Has any one mentioned SupplementsSsSs!? 

Mito Information Day, Melbourne

18th Mar 2017
Christina Liang
Royal North Shore Hospital
Mitochondrial Cocktails
Supplements

• How we think about supplements
  – Why do we take them?
• How we & others use supplements
  – Compared: Australia, US, Netherlands
  – What are we trying to treat?
• Current therapies and supplements
  – Supplements vs what are still in the pipeline
• Examples of some supplements
  – And how they might work
Why crazy about the supplements?

• Patients point of view
  • No specific or curative treatment

  – Pros
  • To improve things
    – Over the counter
    – No prescription
  • Hope: the NEXT BEST THING NOW

  – Cons
  • $$$
  • Tablets/ Powder/ Capsule burden
  • Information overload
Why crazy about the supplements?

• **Doctor’s point of view**
  - No specific or curative treatment

  – **Pros**
    - Try something than do nothing
      - Low risk
    - Hope: “MAYBE something MIGHT WORK a little NOW”

  – **Cons**
    - Unclear evidence – what to advise
    - $$$
    - Tablets/ Powder/ Capsule burden
Not enough data

- None shown to be clearly effective
  - Case reports
  - Open-label trials
  - Retrospective studies
  - Small-scale clinical trials

“Hmm... better go with these.”
Supplements

• How we think about supplements
  – Why do we take them?

• How we & others use supplements
  – Compared: Australia, US, Netherlands
  – **What** are we trying to treat?

• Current therapies and supplements
  – Supplements vs what are still in the pipeline

• Examples of some supplements
  – And how they might work
For 1 gentleman

• Prescribed:
  • Testosterone topical

• Self-prescribed:
  • Ubiquinol 300mg d, D-ribose 1-2 tsp d, Acetyl-carnitine 1-2 tsp d, “Meta B” 1 d, “Cell Food” 10 drops d, Glutamine 1 tsp d

  “Tried many things, these WORK!”

= 1 medication + 6 supplements
For another gentleman

- **Prescribed**
  - Warfarin 5mg nocte, Mirtazapine 15mg nocte, Targin 30/15mg bd, Tramadol 50mg PRN, Paracetamol 1g tds/PRN, Dutasteride 500 mcg/ tamsulosin HCl 400 mcg) d, Candesartan 8mg m, Ezetimibe 10mg d, Tiotropium 18ug cap d, Seretide 250/50 ug inh bd, Natural tears, Zoledronic acid 5mg inf yearly, Creon 25000x2 tds, Omeprazole 20mg mane, Valium 2.5-5mg nocte; Motilium 10mg tds,

- **Self prescribed**
  - Policosinol 1 d, Bitter melon 1 d, CoEnzyme Q10 400mg bd, Magnesium chelate 400mg bd, Ginseng 1 d, “Digestive Enzymes”, “Liver Tonic”, Diatomaceous Earth 1 tsp

= 16 medications + 8 supplements…in 1 day
One more example

- **Prescribed:**
  - Keppra 500mg/1g, Luvox 250mg nocte, Motilium 10mg m, Omeprazole 20mg d, Novorapid 4 units tds ac, Lantus 13 units, Minocycline 50mg d units, Nurofen 2 caps PRN, Aspro, Bactroban 2%

- **Advised**
  - L-Arginine 0.75mg x7 caps qid, Taurine 1000mg x5 bd, 1000mg x 4 bd;

- **Additional supplements:**
  - Lysine 800mg tds, Acetyl L-Carnitine 1g, Pyrroloquinoline 20mg 4x/day, Magnesium 500mg chelate, Fish Oil 2000mg d, MultiEssentials – Ethical Nutrients 1 d, Vit D 1000 IU d, Macuvision Plus 2 d, Bilberry 12000mg 2/d, CoEnzyme Q10 150mg/Vit E 15 IU, “Executive B” 1 d, “Clear Skin” Zinc 12mg, Vit A 1500 IU 2/d; Tumeric 12.5g x 2 tabs bd, “Memory Recall”, “Mega Memory and Stress Clear” 1 d, Lacteze d, Inner Health Plus

