DOI: 10.1111/ceo.13849

EDITORIAL

Clinical & Experimental Ophthalmology WILEY

Vitamins for glaucoma

Glaucoma continues to be one of the leading causes of vision loss worldwide. In 2020, an estimated 4.5 million persons will suffer moderate to severe vision impairment and an estimated 3.2 million blind will be blind due to this ophthalmic condition.[1]

For multiple decades, treatment of glaucoma has focused on the reduction of intraocular pressure—pharmacologically or by laser or surgical interventions—to protect the retinal ganglion cells and their axons, which are the primary casualties in the disease.[2] However, there has been increasing interest in the possibility of neuroprotective approaches to improve the resilience of this cell population. Vitamins—in particular, antioxidant vitamins—have received considerable attention, albeit with little practical clinical application.[3] In contrast, the AREDS2 supplement, which includes vitamin C and vitamin E, is commonly given to patients with intermediate or late age-related macular degeneration in one eye.[4]

In this issue of *Clinical and Experimental Ophthalmology*, Hui et al[5] report, for the first time, the neuroprotective effect of nicotinamide in patients with glaucoma. Nicotinamide is the water-soluble amide form of niacin or vitamin B3. It is an essential substrate in the metabolic pathway that ultimately generates nicotinamide adenine dinucleotide (NAD+), which is required for the production of adenosine triphosphate in mitochondria.[6] Nicotinamide supplementation is under investigation for a range of traumatic, vascular and neurodegenerative diseases. This treatment is generally well tolerated, in contrast to niacin, which has been associated with macular oedema.[7]

Introduction of nicotinamide into the glaucoma clinic has occurred remarkably quickly. Just 3 years ago, Williams et al[8] published a highly significant report in *Science*, in which they demonstrated that mitochondrial dysfunction and reduced levels of NAD+ occurred early in retinas of glaucoma-prone mice, and that addressing this defect—by methods that included supplementing the diet with nicotinamide—had preventive and therapeutic effects in the mice. Subsequently, an independent group reported lower levels of nicotinamide in patients with primary open-angle glaucoma.[9] In response to this groundbreaking discovery, Liebmann and Cioffi[10] published a perspective in the *New England Journal of Medicine* entitled, *"Nicking Glaucoma with Nicotinamide*?", which ended with the question, "Should nicotinamide be tested in humans with glaucoma?" The present work, reported by a team of largely Australian-based ophthalmologists, addresses this question and provides strong evidence that the answer may be "yes."

Hui et al[5] enrolled 57 patients with different forms of glaucoma—including primary open-angle glaucoma, chronic angle-closure glaucoma, pseudoexfoliative glaucoma and pigment dispersion glaucoma—in a 24-week crossover, double-masked randomized clinical trial that compared treatment with oral nicotinamide to appearance and texture-matched placebo tablets. Enrolees had well-controlled intraocular pressure and continued their regular pressure-lowering medications throughout the study. During the nicotinamide treatment period, patients were supplemented at 1.5 g/d for 6 weeks, followed by 3.0 g/d for 6 weeks. Greater than 90% adherence to the nicotinamide treatment indicated good tolerability and the reported side effects were mild, including nausea, gastrointestinal disturbances and headaches.

A total of 49 patients completed this study. The main outcome measures were designed to assess inner retinal function, which was judged at the end of the 6-week period of higher dose nicotinamide. The investigators selected several electrophysiological parameters previously shown to evaluate retinal ganglion cell function reliably and have clinical applicability: saturated photopic negative amplitude or voltage (*V*max), and ratio of saturated photopic negative and b-wave amplitudes (*V*max ratio).[11,12] Treatment with nicotinamide resulted in significantly higher *V*max and *V*max ratio in comparison to placebo tablets, by approximately 4-fold for both measures. There may also have been a positive effect on visual field mean deviation. Changes were not observed in visual acuity, intraocular pressure or retinal nerve fibre layer thickness as a result of treatment with nicotinamide.

That protecting retinal ganglion cells—and preventing progression of, or even reversing, glaucoma—could be as simple as taking a vitamin supplement, is certainly attractive. Questions about patient and disease characteristics spring to mind. Might therapeutic effects

depend on age, sex, ethnic origin, lifestyle factors and/or co-morbidities? There was no correlation between treatment effect and age, sex or body mass index in this study, but patient numbers were small. Might certain forms of glaucoma be more amenable to this treatment? Clearly, this carefully designed and executed clinical trial is just the first step in evaluating nicotinamide supplements for patients with glaucoma. Indeed, in discussing this important work, Hui et al[5] indicate plans for an extended clinical trial "to determine whether (the) functional improvements (linked to nicotinamide supplements) are sustained and associated with delayed glaucoma progression."

ACKNOWLEDGEMENT

The authors wish to thank Ms Janet Matthews for administrative support in preparing this editorial.

CONFLICT OF INTEREST

None declared.

Anna Galanopoulos FRANZCO[1]
Justine R. Smith FRANZCO PhD[2]

[1]*Department of Ophthalmology, Royal Adelaide Hospital, Adelaide, South Australia, Australia*
[2]*Flinders University College of Medicine and Public Health, Adelaide, South Australia, Australia*

REFERENCES

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):e1221-e1234.
2. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. *Lancet*. 2017;390(10108):2183-2193.
3. Ramdas WD, Schouten J, Webers CAB. The effect of vitamins on glaucoma: a systematic review and meta-analysis. *Nutrients*. 2018;10(3):359.
4. Chew EY. Age-related macular degeneration: nutrition, genes and deep learning-the LXXVI Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2020;217:335-347. https://doi.org/10.1016/j.ajo.2020.05.042.
5. Hui F, Tang J, Williams PA, et al. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: a crossover randomized clinical trial. *Clin Experiment Ophthalmol*. 2020;48(7):903-914.
6. Fricker RA, Green EL, Jenkins SI, Griffin SM. The influence of nicotinamide on health and disease in the central nervous system. *Int J Tryptophan Res*. 2018;11:1178646918776658.
7. Domanico D, Verboschi F, Altimari S, Zompatori L, Vingolo EM. Ocular effects of niacin: a review of the literature. *Med Hypothesis Discov Innov Ophthalmol*. 2015;4(2):64-71.
8. Williams PA, Harder JM, Foxworth NE, et al. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. *Science*. 2017;355(6326):756-760.
9. Kouassi Nzoughet J, Chao de la Barca JM, Guehlouz K, et al. Nicotinamide deficiency in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2019;60(7):2509-2514.
10. Liebmann JM, Cioffi GA. Nicking glaucoma with nicotinamide? *N Engl J Med*. 2017;376(21):2079-2081.
11. Tang J, Hui F, Hadoux X, et al. A comparison of the RETeval sensor strip and DTL electrode for recording the photopic negative response. *Transl Vis Sci Technol*. 2018;7(6):27.
12. Tang J, Hui F, Coote M, Crowston JG, Hadoux X. Baseline detrending for the photopic negative response. *Transl Vis Sci Technol*. 2018;7(5):9.