Challenging the Glaucoma Archetype 2

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ANATOMICAL ISSUES AND GLAUCOMA

CENTRAL CORNEAL THICKNESS

Patients with Normal Tension Glaucoma have Thinner Corneas.

WHY?

SLEEP APNEA AND GLAUCOMA

...the odds of an individual diagnosed with sleep apnea having glaucoma is 1.736 times the odds of individuals without sleep apnea having glaucoma in this patient population. We recommend that questions concerning sleep-disturbed breathing be included for patients suspected of having glaucoma. Similarly, we recommend that patients diagnosed with glaucoma be questioned about the risk factor of sleep-disturbed breathing.

Boyle M, Semes L, Fuhr P, Clay O. AAO Poster Session
**Obstructive sleep apnea leads to reduced sensitivity in the visual field.**

**Oxygen desaturation was not found to be statistically related to glaucoma or sleep disorder.** Roberts TV, Hodge C, Graham SL, et al. Prevalence of nocturnal oxygen desaturation and self-reported sleep-disordered breathing in glaucoma. J Glaucoma 2009;18:114-118.


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**Sleep apnea patients should be referred for assessment of associated eye disorders.** McNab AA. The eye and sleep apnea. Sleep Med Rev 2007;11:269-276

**The prevalence of glaucoma in patients with obstructive sleep apnoea is an estimated 27%.** Sex, age, body mass index or apnoea plus hypopnoea index are not factors influencing the presence of glaucoma in this population of patients. Bendel RE, Kaplan J, Hecken M, et al. Prevalence of glaucoma in patients with obstructive sleep apnoea: a cross-sectional case-series. Eye (Lond) 2008;22:1105-1109

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**There is not a strong support of the impact of sleep apnea on the eventual development of glaucoma relative to other putative factors.** Girkin CA, McGraw G, McNeal SF, Overley C. Is there an association between pre-existing sleep apnea and the development of glaucoma? Br J Ophthalmol 2005;90:679-681

Prevalence of sleep apnea in NTG 0% under 45, 50% ages 45-64, 63% over 64. NTG patients should be checked for sleep apnea. Mojon DS, Hess CW, Goldblum D, et al. Normal-tension glaucoma is associated with sleep apnea syndrome. Ophthalmologica 2002;216:180-184.


There is also an association to ION and ODE Br J Ophthalmol 2007;91:1524, Am J Ophthalmol 2007;144:953

Moderate to severe OSA is associated with a higher incidence of VF defect and glaucomatous optic nerve changes. Tsang CS, Chong SL, Ho CK, Lo MF. Moderate to severe obstructive sleep apnea patients is associated with a higher incidence of visual field defect. Eye (LOND) 2006;20:38-42.

The sleep apnoea syndrome is correlated with a proportional decrease in the RNFL. Decreased ocular perfusion related to hypoxia and vasospasm associated with OSAS may cause RNFL thinning, which may precede clinically detectable glaucoma. Kargi SH, Altin R, Koksal M, et al. Retinal nerve fibre layer measurements are reduced in patients with obstructive sleep apnea syndrome. Eye (Lond) 2005;19:575-579

SO SHOULD PATIENTS WITH SLEEP APNEA BE WORKED UP FOR GLAUCOMA AND SHOULD GLAUCOMA PATIENTS BE UNDER SUSPICION FOR SLEEP APNEA???

Conclusion???
BEHAVIORAL ISSUES AND GLAUCOMA

SMOKING AND GLAUCOMA

The direct relationship to glaucoma, however, appears to be controversial as studies and reviews fail to establish a firm link between either smoking or environmental smoke and glaucoma development. Yet the same studies recommend that cessation of smoking is important in the management of glaucoma patients. Arch Ophthalmol 2003;121(12):1762-1768, J Glaucoma 2008;17(7):558-566, Br J Ophthalmol 2008;92(10):1304-1310.

The issue of smoking is proven to be a risk factor for the presence of glaucoma. J Glaucoma 2009;18(6):423-428.

The most critical risk factors associated with blindness in high tension glaucoma, however, were elevated initial IOP, fluctuation, poor control, noncompliance and late detection. Clin Ophthalmol 2008;2(4):757-762 while the for angle-closure the risks include hypertension, family history, shallow anterior chamber and large CD. Zhonghua Yan Ke Za Zhi 2008;44(6):503-506.

