Lifestyle in glaucoma and systemic diseases can be modified

Avoidance also applies to certain lifestyle behaviours that are relevant both to glaucoma and general, particularly cardiovascular, health: smoking, obesity, physical inactivity, and poor nutrition. This association was documented in 2016 in a large cohort study spanning 11 years**: glaucoma patients suffer significantly more often from ischemic heart disease than people without glaucoma. According to C. Erb 's assessment, it is an essential necessity to also treat the systemic underlying diseases of glaucoma patients: up to 75% suffer from arterial hypertension, 50% show lipid metabolism abnormalities, and around 30% have diabetes mellitus.

It may be somewhat unusual for eye care professionals to concern themselves with the enteral microbiome — the approximately 100 trillion bacterial inhabitants of the human gut (primarily in the large intestine). However, disturbances of the microbiome can lead to the development of autoimmune diseases and neurodegeneration, including retinal neurodegeneration.

Improvement of the microbiome can be supported by a healthy diet including probiotics and dietary supplements, avoidance of toxic substances, as well as exercise and physical activity. In particular, physical activity represents a neuroprotective strategy, even independently of the microbiome. Multiple studies have associated physical activity with a lower incidence of degenerative diseases such as Alzheimer's disease and dementia.

Micronutrients: Global deficiency; effective in reducing oxidative stress.

C. Erb emphasised the significance of micronutrients and pointed out the widely underrecognised fact, which was presented in August 2024 by an American research group in an analysis published in The Lancet: The global insufficiency and the fact that four billion people do not consume adequate amounts of iron, riboflavin, folate, and vitamin C. Europe, for example, is particularly deficient in vitamin C intake. The widespread assumption that we obtain all necessary nutrients from our diet is not accurate, according to C. Erb.

Particularly vitamin C, which plays a crucial role in the mitochondrial respiratory chain, is relevant in the context of neurodegeneration. Only two years ago, a meta-analysis demonstrated an association between Alzheimer's disease and low or inadequate vitamin C intake. Similarly, in primary open-angle glaucoma, vitamin C — a principal scavenger of free radicals in the aqueous humour — is reduced both in the aqueous humour and in plasma. Conversely, oral supplementation can significantly increase vitamin C levels in the aqueous humour. Vitamin C is also relevant in the trabecular meshwork. There, it promotes, among other functions, the production of fibronectin, which acts as a sensor totransmit intraocular pressure (IOP)-induced mechanical strain to trabecular meshwork cells and to counteract it through IOP reduction.

Furthermore, vitamin C also supports the production of laminin and hyaluronic acid. In a large study published in 2022 with more than 19,000 participants, a high intake of vitamins (a combination of vitamins A, C, and E) led to a 27% reduction in the risk of developing glaucoma, with an odds ratio (OR) of 0.73. C. Erb summarised that much can be achieved by intervening in degenerative and regenerative pathways with a sensible combination of micronutrients. "With what we have today," concluded the speaker, "we can achieve a great deal. If we apply the insights on the influence of lifestyle sensibly, we have already gained much."

Stephanie Joachim additionally reported on another successful neuroprotection approach, albeit under laboratory conditions: intermittent fasting. In the animal model, rats were deprived of food every other day. In those animals in which glaucoma was experimentally induced, fasting resulted in protection of the ganglion cells. However, as the researcher repeatedly emphasised, such laboratory conditions cannot be readily extrapolated to humans. It may be assumed that, for glaucoma patients, the administration of micronutrients as a neuroprotective strategy would be clearly preferable to a regular zero-calorie diet, in addition to IOP reduction.

The video of the symposium can be accessed online at:

https://ebiga-vision.com/neurodegeneration-beim-glaukomgrundlagen-forschungsansaetze-therapiestrategien/

** https://pubmed.ncbi.nlm.nih.gov/27649414/

ZPA-Special Publication in collaboration with ebiga-VISION GmbH, Greifswald (Gemany)

Publisher: KIM–Communication in Medicine
Author: Dr. med. Dr. phil. R. D. Gerste
Project Management: Katja Lorenz-Kaden

Dr. R. Kaden Verlag GmbH & Co. KG
Stresemannstraße 12
68165 Mannheim (Gemany)

English Translation

ZPA

Special Publication

Zeitschrift für praktische Augenheilkunde & Augenärztliche Fortbildung
Journal of Practical Ophthalmology & Ophthalmological Education

Is lowering intraocular pressure always sufficient? On the benefits of neuroprotective therapeutic strategies in glaucoma

Therapeutic advances achieved in ophthalmology in recent years are indeed impressive. For vascular retinal diseases, a range of intravitreally administered substances is now available. For rare, genetically determined optic nerve disorders, gene therapy has become an established treatment option. Cataract surgery now offers such a wide variety of possibilities that even experts can scarcely maintain an overview of the different intraocular lens (IOL) designs—much to the benefit of patients. As a result, patients enjoy a high level of postoperative visual comfort and frequently achieve the much-desired freedom from spectacles.