= 7 medications, 2 advised, 20 other supplements… still in 1 day
ARTG - Labelling

• Therapeutic goods –
  Australian Register of Therapeutic Goods (ARTG)
  – can be lawfully supplied in Australia

• “AUST R” (registered) medicines
  – assessed for: safety, quality, **effectiveness**
    • all prescription-only medicines
    • over-the-counter: pain relief, coughs & colds, antiseptics

• “AUST L” (listed) medicines
  – assessed for: safety, quality, __________
    • Pre-approved low-risk ingredients.
    • E.g. sunscreens > SPF4, vitamins, minerals, herbal and homoeopathic products.
    • A **purpose** must be included on the label.
Mitochondrial disease patients’ perception of dietary supplements’ use

Amel Karray, Joshua Kriger, Johnston Grier, Amy Holbert, John L.P. Thompson, Sumit Parikh, Michio Hirano

- Any mitochondrial disease
  - Retrospective
  - Self-reported data
  - N = 162

- Majority are/ have been on dietary supplements
  - 75% take > 4 supplements:
    - Majority reported benefits
    - Perceived benefits
      - at 2 weeks – 4 months
    - Safe

- 95% pay up to US$500/month

- Despite other Rx:
  - Medications
  - Physical therapy
  - Diet

- 45.5% thinks supplements are the only intervention improving their symptoms
Most reported symptoms

- Fatigue 61%
- Subjective weakness 50%
- Temperature instability 48%
- Exercise intolerance 42.5%
- Myalgia 38%
- Irritable bowel 33%
- Ptosis 30%
- Headaches/Migraines 28%
- Anxiety 25%
Table 2
Most frequent patients/parents reported symptoms.*

<table>
<thead>
<tr>
<th>Constitutional</th>
<th>Musculoskeletal</th>
<th>Neurological</th>
<th>Gastro-Intestinal</th>
<th>Cardiac</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High frequency symptoms (in &gt;50% of patients)</td>
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<tr>
<td>Chronic fatigue</td>
<td>61%</td>
<td>Weakness</td>
<td>50%</td>
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<tr>
<td></td>
<td></td>
<td>Medium frequency symptoms (in 25-50% of patients)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Temperature instability</td>
<td>48%</td>
<td>Myalgia</td>
<td>38%</td>
<td>Ptois</td>
<td>30%</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>42.5%</td>
<td>Headaches/Migraines</td>
<td>28%</td>
<td>Developmental delay</td>
<td>27%</td>
</tr>
</tbody>
</table>
Karaa et al 2016

- Most common supplements
  - CoEnzyme Q10 (Ubiquinol/ Ubiquinone) 42.5%
  - L-carnitine 36%
  - Riboflavin 26.5%
  - Vitamin D 24%
  - Vitamin C 15%

