

# Neuro-rescuing glaucomatous damage

High doses of omega-3 fatty acids could help treat glaucoma

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High doses of omega-3 fatty acids, rich in eicosapentaenoic acid (EPA), could help battle neuro-inflammation in glaucoma patients and, therefore, improve visual acuity (VA) and visual field (VF) within 3 months, according to the results of a new study.

Glaucoma is a chronic, neurodegenerative disease characterized by progressive death of retinal ganglion cells (RGC) and loss of RGC axons in the optic nerve. It has a long slow course with an unpredictable rate of progression.

It is the second most common cause of blindness globally. In 2010, there were 61 million people worldwide with glaucoma, 25 million of who live in Europe, and these numbers are expected to increase 30% by the year 2020.<sup>1</sup>

During the last 20 years, controlled clinical trials have shown that lowering intraocular pressure (IOP) is an effective way to slow progression of glaucoma damage. All available treatments focus on lowering IOP to slow the progression of the disease. The mean loss of VF tests in untreated adults with primary open angle glaucoma, which is the most common type of glaucoma, is 0.5–1.0 dB/year and the IOP lowering therapy slows the untreated rate of progression by 50–60%.<sup>2</sup> There is no therapy that reverses glaucomatous VF loss or improves VA.

## Inflammation and glaucoma

Chronic low-grade inflammation has been shown to play a major role in the pathogenesis of glaucoma. Inflammatory molecules such as VEGF, TNF- $\alpha$ , interleukins (IL-1 $\alpha$ , IL-2 $\beta$ ), have been shown to be upregulated in glaucoma.<sup>3</sup>

Nguyen *et al.*<sup>4</sup> studied the effect of omega-3 and repeated acute IOP insults on RGC function in dams. Their results indicated that sufficient dietary omega-3 improves RGC function making it less susceptible to IOP stress.

Nakazawa *et al.*<sup>5</sup> demonstrated, in induced high IOP in mice, the upregulation of TNF- $\alpha$ , followed by oligodendrocytes death and delayed RGC loss. They suggested blocking TNF- $\alpha$  signalling or

inflammation maybe helpful in the treatment of glaucoma.

One study showed the RGCs from glaucomatous rat eyes can have a regenerative potential.<sup>6</sup> This suggests that a repair mechanism exists in glaucomatous eyes.

The resolution of inflammation is an active process primarily driven by a new family of mediators termed proresolving lipid mediators (resolvins, protectins and maresins) derived from the omega-3 fatty acids, EPA and docosahexaenoic acid (DHA).<sup>7</sup> They stop leukocyte infiltration with accompanied active clearance of macrophages, promoting resolution of inflammation and stimulating tissue regeneration.

A pilot study has recently shown improvement of VA in patients with dry macular degeneration with high doses of omega-3 fatty acids rich in EPA.<sup>8</sup>

We have used high doses of omega-3 fatty acids on patients who are already receiving IOP-lowering treatment, and who have advanced glaucomatous damage with reduced VA, to study whether there are any neuro-rescue effects, in terms of VA and VF.

## Study

Twenty four eyes of 18 patients with advanced glaucoma controlled with IOP-lowering medications were included in the study. All patients had reduced VA and advanced damage on Humphrey VF (MD < -12 dB).

## In short...

Glaucoma is a chronic, neurodegenerative disease that is the second most common cause of blindness in the world. All available treatment is focused on lowering IOP to slow the progression of the disease, with no current therapy to reverse visual field loss or improve visual acuity available. Therefore, in this article, the authors describe the use of high dose omega-3 fatty acids to combat the neuro-inflammation in glaucoma patients, thereby improving visual acuity and visual field in glaucoma patients.

Patients received daily oral supplements of 5 g to 8 g of EPA and DHA (ratio 2:1). The mean dose was 7.0 g/day. They also received oral polyphenols to act as antioxidants. (Led by the author and his research team at Ophthalmos Research and Educational Institute in Cyprus.)

The VA ranged from 6/7.5 to 6/36 with a mean of 6/12+2 and was recorded according to the ETDRS electronic chart. The MD of field loss using Humphrey VF ranged from -12 to -30 dB with a mean of -23.35 dB.

The mean age of patients was 62 years old and the mean number of glaucoma drops used was 2.8. These patients were followed up at 6 weeks and 3 months.

Figure 1 presents the results of VA gained over the 3 month period. By the third month the average increase in vision was nearly 2 lines ( $p < 0.01$ ).

Figure 2 presents the average MD of field loss gained over the 3 months. The mean improvement of the MD at 3 months was 3.04 dB ( $p < 0.01$ ).

All patients had a blood ratio of arachidonic acid (AA)/EPA and the dosage of omega-3 fatty acids was adjusted to ensure a therapeutic ratio between 1 and 2.

As there is no existing treatment to improve the vision and VF test in patients with glaucoma, the positive clinical improvements obtained in this pilot study should be considered striking and demonstrate the value of high doses of EPA and DHA for neuroinflammation and neurodegeneration in glaucoma patients.