In contrast, glaucoma therapy appears almost like a relic: as in the days of Albrecht von Graefe, its central focus remains the reduction of intraocular pressure (IOP). To this end, a broad spectrum of pharmacological, surgical, and laser-based treatment options is available. Elevated IOP is often described as the "most important risk factor" for the disease. At the same time, however, this risk factor no longer features in contemporary definitions of glaucoma—such as that of the European Glaucoma Society.

Ophthalmology is far from exploiting its full potential if glaucoma therapy is equated solely with IOP reduction. This point was emphasised by three experts—Prof. Dr. Verena Prokosch (Cologne), Prof. Dr. Stephanie Joachim (Bochum), and Prof. Dr. Carl Erb (Berlin)—during a symposium held as part of the DOG Congress 2024, organised by ebiga-VISION GmbH. The aim of alternative or complementary therapeutic approaches is neuroprotection, intended to safeguard retinal ganglion cells from apoptosis—or, more broadly, from neurodegeneration.

Neurodegeneration—or more precisely, the degeneration of retinal ganglion cells—is a pathognomonic feature of glaucoma. According to Prof. Verena Prokosch, neurodegeneration is a process that patients usually do not notice, or only become aware of at a very advanced stage. A key contributing factor is the brain's capacity to compensate for the loss of ganglion cells and the deficits caused by glaucoma-typical scotomas over extended periods.

The long-term burden/impact of glaucoma was highlighted by a study from Sweden: of more than 500 glaucoma patients followed, 42% became blind in one eye, and 16% in both eyes, over the course of their lifetimes. Even in the absence of this ultimate visual loss, glaucoma patients experience a marked reduction in quality of life. For instance, already a relatively mild visual field loss of 5 dB necessitates that almost one-third of affected individuals cease driving. Moreover, many patients report a significant slowing of reading speed.

Numerous additional factors are involved in the pathogenesis of glaucoma

Prof. V. Prokosch emphasised that lowering intraocular pressure (IOP) is, of course, desirable and effective. However, she stressed that it is "not everything" in glaucoma therapy. IOP represents a classic trigger factor for further neurodegeneration and requires treatment. Even a supposedly well-controlled IOP often cannot halt disease progression. Or, as the

Cologne glaucoma specialist put it: "We need neuroprotective measures that tackle the problem at its root."

The factors contributing to neurodegeneration are manifold: mechanical stress, vasospasms, impaired autoregulation, perfusion disturbances, ischemia, reactive oxygen species, axonal transport dysfunction, growth factor deficiency, and many others—the list is by no means exhaustive.

These are factors that also play a significant role in other neurodegenerative disorders, such as Alzheimer's and Parkinson's disease. In the case of glaucoma, the neurodegenerative processes are not limited to the ganglion cells; microglia, Müller cells, and astrocytes also show changes that have a secondary significance in the disease process. Prof. V. Prokosch emphasised that, although neuroregeneration can be achieved under certain conditions in the laboratory, the reality for patients is that what has been lost cannot be restored. Consequently, IOP-independent glaucoma therapy must focus on slowing the progression of neurodegeneration.

Numerous studies have demonstrated protection of retinal ganglion cells in animal models.

The concept of neuroprotection has circulated in clinical practice for many years and embodies the vision of safeguarding retinal neurons and their axons, according to Stephanie Joachim. Given the complex pathogenesis of glaucoma, numerous approaches in addition to IOP reduction are conceivable. However, as promising as the results from experimental studies often are, translating them into clinical practice remains challenging. Moreover, as the Bochum-based researcher points out, animal models typically involve young animals, whereas the organism of a typical glaucoma patient has usually already undergone significant ageing. The side effects of neuroprotective agents must also be taken into consideration.

Nevertheless, St. Joachim expressed optimism that a light at the end of the tunnel would appear in the field of neuroprotection. She focused her presentation on evidence-based approaches in research on potential neuroprotective agents.

For instance, Ginkgo biloba exhibits antioxidant properties and acts as a free radical scavenger, and coenzyme Q10 has a similar protective effect against oxidative stress.

St. Joachim reported her own research findings, in which, following the induction of oxidative stress in the porcine retina, administration of coenzyme Q10 prevented cellular loss and demonstrably protected mitochondria from oxidative damage. In an animal study, alpha-lipoic acid was shown to provide substantial protection of retinal ganglion cells and their axons.

Citicoline acts as a membrane stabiliser and resulted in axonal protection and regeneration in experimental studies. Another potential neuroprotective agent is nicotinamide (vitamin B3), which exhibits both antioxidant and anti-inflammatory effects. This compound has been tested at various concentrations in a high-pressure glaucoma model, demonstrating protective effects on retinal ganglion cells.