- 72% no side-effects

- Most common side effects
  - Nausea/ upset stomach 47%
  - Diarrhoea 17%

- < 6% patients discontinued Rx due to side effects
### Types of supplements

<table>
<thead>
<tr>
<th>Supplements</th>
<th>Frequency of intake (%)</th>
<th>Daily doses</th>
<th>Supplements</th>
<th>Frequency of intake (%)</th>
<th>Daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-carnitine</td>
<td>58 (36)</td>
<td>330–5000 mg</td>
<td>Vitamin H (biotin)</td>
<td>7 (4)</td>
<td>100–1000 mcg</td>
</tr>
<tr>
<td>Ubiquinol</td>
<td>51 (31.5)</td>
<td>30–2000 mg</td>
<td>Vitamin K (phytonadione)</td>
<td>7 (4)</td>
<td>25–3200 mcg</td>
</tr>
<tr>
<td>Vitamin B2 (riboflavin)</td>
<td>43 (26.5)</td>
<td>5–400 mg</td>
<td>Folinic acid</td>
<td>7 (4)</td>
<td>0.1–150 mg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>39 (24)</td>
<td>400–50,000 IU</td>
<td>N-acetyl cysteine (NAC)</td>
<td>7 (4)</td>
<td>100–1000 mg</td>
</tr>
<tr>
<td>Vitamin C (ascorbic acid)</td>
<td>24 (15)</td>
<td>120–1500 mg</td>
<td>Citrate (bi, tri, poly)</td>
<td>3 (2)</td>
<td>Variable</td>
</tr>
<tr>
<td>Vitamin B12 (cobalamin)</td>
<td>22 (13.5)</td>
<td>48–1000 mcg</td>
<td>Selenium</td>
<td>2 (1)</td>
<td>75–200 mcg</td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>22 (13.5)</td>
<td>50–2400 mg</td>
<td>l-citrulline</td>
<td>2 (1)</td>
<td>100–1500 mg</td>
</tr>
<tr>
<td>Creatine</td>
<td>22 (13.5)</td>
<td>0.5–12 g</td>
<td>Phosphorus</td>
<td>1 (0.6)</td>
<td>Unknown</td>
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<tr>
<td>Vitamin B1 (thiamin)</td>
<td>21 (13)</td>
<td>5–300 mg</td>
<td>Uridine</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Vitamin E (tocopherol)</td>
<td>20 (12)</td>
<td>200–2000 IU</td>
<td>Succinate</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Ubiquinone</td>
<td>18 (11)</td>
<td>30–2400 mg</td>
<td>Calcium</td>
<td>16 (10)</td>
<td>200–2000 mg</td>
</tr>
<tr>
<td>Magnesium (bisglycinate, gluconate, citrate, rotate)</td>
<td>13 (8)</td>
<td>5–100 mg</td>
<td>Vitamin B6 (pyrodoxin)</td>
<td>14 (8.6)</td>
<td>133–1200 mg</td>
</tr>
<tr>
<td>Vitamin B3 (niacin)</td>
<td>13 (8)</td>
<td>25–550 mg</td>
<td>Magnesium</td>
<td>13 (8)</td>
<td>133–1200 mg</td>
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<tr>
<td>Folic acid</td>
<td>12 (7)</td>
<td>0.8–800 mg</td>
<td>Methionine</td>
<td>14 (6.6)</td>
<td>Blue green algae</td>
</tr>
<tr>
<td>l-arginine</td>
<td>10 (6)</td>
<td>0.5–18 g</td>
<td>NADH</td>
<td>14 (6.6)</td>
<td>Taurine</td>
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<tr>
<td></td>
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<td></td>
<td>Coconut oil</td>
<td>14 (6.6)</td>
<td>Tocotrienols</td>
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<td></td>
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<td></td>
<td>Potassium gluconate</td>
<td>14 (6.6)</td>
<td>Ornithine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SAM-e</td>
<td>14 (6.6)</td>
<td>Alpha-ketoglutarate</td>
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<tr>
<td></td>
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<td></td>
<td>Milk thistle</td>
<td>14 (6.6)</td>
<td>Tart cherry juice</td>
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<td></td>
<td>Green tea extract</td>
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<td>Garlic</td>
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<td>Carotinoids</td>
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<td>Flavonoids</td>
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<td>Turmeric</td>
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<td>Ginger</td>
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<td>Sodium pyruvate</td>
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<td>Spirulina</td>
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</table>
Karaa et al 2016

• Effective
  – 54% reported 5 most bothersome symptoms alleviated
    • Fatigue 49% improved
    • Exercise intolerance 26% improved
    • Muscle pains 26%
    • Weakness 26%

• Less responsive
  <12% improved
  – Gastrointestinal dysmotility symptoms
  – Neurological symptoms
    • Headache, seizures, myoclonus, spasticity
Interesting observations