## Discussion

Glaucoma is associated with progression of RGC and axonal loss and can lead to blindness. Related IOP is considered as only one of the risk factors for glaucoma and even with normal IOP glaucoma can

Figure 1: Number of letters gained following treatment.

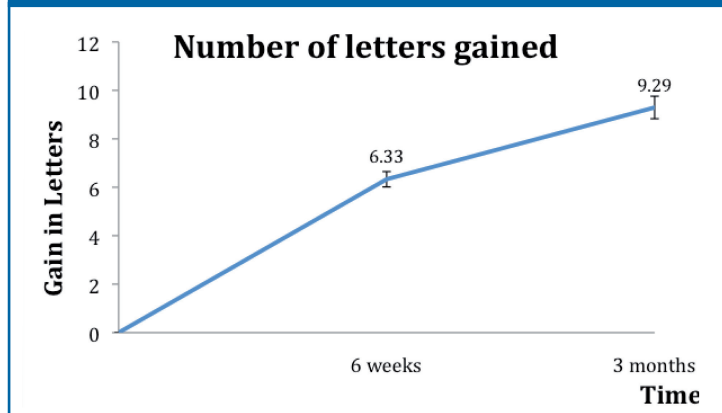
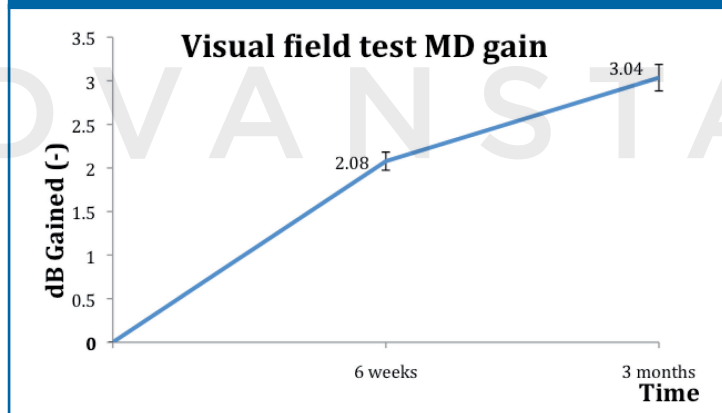


Figure 2: Visual field test mean MD gain following treatment.



occur. All available treatments to lower IOP only slow the progression of the disease.

All of the evidence supports that future therapy for glaucoma will not only be to lower IOP but also to protect the viability of RGCs, retina and optic nerve. Neuroprotective aspects should focus on the multiple pathogenic mechanisms that result in axonal degeneration and RGCs death. To have a successful neuroprotection you need to target neurodegeneration and neuroinflammation.

A neuroprotective treatment must have minimal systemic and visual side effects, otherwise it will be poorly tolerated by patients who would view the treatment as worse

as the disease.<sup>2</sup>

Neuroinflammation is a major contributor in glaucomatous neurodegeneration. EPA has significant anti-inflammatory properties through the anti-inflammatory eicosanoids (mainly Resolvins-E). It is also a structural competitor to AA, which produces inflammatory eicosanoids. The AA/EPA plasma ratio is an important marker for the balance of these two fatty acids in the brain.<sup>9</sup> DHA is more powerful than EPA for stimulating neurogenesis.

For neurodegeneration, both metabolites of EPA (to reduce inflammation) and DHA (to stimulate neurogenesis) appear

**Table 1:** The mean visual acuity and standard deviation at each visit and the *p* values.

Visual Acuity (Decimal)	Start	6 weeks	3 months
Mean	0.54 ± 0.19	0.73 ± 0.26	0.83 ± 0.22
		<i>P</i> < 0.01	<i>P</i> < 0.01

**Table 2:** The mean visual field MD and standard deviation at each visit and the *p* values.

Visual Acuity (Decimal)	Start	6 weeks	3 months
Mean	23.35 ± 6.77	21.27 ± 7.48	20.31 ± 6.96
		<i>P</i> < 0.01	<i>P</i> < 0.01

to be required. Optimal delivery of EPA/DHA may open up new avenues in improving visual recovery in glaucomatous and optic nerve damage patients.

We used a finger stick test for AA/EPA blood ratio and aimed for a lower limit of AA/EPA ratio of 1 and on upper limit of 2. The ratio would exclude any bleeding concerns and would provide data whether or not the patient is taking a therapeutic dosage of EPA and DHA.

The polyphenols are powerful anti-oxidants and were used to prevent oxidation of the omega-3 fatty acids before they enter into the brain.

Omega-3 fatty acids are well tolerated by patients and have been shown to be safe, especially when the AA/EPA blood ratio is monitored. Administration of Omega-3 fatty acids with antioxidants for glaucomatous patients as a neuroprotective to improve VA and VF loss deserves consideration as a promising and innovative approach in glaucomatous management. If we intervene during the early stages of the disease then we would keep the existing RGCs alive through the use of IOP-lowering drops and the neuroprotective agent.

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Dr Georgiou has pending patents on the use of omega-3 fatty acids and eye diseases. There are no other financial interests to disclose.