In one large collaborative study it was shown that surgically treated patients with glaucoma had lower IOPs if they were non-smokers. Ophthalmology 2008;15(6):927-933.


In an interesting study on the effects of smoking on normotensive patients it was found that both IOP and BP increased secondary to the nicotine in cigarettes. Niger J Physiol Sci 2007;201-2;33.36.

Conclusion???
OBESITY AND GLAUCOMA

Presence of metabolic syndrome increases risk of OHTN in males 2X and females 5X. Metabolic syndrome defined as having three or more of the following:
1. high blood pressure
2. elevated serum triglycerides
3. low HDL
4. elevated fasting glucose levels
5. large waist circumference

Imai K, Hamaguchi M, Mori K et al. Metabolic syndrome as a risk factor for high-ocular tension. Int J Obes 2010;34:1209-1217

There is certainly a suggestion that there is an association of insulin resistance and the metabolic syndrome to increased intraocular pressure.


Body Mass Index appears to have an association with elevated intraocular pressure.

Certainly initial reaction to this fact among clinicians would be to point to neck size and positive pressure as a related factor with sleep apnea falling into the picture. 

The relationship of cerebrospinal fluid pressure elevation, Idiopathic Intracranial Hypertension, serum cortisol, and sleep apnea also create an interesting scenario for elevated intraocular pressure.

**EXERCISE AND GLAUCOMA**

Caution: Pigmentary Dispersion

Exercise reduces IOP and the reduction is sustainable. In another study it was shown that in persons with increased IOP, regular, moderately intense aerobic exercise rather than short-lived intense exercise is more useful. Another study showed that exercise changes Ocular Perfusion Pressure and produces increased tissue blood flow in the retina in the immediate post-exercise period, while blood flow increases more persistently in the choroid-retina.
Exercise has an additive effect of lowering intraocular pressure regardless of the class of IOP medication or the number of medications. There is a 2-3 mm Hg reduction after just 5 minutes of aerobic activity. **CAUTION WITH PIGMENTARY DISPERSION.**


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**Conclusion??**
Inflammation is the Root of All Evil

RELATIONSHIPS

- **CELL SURVIVAL FACILITATED BY T-CELLS**

MMP INHIBITORS Like Doxycycline

- **MMP is ELEVATED IN GLAUCOMA PATIENTS**

- **MMP INHIBITION BLOCKS RGC APOPTOSIS AND THE BLOCKERS ARE EFFECTIVE AS ANTI-INFLAMMATORY AGENTS**

- **CAUTION: ENHANCE ANTICOAGULATION EFFECTS OF WARFARIN**
  (Cornea, 2002;21:542)

Omega 3 Fatty acids, particularly docosahexaenoic acid (DHA), are highly concentrated in brain and retinal tissue and may prevent or delay the progression of dementia and AMD. Low dietary intakes and plasma concentrations have been reported to be associated with dementia, cognitive decline, and AMD risk. ...unpublished observations from the Framingham Heart Study suggest that > or =180 mg/d of dietary DHA (approximately 2.7 fish servings/wk) is associated with an approximately 50% reduction in dementia risk. Am J Clin Nutr 2006;83:1484S
Altering free radicals with steroids, which paradoxically could increase intraocular pressure, may block lipid peroxidation. This is primarily achieved through suppression of inflammation. 


**Immune System influences including antibodies generated by B-cells within the rubric of the general inflammatory process lead to cell death in glaucoma. Protection also occurs through the immune system pointing to the importance of proper modulation of the immune system.**

*Cell Mol Neurobiol* 2001;21:817

C-reactive protein (CRP) elevation is also associated with CSVD indicating an inflammatory process, and the elevated CRP levels are also found in NTG patients. The CRP increases endothelin which has been implicated in the proliferation of astrocytes in the nerve head and changes in the trabecular meshwork and has been found to be elevated in glaucoma and NTG after exposure to cold temperatures.


**Immune System influences including antibodies generated by B-cells within the rubric of the general inflammatory process lead to cell death in glaucoma. Protection also occurs through the immune system pointing to the importance of proper modulation of the immune system.**

*Cell Mol Neurobiol* 2001;21:817

Autoimmunity is at the root of most disorders and is defined as an attack on the host cell by activated T cells. It has actually been shown that survival of RGCs after optic nerve injury is facilitated by the autoimmune response via activated T cells. This response can either be by active immunization with a protein or by transfer of activated T cells.