• No correlation between type of disease & response
• 62/162 thought no improvement
  – But 38% - benefit noted once off supplements
• Among patients reporting no subjective benefits
  – Only 26% discontinued use!
    • Supplements covered by insurance in only 9%
    • 26% respondents pay US$200-500/mo
Dutch study – paediatric n= 24/38, adult n= 33/46 -> 57 responses

88% Children, 91% adults – uses complementary/alternative medicine
  - Children: €489/year
  - Adults: €359/year ~ $580/year

60% adults reported therapies to be effective – Food supplements, homeopathy, self-help techniques

Vitamin supplements e.g. riboflavin, CoEnzymeQ10, Thiamine – *not* perceived to be effective

Self-help techniques e.g. massage, yoga – rated positively
Supplements

• How we think about supplements
  – Why do we take them?

• How we & others use supplements
  – Compared: Australia, US, Netherlands
  – What are we trying to treat?

• Current therapies and supplements
  – Supplements vs what are still in the pipeline

• Examples of some supplements
  – And how they might work
Many different ways of trying to manipulate genetics
  - Difficulty introducing gene/product
    • To various tissues
    • Crossing the blood brain barrier
    • Through the mitochondrial membrane
  - Can be risky - while cell/animal models may show promise
    • Effects unknown in human
      - Some likely detrimental
  - Await further animal models
  - Early human trials
• Small molecules
  - Aiming to boost residual mitochondrial function
<table>
<thead>
<tr>
<th>Manipulating DNA</th>
<th>Examples</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrially-targeted nucleases</td>
<td>Zinc Finger Nucleases</td>
<td>Lack of mutation-derived restriction sites for restriction endonucleases to target</td>
</tr>
<tr>
<td></td>
<td>Transcription Activator Like Effector Nucleases</td>
<td>Specificity of restriction endonuclease targeting</td>
</tr>
<tr>
<td>Manipulating mtDNA with peptide nucleic acids</td>
<td>Peptide nucleic acid</td>
<td>Efficiency of targeting recombinant proteins into cells and mitochondria</td>
</tr>
<tr>
<td>Manipulating tRNA enzymes</td>
<td>Human non-cognate mitochondrial leucyl tRNA synthetase</td>
<td>Solubility</td>
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<tr>
<td></td>
<td>Carboxy-terminal domain of human mitochondrial leucyl tRNA synthetase</td>
<td>Efficiency of delivery</td>
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<tr>
<td>Gene transfer using adeno-associated viral vectors</td>
<td>AAV-ETNE1 (nuclear gene)</td>
<td>Cross reactivity</td>
</tr>
<tr>
<td></td>
<td>AAV-ND4 (mitochondrial gene)</td>
<td>Efficiency of delivery</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>New protein delivery</th>
<th>Examples</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic protein delivery</td>
<td>Transfusion of platelets or erythrocyte encapsulated thymidine phosphorylase</td>
<td>Sustaining thymidine phosphorylase levels</td>
</tr>
<tr>
<td>Cellular and mitochondrial protein delivery</td>
<td>Mitochondrially targeted transcription factor A</td>
<td>Over expression is reported to increase mtDNA copy number, mtDNA deletions and respiratory deficiency</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Small molecule pharmaceuticals</th>
<th>Examples</th>
<th>Challenges</th>
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</thead>
<tbody>
<tr>
<td>Manipulating mitochondrial and nuclear DNA</td>
<td>Bezafibrate</td>
<td>Hepatomegaly and abnormal lipid metabolism in animal models</td>
</tr>
<tr>
<td></td>
<td>AICAR</td>
<td>Potential hepatic side effects</td>
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<td></td>
<td>Resveratrol</td>
<td>Mild gastrointestinal side effects</td>
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<tr>
<td></td>
<td>PAPR inhibitors</td>
<td>Mild side effects including fatigue, nausea vomiting and anemia</td>
</tr>
<tr>
<td></td>
<td>Rapamycin</td>
<td>Hyperlipidemia, poor wound healing and Immunosuppression</td>
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<tr>
<td></td>
<td>Cyclosporin A</td>
<td>Immunosuppression</td>
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<tr>
<th>Stem cell approaches</th>
<th>Examples</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous stem cell therapy for nuclear gene mutations</td>
<td>Bone marrow and stem cell transplantation</td>
<td>Availability of stem cell transplants</td>
</tr>
<tr>
<td>A source of thymidine phosphorylase</td>
<td>Sustaining effect</td>
<td>Side effects of myeloablative protocol</td>
</tr>
<tr>
<td>Endogenous stem cells shifting heteroplasmy</td>
<td>Bupivicaine Injections</td>
<td>Platelet capacity of repair</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>Limited to patients with isolated mitochondrial myopathies</td>
</tr>
</tbody>
</table>
Figure 4: Schematic representation of pharmaceutical modulators of mitochondrial biogenesis. There are multiple signalling pathways involved in mitochondrial biogenesis. PGC-1α (encoded by PPARGC1A), which is a co-activator for a family of transcriptional factors known as PPARs, co-ordinates via a cascade of nuclear encoded proteins the vast majority transcriptional mitochondrial biogenesis. Novel pharmacological therapies aim to modulate PGC-1α mtDNA expression (e.g. PPARα) and protein expression or target downstream pathways. Bezafibrate is pharmacological ligand for the transcriptional co-factor PGC-1α. AICAR activates AMP-activated protein kinase (AMPK) and is thought to modulate increased mitochondrial biogenesis through PGC-1α. The natural polyphenol resveratrol activates sirtuin 1 (SIRT1). Sirtuins are part of a group of oxidizing NAD-dependent protein deacetylases. Upon activation, for example, by PGC-1α or transcription factor A, mitochondrial (TFAM) they promote mitochondrial respiratory chain activities and the transcription of genes modulating mitochondrial biogenesis and function. Nicotinamide riboside can be used to supplement NAD+ levels. PARP1 functions as a NAD+ consuming enzyme. Thus in turn inhibition of PARP1 has been demonstrated to increase NAD+ bioavailability and SIRT1 activity (not shown above) promoting oxidative phosphorylation. Rapamycin inhibits mTOR, which in turn releases mTOR inhibition of autophagy. Cyclosporin A inhibits the mitochondrial permeability transition pore (MPTP). Opening of the mitochondrial permeability transition pore is thought to deplete pyridine nucleotides thus impairing mitochondrial oxidative respiration.
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New treatments for mitochondrial disease—no time to drop our standards