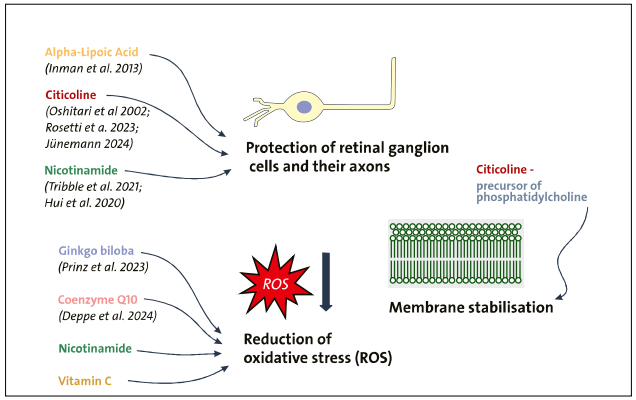

Figure 1: Neuroprotective approaches in research (adapted from St. Joachim, 2024)

A novel perspective: glaucoma as a neurodegenerative brain disorder

Carl Erb emphasised that, although direct neuroprotection of ganglion cells is challenging in clinical practice, insights can be drawn from experiences with neurodegenerative brain disorders. Glaucoma is also classified by neuroscientists as such a disorder, involving several non-visual brain structures, including the angular gyrus, the right inferior occipital cortex, and the cerebellum.

The Berlin-based expert described numerous pathophysiological mechanisms underlying primary open-angle glaucoma, highlighting primary glaucomatous mitochondriopathy. Various mitochondrial DNA alterations have been identified in open-angle glaucoma. On average, patients exhibit a 21% reduction in mitochondrial respiratory activity. These changes are often triggered by primary mitochondrial genetic defects, with oxidative stress also contributing, the markers of which have been detected in multiple studies both in the serum and in the aqueous humour of patients with open-angle glaucoma. According to C. Erb 's assessment, protection against the effects of oxidative stress and other pathogenic factors should also definitely be provided, even in cases of advanced glaucomatous damage. In particular, for older individuals, it is advisable to explore novel and supplementary strategies to preserve the remaining visual function.

Limitations in the efficacy of intraocular pressure reduction

C. Erb began his overview of established and potential methods for ganglion cell protection with the classic approach—lowering intraocular pressure (IOP). He offered a somewhat sobering assessment for the audience. Naturally, [FW4.1][TP4.2] IOP should be controlled in patients with glaucoma. However, a major review* from the United States found no classical evidence supporting the efficacy of this strategy.

C. Erb noted that it took 138 years following the introduction of pharmacological glaucoma therapy before the first truly prospective, controlled study on the effectiveness of this classic approach — the United Kingdom Glaucoma Treatment Study (UKGTS)—was conducted, and this without severe glaucoma cases in the patient cohort. The study determined a "number necessary to treat" (NNT) of 10, meaning that 10 patients need to be treated for one of them to avoid disease progression. Put differently: among 100 patients receiving topical therapy, after two years (the observation period of the UKGTS), only 10 showed no visual field progression.

A sensible and complementary step alongside pharmacological glaucoma therapy is the avoidance of preservatives in antiglaucoma agents. In particular, benzalkonium chloride contributes to mitochondrial dysfunction—also because the compound does not remain on the surface but can be detected in the trabecular meshwork and even in the choroid. "If we aim to achieve neuroprotection," stated Carl Erb, "the first step is to eliminate preservatives."

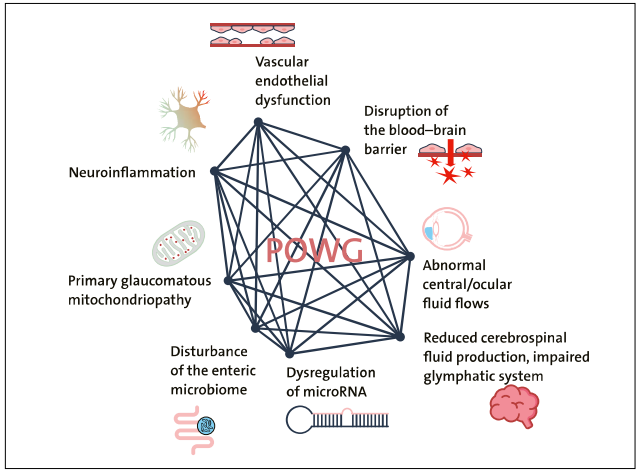

Figure 2: Fundamentals of the neurodegenerative disease POWG (adapted from C. Erb, 2024)

* https://effectivehealthcare.aahrq.gov/products/glaucoma-treatment/research

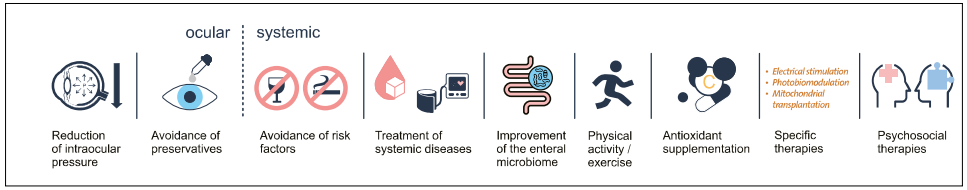

Figure 3: Neuroprotective strategies in POWG (based on C. Erb, 2024