TNF-α is a pro-inflammatory cytokine that is present during excitotoxic and ischemic brain injury. Among other functions, it binds to the death receptor and can induce caspase components of the mitochondrial cell death pathway. TNF-α has been implicated as a mediator in RGC death.


TNF-α inhibitors (GLC756) are being investigated for the treatment of glaucoma.


**Immune System Changes in AD**
- Elevated IL-1a, IL-2, IL-6, IL-12, TNF-α
- Elevated inflammatory Eicosanoids, PG-D2, PG-E2, TXB2
- Elevation in Complement
- Elevation in Matrix Metalloproteinase
- Elevation in Adhesion Molecules
- Elevation in levels of Zinc

**SO SHOULD WE LOOK AT WAYS TO MINIMIZE INFLAMMATION IN GLAUCOMA??**

**How about**
- Obesity
- Exercise
- Lack of Sleep (Raises Inflammation)
- Diet
- Supplements
- Smoking and Air Pollution
- BALANCE ☯☯
THE rTG VS EE FISH OIL CONTROVERSY

TABLE 2. THE DOSAGE AND COMPOSITION OF THE CAPSULES WITH RELATIVE AND ABSOLUTE AMOUNTS OF EPA AND DHA

<table>
<thead>
<tr>
<th></th>
<th>Re-Ester</th>
<th>Free FA</th>
<th>Ethyl Esters</th>
<th>Fish Body Oil</th>
<th>Cod Liver Oil</th>
<th>Com Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of Caps</td>
<td>650</td>
<td>650</td>
<td>650</td>
<td>1000</td>
<td>500</td>
<td>650</td>
</tr>
<tr>
<td>Caps/Day</td>
<td>5 + 5</td>
<td>5 + 5</td>
<td>5 + 5</td>
<td>6 + 7</td>
<td>17 + 17</td>
<td>5 + 5</td>
</tr>
<tr>
<td>EPA %</td>
<td>28.5</td>
<td>33.5</td>
<td>26.8</td>
<td>19.7</td>
<td>8.1</td>
<td>9</td>
</tr>
<tr>
<td>DHA %</td>
<td>19.8</td>
<td>21.5</td>
<td>21.4</td>
<td>11.4</td>
<td>11.0</td>
<td>9</td>
</tr>
<tr>
<td>n-6 FA %</td>
<td>4.9</td>
<td>2.2</td>
<td>3.9</td>
<td>2.5</td>
<td>2.2</td>
<td>96.7</td>
</tr>
<tr>
<td>Mono unsat FA %</td>
<td>13.3</td>
<td>12.1</td>
<td>15.7</td>
<td>26.9</td>
<td>51.8</td>
<td>29.0</td>
</tr>
<tr>
<td>1 Sat fat FA %</td>
<td>1.0</td>
<td>2.8</td>
<td>6.0</td>
<td>27.5</td>
<td>16.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Tocoph mg/day</td>
<td>3.7</td>
<td>3.5</td>
<td>3.9</td>
<td>1.1</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>EPA g/day</td>
<td>1.85</td>
<td>2.18</td>
<td>1.97</td>
<td>2.04</td>
<td>1.38</td>
<td>0</td>
</tr>
<tr>
<td>DHA g/day</td>
<td>1.29</td>
<td>1.40</td>
<td>1.39</td>
<td>1.48</td>
<td>1.87</td>
<td>0</td>
</tr>
<tr>
<td>EPA + DHA g/day</td>
<td>3.1</td>
<td>3.6</td>
<td>3.3</td>
<td>3.5</td>
<td>3.2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note the levels of saturated fats for each supplement.