Table 1 | Treatments evaluated in patients with mitochondrial diseases

<table>
<thead>
<tr>
<th>Agent</th>
<th>Specific mechanism(s) of action</th>
<th>Highest level of clinical study in humans</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase of substrate supply to respiratory chain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carnitine</td>
<td>Fatty acid transport for citric acid cycle intermediates</td>
<td>Case report⁷¹</td>
</tr>
<tr>
<td>Niacin</td>
<td>Precursor for NADH, which transfers electrons from intermediates to the respiratory chain</td>
<td>Case report⁷²</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Enhancement of pyruvate dehydrogenase to decarboxylate pyruvate for oxidation</td>
<td>Case report⁷³</td>
</tr>
<tr>
<td>Dichloroacetate</td>
<td>Inhibition of pyruvate dehydrogenase kinase to increase availability of pyruvate for oxidation</td>
<td>Randomized, placebo-controlled crossover trial in MELAS due to m.3243A&gt;G mutation (negative outcome)⁷⁴</td>
</tr>
<tr>
<td><strong>Augmentation of respiratory chain components</strong></td>
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<tr>
<td>Riboflavin</td>
<td>Precursor for flavin adenine dinucleotide, an electron carrier bound to complexes I and II</td>
<td>Open-label study in complex I deficiency (positive outcome)⁴⁹</td>
</tr>
<tr>
<td>Coenzyme Q₁₀</td>
<td>Electron carrier from complexes I and II to complex III</td>
<td>Randomized, placebo-controlled crossover trial (negative outcome)⁷²</td>
</tr>
<tr>
<td>Idebenone</td>
<td>Analogue of coenzyme Q₁₀</td>
<td>Randomized, placebo-controlled crossover trial in Leber hereditary optic neuropathy (negative outcome)⁷⁵</td>
</tr>
<tr>
<td>EPI 743</td>
<td>Analogue of vitamin E</td>
<td>Open-label study in Leigh syndrome and Leber hereditary optic neuropathy (positive outcome)⁷⁶,⁷⁷</td>
</tr>
<tr>
<td><strong>Bypass of respiratory chain components</strong></td>
<td></td>
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<tr>
<td>Succinate</td>
<td>Citric acid cycle intermediate which donates electrons directly to complexes I and II, thus partially bypassing complex I</td>
<td>Case report⁷¹</td>
</tr>
<tr>
<td>Vitamins C and K</td>
<td>Bypass of complex III</td>
<td>Case report⁷³</td>
</tr>
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<table>
<thead>
<tr>
<th>Energy buffering</th>
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<tbody>
<tr>
<td>Creatine</td>
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<tr>
<th>Antioxidant activity</th>
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<tbody>
<tr>
<td>Cysteine</td>
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<td>Lipoic acid</td>
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<td>Dimethylglycine</td>
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<th>Oxidative capacity adaptations</th>
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<tr>
<td>Aerobic exercise training</td>
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<tr>
<td>Resistance exercise training</td>
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<tr>
<th>Nitric oxide metabolism</th>
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<tbody>
<tr>
<td>Arginine</td>
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</table>

