
Digestive Support			
Probiotics		10 B CFU	
Pancreatic Enzymes		5,000 IU	

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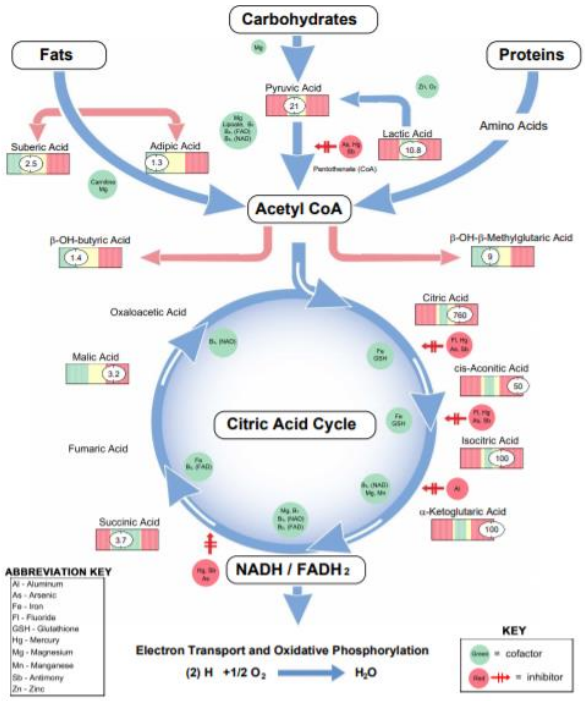

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Metabolic Analysis Markers

All biomarkers reported in mmol/mol creatinine unless otherwise noted.

Malabsorption and Dysbiosis Markers

Malabsorption Markers		Reference Range
Indolelacetic Acid (IAA)	4.0	<= 4.2
Phenyllactic Acid (PAA)	<8	<= 0.15
Bacterial Dysbiosis Markers		
Dihydroxyphenylpropionic Acid (DHPPA)	18.9	<= 12.3
3-Hydroxyphenyllactic Acid	5.8	<= 9.2
4-Hydroxyphenyllactic Acid	19	<= 37
Benzoic Acid	0.10	<= 0.10
Hippuric Acid	340	<= 921
Yeast / Fungal Dysbiosis Markers		
Arabinose	150	<= 132
Citramalic Acid	2.6	<= 5.3
Tartaric Acid	5	<= 20

Cellular Energy & Mitochondrial Metabolites

Carbohydrate Metabolism		Reference Range
Lactic Acid	10.8	3.7-14.6
Pyruvic Acid	21	12-39
β-OH-Butyric Acid (BHBA)	1.4	<= 3.4
Energy Metabolism		
Citric Acid	760	62-648
Cis-Aconitic Acid	50	13-33
Isocitric Acid	100	38-97
α-Ketoglutaric Acid (AKG)	100	12-55
Succinic Acid	3.7	0.8-10.4
Malic Acid	3.2	<= 2.7
β-OH-β-Methylglutaric Acid (HMG)	9	<= 19
Fatty Acid Metabolism		
Adipic Acid	1.3	<= 5.0
Suberic Acid	2.5	<= 4.2

Creatinine Concentration

		Reference Range
Creatinine *	4.1	3.1-19.5 mmol/L

Neurotransmitter Metabolites

		Reference Range
Vanillmandelic Acid	4.2	1.5-5.0
Homovanillic Acid	14.7	1.8-8.6
5-OH-Indoleacetic Acid	24.2	6.4-24.3
3-Methyl-4-OH-phenylglycol	0.13	0.07-0.41
Kynurenic Acid	8.7	<= 9.2
Quinolinic Acid	4.2	<= 11.6
Kynurenic / Quinolinic Ratio	2.07	>= 0.46

Vitamin Markers

		Reference Range
α-Ketoadipic Acid	1.9	<= 2.1
α-Ketoisovaleric Acid	<8	<= 0.85
α-Ketoisocaproic Acid	<8	<= 0.91
α-Keto-β-Methylvaleric Acid	<8	<= 2.3
Formiminoglutamic Acid (FIGlu)	0.6	<= 1.8
Glutaric Acid	0.97	<= 0.92
Isovalerylglycine	1.8	<= 5.4
Methylmalonic Acid	2.7	<= 2.2
Xanthurenic Acid	0.58	<= 1.07
3-Hydroxypropionic Acid	15	6-23
3-Hydroxyisovaleric Acid	25	<= 38

Toxin & Detoxification Markers

		Reference Range
α-Hydroxyisobutyric Acid (from MTBE)	7.5	<= 8.7
Orotic Acid	0.81	0.38-0.91
Pyroglutamic Acid	68	22-64

Tyrosine Metabolism

		Reference Range
Homogentisic Acid	<8	<= 33
2-Hydroxyphenylacetic Acid	0.96	<= 0.99

Metabolic Analysis Reference Ranges are Age Specific

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with *, the assay has not been cleared by the U.S. Food and Drug Administration.

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