TABLE 3. MEAN DIFFERENCE BETWEEN BASELINE AND END OF STUDY REGARDING THE AMOUNT OF EPA AND DHA IN SERUM LIPIDS IN MG/L

<table>
<thead>
<tr>
<th></th>
<th>CE</th>
<th>PL</th>
<th>TG</th>
<th>FFA</th>
<th>FO</th>
<th>CLO</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA</td>
<td>71.0</td>
<td>4.8</td>
<td>75.8</td>
<td>60.5</td>
<td>27.1</td>
<td>87.6</td>
<td>15.9</td>
</tr>
<tr>
<td>DHA</td>
<td>53.1</td>
<td>3.5</td>
<td>56.6</td>
<td>52.8</td>
<td>5.6</td>
<td>58.4</td>
<td>15.4</td>
</tr>
<tr>
<td>EPA + DHA g/l</td>
<td>94.1</td>
<td>8.3</td>
<td>95.9</td>
<td>72.3</td>
<td>32.7</td>
<td>96.0</td>
<td>21.3</td>
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<td>96.0</td>
<td>21.3</td>
</tr>
</tbody>
</table>
Table 5. Costs of obtaining 1000 mg of EPA utilizing the bioavailability factor

<table>
<thead>
<tr>
<th>Ethyl Ester Product</th>
<th>TG Backbone Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products 1 and 2</td>
<td>$1.67/day to achieve 1700 mg</td>
</tr>
<tr>
<td>Products 3 and 4</td>
<td>$1.89/day to achieve 1700 mg</td>
</tr>
<tr>
<td>Products 1 and 2</td>
<td>$0.96/day to achieve 1000 mg</td>
</tr>
<tr>
<td>Products 3 and 4</td>
<td>$1.69/day to achieve 1000 mg</td>
</tr>
</tbody>
</table>

Table 6. Costs of obtaining 1000 mg of EPA without using the bioavailability factor

<table>
<thead>
<tr>
<th>Ethyl Ester Product</th>
<th>TG Backbone Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products 1 and 2</td>
<td>$0.98/day to achieve 1000 mg</td>
</tr>
<tr>
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<td>$1.10/day to achieve 1000 mg</td>
</tr>
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</tr>
</tbody>
</table>

Figure 4. Formula for calculating cost per day for supplement requirements

\[
	ext{COST$ /day} = \text{COST$ /capsule} \times \text{Number of capsules needed / day}
\]

Alexander 2010

The Omega Rx Zone

- Adults with specific chronic conditions should consume at least 4 grams of EPA/DHA per day – Loading Dose
- After loading (one month) adults should consume at least 2 grams of EPA/DHA per day – Maintenance Dose
- Children/Infants should consume at least 1/2 gram of EPA/DHA per day

As recommended by: Food & Drug Administration (FDA); American Heart Association (AHA); American Associate of Family Practitioners (AAFP); and American Cardiology Association (ACA)

Lovaza (Omega-3-Acid Ethyl Esters)

Drug Information

- Impotence
- Asthma
- Endometrial Carcinoma
- Gastrointestinal

Omega-3 Fatty Acids and Bleeding

The relevant clinical question is the following: What is the evidence that taking omega-3 fatty acids at doses of 4 grams per day causes clinically significant bleeding?
Conclusion???

**NewsFlash!!!**

- 528 IU/DAY D3 ASSOCIATED WITH 7-8% DECREASE IN DEATH RATE
- Therefore

  **DO NOT RECOMMEND VIT D3 SUPPLEMENT AS YOU WANT YOUR GLAUCOMA PATIENT TO DIE BEFORE THEY GO BLIND**

**NUTRITIONAL ISSUES AND GLAUCOMA**

Natural and synthetic compounds have been reported to have neuro-protective capabilities including all antioxidants, inhibitors of glutamate release, calcium channel blockers, polyamine antagonists, nitric oxide synthase inhibitors, cannabinoids, aspirin, melatonin and vitamin B-12. *(Curr Opin Ophthalmol 2000;11:78)*

It has also been suggested that metabolic inhibition-EATING LESS- is also neuroprotective. *(Ann NY Acad Sci 1999;890:240)*
Mitrogenol-bilberries + pycnogenol significantly increased velocity of blood flow through ophthalmic arteries, central retinal arteries, and posterior ciliary arteries while lowering IOP in ocular hypertension.


Ascorbate and glutathione concentrations decreased in exfoliation syndrome while reactive oxygen species are increased. Antioxidant potential (ROS) plays some role in the pathogenesis of glaucoma.


….. unpublished observations from the Framingham Heart Study suggest that > or =180 mg/d of dietary DHA (approximately 2.7 fish servings/wk) is associated with an approximately 50% reduction in dementia risk.

At least this amount of DHA is generally found in one commercially available 1-g fish oil capsule given daily.