Pfeffer, G. et al. Nat. Rev. Neurol. 9, 474–481 (2013); published online 2 July 2013;
• As of 2013:
  – Of 1039 publications on treatment for mitochondrial disease
    • Only 35 included observations on > 5 patients
The Respiratory Chain

Aiming to improve mitochondrial function

• Enhance respiratory chain function:
  – Thiamine
    • enhance pyruvate dehydrogenase activity
  – Nicotinamide riboside
  – Carnitine
    • Help transfer of fatty acid
• Enhance electron transfer
  – Riboflavin
    • Flavin adenine dinucleotide in Complex I, II
  – CoEnzyme Q10
    • From Complexes I and II to III
  – Idebenone, EPI-743

• Bypass specific respiratory chain complexes
  – Vitamin C, K
    • Bypasses Complex III

• Antioxidants – ↓ toxic metabolites
  – Vitamin C, E
  – Alpha lipoic acid
  – Idebenone, CoEnzyme Q10

• Energy buffering
  – Creatine
    • Increase ATP storage through the creatine phosphokinasen system
CoEnzyme Q10

• Final synthesis steps in the mitochondria
  • Involve >12 proteins in yeast, by COQ genes
• ↓ in 22-36% mitochondrial myopathies
  • (Sacconi et al. 2010; Montero et al. 2005)
    – Improved ex tolerance, fatigue, cramps, stiffness 7/8 patients

• Anti-Oxidant
  – Scavenges reactive oxygen species
• Transports electron: Complex I & II to III
• 150mg x 2 tabs (300mg) daily
  ~ $2/day
Coenzyme Q

- **Ubiquinone (oxidised form)**
  - Lipophilic molecule, in cell membranes, mitochondria
  - Transfers electron: Complexes I & II to Complex III
  - Cofactor of dehydrogenases
  - Modulator of permeability transition pore
  - Essential antioxidant

- **Ubiquinol (reduced form)**
  - Better bioavailability shown in rats

$24.99 - 33.99

$54.77 + 8 shipping
CoEnzyme Q10

- Safe
  - No adverse effects to 3000-3600mg/d
- Randomised, placebo-controlled, double-blind, cross-over trial
  - N = 30
    - 15 with MELAS, 11 with CPEO
  - CoQ10 at 600mg twice a day for 60 days
  - Minor effects on
    - Cycle exercise aerobic capacity (15 mins)
    - Post-exercise lactate