HYPERHOMOCYSTEINEMIA AND GLAUCOMA
The plasma level of Hcy was found to be increased only in PXG patients and the plasma levels of vit-B6 were found to increase in the NTG and POAG sample groups. Using homocysteine and vit-B6 levels as the determinants of hyperhomocysteinemia still needs further research. Turgut B, Kaya M, Arslan S, et al. Levels of circulating homocysteine, vitamin B6, vitamin B12, and folate in different types of open-angle glaucoma. Clin Interv Aging 2010;26:133-139.

Hyperhomocysteinemia was found in 27.1% of PXFG patients, 30.6% of POAG patients, and 29.4% of NTG patients. Clement CL, Goldberg I, Healey PR, Graham SL. Plasma homocysteine, MTHFR gene mutation, and open-angle glaucoma. J Glaucoma 2009;18:73-78

PEXG and Alzheimer's disease share common associations such as the higher prevalence of hyperhomocysteinemia in both disorders. Folate, vitamin B12 and B6 levels were significantly decreased and associated with elevated Hcy levels in PEXG. Rowell JB, Bleich S, Reulbach U, et al. Vitamin deficiency and hyperhomocysteinemia in pseudoexfoliation glaucoma. J Neural Transm 2007;114:571-575.

Hyperhomocysteinemia is a risk factor for thromboembolic vasculopathy in patients with PEXS and PEXG. Therefore, vitamin B supplementation should be considered in these patients when hyperhomocysteinemia is detected. Sarıçoğlu M, Korkut A, Songen A, Hastig H. Plasma homocysteine levels and vitamin B status in patients with pseudoxfoliation syndrome. Saudi Med J 2006;27:833-837.


Elevated homocysteine levels have also been associated with WMLs. (ISR 2007:6:18)

400 to 1000 mcg of folic acid per day, 10 to 50 mg of vitamin B6, and 50-300 mcg of vitamin B12 per day + N-ACETYLCYSTEINE (Acta Cardiol. 2007;62:579)

Conclusion???

HOW DO YOU MANAGE GLAUCOMA?
Let’s Go Outside the Box

GET THE PRESSURE DOWN WITH MINIMAL FLUCTUATION
HOPE THAT THE PATIENT COMPLIES
HOPE THAT THE PATIENT DOES NOT RUN OUT OF MONEY
HOPE THE PATIENT GOES TO A BETTER PLACE BEFORE THEY GO BLIND

OHTS benefit of IOP reduction. 4.4% of treatment and 9.5% of non treatment reached end point. 91.5% of non treatment did not. 13 year follow up showed: delay in treatment did not result in more severe vf loss once treated

What is the overall recommendation for patients with glaucoma?
- Do Not Smoke
- Get Quality Sleep
- Maintain the Ideal Weight
- Exercise Daily
- Control Hypertension and Cholesterol
- Control Diabetes
- Eliminate Stress
- Control Inflammation
- Maintain an Anti-Inflammatory Diet

Use Nutritional Supplementation if Needed (Conservative)
<table>
<thead>
<tr>
<th>Minimal Supplement</th>
<th>Beneficial Action</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg Triglyceride</td>
<td>Immune System Modulation</td>
<td>b.i.d. but no recommended RDA</td>
</tr>
<tr>
<td>Bac Idone Omega 3</td>
<td>Neuroprotection, Immune System Modulation</td>
<td>b.i.d. with RDA in flux as measurement of blood levels becoming more important</td>
</tr>
<tr>
<td>500 IU Vitamin D3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Quality Multivitamin with</td>
<td>Anti-Oxidation, Balance and Control of Homocysteine</td>
<td>q.d. or b.i.d. based on brand. Folic acid competes with methotrexate.</td>
</tr>
<tr>
<td>400 mcg Folic Acid, 2 mg B6, 6 mcg B12, Vit E, based on AHA recommendations.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg Co-enzyme Q10</td>
<td>Anti-Oxidation</td>
<td>q.d. but more needed if on Statins or Red Yeast Rice. There is no established RDA</td>
</tr>
<tr>
<td>Desirable Optional Supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial Protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg Alpha Lipoic Acid and 400 mg Acetyl L Carnitine</td>
<td>Anti-Oxidant Crossing Blood Brain Barrier, Raises Glutathiones, Together Maximize Lipid Metabolism</td>
<td>q.d. to b.i.d. but there is no established RDA</td>
</tr>
<tr>
<td>500 mg Curcumin</td>
<td>Neuroprotection, Immune System Modulation</td>
<td>q.d. but there is no established RDA</td>
</tr>
<tr>
<td>60 mg Ginkgo Biloba</td>
<td>Anti-Oxidant, Facilitates Blood Flow</td>
<td>q.d. to b.i.d. with caution as it can thin blood</td>
</tr>
</tbody>
</table>

**Three fold increased risk of nuclear cataract in patients taking topical beta-blockers.**


**PHARMACEUTICALS AND GLAUCOMA**

**INTRANASAL and INHALED STEROIDS**
In a large cohort of elderly patients treated for airways disease, it was found that current use and continuous use of high-dose ICS did not result in an increased risk of glaucoma or raised intra-ocular pressure requiring treatment. Gonzalez AV, Li G, Suissa S, Ernst P. Risk of glaucoma in elderly patients treated with inhaled corticosteroids for chronic airflow obstruction. Pulm Pharmacol Ther 2010;23:63-78.

More than 20% of Americans suffer from allergic rhinitis and is present in up to 75% of patients with asthma. Blaiss MS. Safety considerations of intranasal corticosteroids for the treatment of allergic rhinitis. Allergy Asthma Proc 2007;28:145-152.

There is the suggestion that there is a dose-related risk of open-angle glaucoma with inhaled corticosteroids for treating moderate to severe COPD. Gartlehner G, Hansen RA, Carson SS, Lohr KN. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. Ann Fam Med 2006;4:253-262.

There is NO RISK of Glaucoma with Inhaled Steroids (JAMA 1997;277:722)

There is INCR RISK (44% MORE LIKELY) of Glaucoma with High Dose Inhaled Steroids > 3 Months of Use (Ear Nose Throat J 1998;77:846)

5-8 % of the General Population are Steroid Responders While 95% of POAG Patients are Steroid Responders (Ann Allergy 1989;62:379, Dermatol Clin 1998;16:277)

Patients Taking Oral Glucocorticoids Should Have Their IOPs Checked Every 6 Months (Brit Med J 1997;314:695)

With a Strong Family History of Glaucoma Inhaled Steroids Increase the Risk (Ophthalmology 1999;106:2301)

IOP was Reduced With the Discontinuatin of Nasal Steroids in Patients with Glaucoma (J Allergy Clin Immunol 2005;116:1042)
**Conclusion???

Invest Ophthalmol Vis Sci. 2008 May 9. [Epub]

"IOP elevation may directly damage mitochondria in the ONH axons by promoting reduction of COX, mitochondrial fission and cristae depletion, alterations of OPA1 and Dnm1 expression, and induction of OPA1 release. Thus, interventions to preserve mitochondria may be useful for protecting ON degeneration in glaucoma."

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**NUTRITION WITH MITOCHONDRIAL IMPACT**

**BIOENERGY SOURCE FOR CELLS. WHEN THEY DIE, THE CELL DIES**

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**MITOCHONDRIAL DECAY AND AGING**

  1. (a) oxidant by-products increase with a concomitant increase in ascorbate, protein, lipid, and nucleic acid oxidation; (b) cardiolipin decreases in mitochondrial membranes; (c) membrane potential decreases; and (d) oxygen utilization decreases.
MITOCHONDRIAL DECAY AND AGING

• IMPROVING MITOCHONDRIAL FUNCTION WITH MICRONUTRIENT SUPPLEMENTATION (LIPOIC ACID, L-CARNITINE) MAY OFFER AN OPTION FOR MAINTENANCE OF FUNCTION

ALPHA-LIPOIC ACID

• FAT AND WATER SOLUBLE ANTIOXIDANT THAT CROSSES BLOOD-BRAIN BARRIER
• RAISES GLUTATHIONE, REGENERATES CO Q10 AND VIT E, PROTECTS NEURONS FROM GLUTAMATE, REMOVES IRON, AND WITH ACETYL-CARNITINE AMELIORATE MITOCHONDRIAL DECAY OF AGING
• ALSO SHOWN TO PROTECT RPE CELLS FROM OXIDATION.