- ✓ Primary CoEnzyme Q10 deficiency
  - Clinically and genetically heterogeneous disorder
    - Onset from birth to 7th decade
Most commonly used:
- CoQ10, L-carnitine, creatine, alpha-lipoic acid, B-vitamins/riboflavin
- CoQ10 – should be offered to most patients
  - Ubiquinol – most bioavailable
- Alpha lipoic acid and riboflavin should be offered
- Folinic acid
  - considered in those with CNS manifestations
- L-carnitine for patients with documented deficiency
  - Levels monitored
Idebenone

- **Short-chain benzoquinone**
  - Synthetic analogue of CoQ10
    - Shorter, less lipophilic tail to quinone
      - Different solubility
  - Antioxidant
  - Mitochondrial electron carrier
    - Bypasses Complex I
    - Transfers electrons to Complex III
      - Helpful in Complex I deficiency
- 150mg tabs x 60 ~ $62 ie $6.2/day
- For 900mg/d for 6 months
  - = $5766.93
Rescue of Hereditary Optic Disease Outpatient Study — a randomised, placebo-controlled, double-blind clinical trial

- Leber’s hereditary optic neuropathy
  - N= 85 Idebenone vs placebo 2:1 ratio
  - First vision loss within 5 years of enrolment
  - Benefitted those with discordant visual acuities
    - Benefit persisted after ~ 30 months

- Idebenone oral 300mg x3 a day
  - for 24 weeks
    - Persistent beneficial effects in preventing further vision impairment
    - Promoting recovery of inactive-but-viable retinal ganglion cells
Idebenone

- Linear dose-proportional pharmacokinetic profile
  - Rapidly absorbed
    - Median time to Max plasma concentration
      - 0.67h to 1.17h after high fat meal
  - Take with food increases bioavailability 5-7x
  - Crosses blood brain barrier
  - Rapid, extensive first-pass metabolism

- Phase 2a Clinical trial of idebenone in MELAS
  - N= 27 completed end 2015
  - Dose 900-2250/day
    - Measure of lactate – on MR spectroscopy, venous
    - Fatigue scale
  - Results pending publication
L-arginine

• Dose oral 0.3mg/kg/d maintenance
  – If 70kg -> 21g/d = 7 capsules x3/day
    • 500, 750, 1000mg capsules, powder
      – 5-20g twice daily

• ~$4400/year

• In patients with recurrent stroke-like episodes
  – MELAS – mitochondrial encephalopathy, lactic acidosis and stroke-like episodes
L-arginine

- Nitric oxide precursor/donor
- In MELAS + stroke-like episodes
  - ✔️ ↓ recovery time from episodes
  - ✔️ ↓ frequency
  - ✔️ ↓ severity
  - N= 24; 34 stroke-like episodes

» Koga et al. 2005)

• Loading dose of L-arginine 0.5g/kg given within 3 h of symptom onset
  – IV infusion for next 3-5 days
    • “though no clinical evidence on how long to continue
• Dextrose containing fluids
  – To avoid catabolism
• Oral L-arginine 0.15-0.30g/kg
  – 3 divided doses to continue
L-Arginine Affects Aerobic Capacity and Muscle Metabolism in MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes) Syndrome

Lance H. Rodan¹, Greg D. Wells²,³, Laura Banks²,³, Sara Thompson³, Jane E. Schnellderman²,³, Ingrid Teln¹,⁴ *

• Perhaps improves aerobic capacity/muscle metabolism in MELAS/m.3243A>G mutation
  – N = 3 MELAS young siblings, 4 controls
    • Only MELAS patients had L-arginine
  – Single dose
  – 6 week supplementation at 0.1g/kg/d
• **Oral L-Citrulline** -> L-Arginine in kidneys

• **N = 5 children with MELAS, 5 controls**
  – Nitric oxide production rate increased
    • Higher with citrulline cf arginine
  – Citrulline supplementation increased de novo arginine synthesis
Taurine