ALPHA-LIPOIC ACID

• LINKED TO INSULIN-SIGNALING CASCADE AFFECTING GLUCOSE UPTAKE
• +VE RESULTS IN DIABETIC AUTONOMIC NEUROPATHY
• RESCUES RETINAL NEURONS UNDER STRESS
• BETTER ABSORBED ON EMPTY STOMACH WITH RACEMIC FORM
• COULD COMPETE WITH BIOTIN SIMILAR STRUCTURE

ACETYL-L-CARNITINE (ALC)

• NATURAL MOLECULE DERIVATIVE OF LYSINE IN CNS THAT TRANSPORTS LONG-CHAIN FFA INTO MITOCHONDRIA FOR ENERGY
• PRODUCED IN LIVER AND KIDNEYS AND STORED IN SKELETAL MUSCLES AND BRAIN
• MAXIMIZES MITOCHONDRIAL FUNCTION
• DEPENDS ON IRON, VIT C, B6, NIACIN
• DEFICIENCY CREATE SEVERE EFFECTS ON CNS.
ACETYL-L-CARNITINE (ALC)

- Neuroprotective (Glutamate Antagonist), Neuromodulatory, Inhibits Cell Death
- Reduces ill effects in lipid metabolism and in combination with CoQ10 and O3s stabilize AMD by protecting RPE
- Used in chronic pain
- Improves cognitive function
- Absorption dependent on high carnitine diet

GINKGO BILOBA

- Botanical antioxidant enhancing blood flow, minimizing vasospasm, inhibits platelet activating factor, lowers serum viscosity, inhibits apoptosis and excitotoxicity
- Recommended to manage neurodegenerative effects of cerebral and retinal insufficiency, glaucoma and and visual fields in glaucoma at 120 mg/day, and retinal choroidal diseases
- Actually enters mitochondria to protect RGC
**COENZYMЕ Q10-UBIQUINONE**

- **FAT SOLUBLE ANTIOXIDANT**
- **WORKS SYNERGISTICALLY WITH**
- **BUFFER THE FREE RADICALS FROM OXIDATIVE PHOSPHORYLATION IN INNER MITOCHONDRIAL MEMBRANE**
- **CRITICAL IN MITOCHONDRIAL ELECTRON TRANSPORT CHAIN**

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**COENZYMЕ Q10-UBIQUINONE**

- **STRONG ASSOCIATION WITH NEURODEGENERATIVE DISORDERS AND PROGNOSTIC FACTOR FOR MELANOMA**
- **SUGGESTED BENEFIT FOR MIGRAINE AND RGC DEATH**
- **REPORTS IN HIV, CYSTIC FIBROSIS, ATAXIA**

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**MELATONIN**

- **HORMONE ACTING AS ANTIOXIDANT POSSIBLE NEUROPROTECTANT**
- **PRODUCED IN PINEAL GLAND, GI TRACT, IMMUNE SYSTEM, AND RETINA**
- **RECEPTORS IN CORNEA, CB, LENS, CHOROID, SCLERA INACTIVATED BY LIGHT**
- **QUESTION ARMD RELATION-HIGH PRODUCTION IN ARMD**

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**MELATONIN**

- **RELATIONSHIP TO INCR IOP, LARGE CD** *(J Circadian Rhythms 2005;3:13)*
**CURCUMIN/TURMERIC**

- Phytophenolic compound with proven antioxidant, anti-inflammatory, antiinfections and anticancer activity
- Ten known neuroprotective actions and downregulates proangiogenic factors (VEGF)

**TAURINE**

- Amino acid concentrated in RPE functioning as water soluble antioxidant
- Protects against neurotoxins
- Incr fluid discharge in POAG and improves hemodynamics

**N-ACETYL-CYSTEINE (NAC)**

- Derivative of AA CYSTEINE converted to glutathione
- Protects against nitric oxide, active in regeneration of C and E
- Chelating agent—must supplement Zn, Cu, Vit C keeps glutathione produced from NAC in reduced form
- RDA of 250-1500 mg/DAY

**RESVERATROL**

- Found in grapes, knotweed plant
- Polyphenol which activates sirtuin-2 enzyme
- Neuroprotective in cerebral ischemia, antiapoptotic, inhibits oxidation of LDL, inhibits platelet aggregation
- Drinking 41 glasses of red wine/day = 1 20mg capsule