- **Role in modifying genetic code**
  - Post-transcriptional modification in tRNAs
  - Defective in mutant mitochondrial tRNA\(^{\text{Leu}}\)
- **In cell model**
  - Taurine ameliorates impaired mitochondrial function
- **Prevented stroke-like episodes in 2 MELAS patients for > 9 years**
  - 21 yo male, 29 yo female
  - High dose 0.25g/kg/d
- **If 70kg -> 17.5g/d**
  - 1g capsules – 100 cap = $15
    - Lasts 5 days
The Sirtuin pathway

• **Resveratrol** (in wine)
  – Mimics anti-ageing effects of caloric restriction
  – Increases SIRT1
    • Helps mice on high fat diet from diabetes, weight gain

• **Pterostilbene**
  – More bioavailable than resveratrol in mice

• **NR** (small amount in milk) -> NAD+
  – Fuels sirtuins activity
    • SIRT 1 helps insure signal between cell’s nuclei and mitochondria
    • SIRT 3 keeps mitochondrial running well
Resveratrol

• Natural polyphenol
  – From red wine
• Increases NAD+ (oxidized nicotinamide adenine dinucleotide)
  – Activate protein deacetylase SIRT1
    • Activates PGC-1alpha
      – Promoting mitochondrial biogenesis and function
        » Canto & Auwerx, 2009; Kanabus et al., 2014
• Showing promise in Friedreich’s ataxia
  – Open-label pilot clinical study
    • Mild GI side effect
      » Delatycki, 2012; Yiu et al., 2013
• Restore normal function in human fibroblasts with problem with mitochondrial fatty acid beta-oxidation
  » Bastin et al., 2011; Mizuguchi et al, 2017

• Cost
  – 1 cap = 420mg trans-resveratrol (70mg grape seed extract)
  – 60 caps = AU$38
Nicotinamide riboside

- Aim to increase NAD+ bioavailability - precursor
  - Form of Vitamin B3
  - To improve oxidative phosphorylation
    - Advertised for “endurance, performance, weight management, cardiovascular health, anti-aging, cognitive function, neuroprotection”

- Promising in
  - Mouse model – Sco2 (nuclear gene) mouse
    - Improved ex intolerance
      » Cerutti et al., 2014
  - Deletor mouse (nuclear gene mutation causing mtDNA deletions)
    - Improve mitochondrial biosynthesis
      » Khan et al., 2014
        - Dose 400mg/kg/d

- 100-125mg tabs
  - 60 tabs = AU$52.48
Folinic Acid

- Folate, Folic acid, Folinic acid
  - dihydrofolate reductase
- Kearns-Sayre Syndrome
  - Cerebral folate deficiency
- N = 6
  - Aged 8-17 years
  - 1-3mg/kg/d
- Outcome
  - MRI
  - Cerebral 5-methyltetrahydrofolate deficiencies
  - Newcastle paediatric mitochondrial disease scale
- 800ug cap
  - 60 cap for $15
    - For a 40 kg person at 1mg/d
    - Need to take 50 caps a day!!
Others

- Riboflavin 100-300mg/d
  - Complex 1 deficiency
    - Riboflavin at high dose effective
  - Case reports N <5
- Creatine 5g bd x14d -> 2g bd x7d
  - N = 7 improved high intensity activities
- L-Carnitine 50-200mg/d…1g/d
  - improved muscle strength
  - N= 21
Supplements

- How we think about supplements
  - Why do we take them?
- How we & others use supplements
  - Compared: Australia, US, Netherlands
  - What are we trying to treat?
- Current therapies and supplements
  - Supplements vs what are still in the pipeline
- Examples of some supplements
  - And how they might work
Home message

• Human clinical trials ongoing
  – Larger, newer agents

• Animal studies not always translate to human use
  • Animal studies - 1/3 -> Human trials – 1/10 to use

• N of 1 trial
  – Don’t keep accumulating
    • If without clear effect
    • Use $$$ wisely

Pfeffer, et al. Nat Rev Neuro 2013
Thank you for your attention

• Thank you for your patience