METABOLIC DYSFUNCTION IN GLAUCOMA: FROM BENCH TO BEDSIDE (AND BACK AGAIN)


A review of nicotinamide treatment for neuroprotection.

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Much like J.R.R. Tolkien's book *There and Back Again: A Hobbit's Tale*, research into glaucoma pathophysiology, mechanisms, and treatments weaves a rich tapestry—from bench to bedside and often back again in multiple iterations. These research themes can seem like a movie narrative, wherein the ending is known before the beginning, much in the way a therapeutic agent or treatment is used before its full mechanisms of action are understood. This review focuses on one such tale that moves from bench to bedside and back again and is starting to demonstrate true clinical potential: nicotinamide treatment for neuroprotection in glaucoma.

IN REGIONE CAECORUM REX EST LUSCUS (IN THE LAND OF THE BLIND, THE ONE-EYED MAN IS KING).

Vision is an essential sense that helps people interact with the world. With age, a small percentage of retinal ganglion cells (RGCs) are lost every year. Because the brain makes up the difference, this loss is often so mild and slow that it goes unnoticed. Sometimes, however, faster progressive loss of RGCs occurs, as in glaucoma, and people can spend a significant portion of their lives without sufficient vision. This risk increases with age, and the number of patients with glaucoma continues to rise as the aging global population grows. Glaucoma, therefore, is a major health and economic burden.

Following are three definitions of glaucoma:

1. "Glaucoma describes a group of ocular disorders of [multifactorial etiology] united by a clinically characteristic optic neuropathy with potentially progressive, clinically visible changes at the optic nerve head, comprising focal or [generalized] thinning of the neuroretinal rim with excavation and enlargement of the optic cup, representing neurodegeneration of [RGC] axons and deformation of the lamina cribrosa; corresponding diffuse and [localized] nerve [fiber] bundle pattern visual field loss may not be detectable in early stages; while visual acuity is initially spared, progression can lead to complete loss of vision; the constellation of clinical features is diagnostic."[1]
2. "Primary open-angle glaucoma (POAG) is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of [RGCs] and their axons. This condition is associated with an open anterior chamber angle by gonioscopy."[2]
3. "The glaucomas are a group of optic neuropathies characterized by progressive degeneration of [RGCs]. These are central nervous system neurons that have their cell bodies in the inner retina and axons in the optic nerve. Degeneration of these nerves results in cupping, a characteristic appearance of the optic disc, and visual loss. The biological basis of glaucoma is poorly understood, and the factors contributing to its progression have not been fully characterized."[3]

Notably, IOP is not mentioned in any of these definitions. As a common but not exclusive risk factor, elevated IOP cannot and should not be the only target to protect the RGCs in glaucoma. Although stabilizing the IOP has been proven to reduce the risk of vision loss,[4] many patients are

refractory to treatment and experience progressive blindness. Despite this, no current therapies in clinical use directly target the retina and optic nerve in glaucoma. This has been well discussed as the future of glaucoma treatment and research.[5,6]

ALL THAT GLITTERS IS NOT GOLD

How well is glaucoma treated now? Probably not well enough. Despite a range of available IOP-lowering treatments, approximately 40% of patients develop monocular blindness (visual acuity < 6/120 and/or central visual field < 10°) in their lifetime.[7] The vision of many who achieve their target pressure continues to worsen, and those with normal-tension glaucoma have a low IOP to begin with. All of this suggests that elevated IOP cannot be the sole driver of glaucoma pathogenesis. Although effective treatments to lower IOP exist, they do not target the neurodegenerative component of glaucoma itself. Thus, new neuroprotective strategies for glaucoma are required.

ONWARD AND UPWARD

RGCs exist on a metabolic knife-edge, meaning they are at great risk of being bioenergetically compromised.[8,9] These cells are constantly under stress from blue light exposure, changes in vascular tone, high metabolic strain, and anatomic stress, and they have limited glial support compared to other neurons in the brain. This renders RGCs vulnerable to metabolic insults and other factors such as age and elevated IOP. RGCs appear to be particularly vulnerable to metabolic insults; many mitochondrial and metabolic diseases (eg, Leber hereditary optic neuropathy and autosomal dominant optic atrophy) have a strong ocular component that can exist alone or with other systemic effects.

An aging RGC is like an old motorcycle trying to climb a hill. The therapies available at the bedside focus on factors extraneous to the motorcycle. Clinicians try to lower the hill (ie, IOP), improve the road surface (develop surgical devices and techniques to alter aqueous humour dynamics), and sometimes ask why the hill is so steep to begin with (conduct genome-wide association studies to identify candidate risk loci for glaucoma development).[10] These strategies are well established and important for glaucoma management, but they do not directly target the motorcycle. As such, they may have little to no effect if the motorcycle is old or broken. New treatment strategies that are intrinsic to the motorcycle are needed—ones that improve the engine efficiency, add a turbocharger, or provide premium fuel. Targeting these factors could enable the motorcycle to climb the hill regardless of its steepness and should be complementary to any existing treatment strategy to manage or improve the hill itself. This may be easier said than done, but considerable research efforts have been devoted to finding ways to support RGCs directly in glaucoma.

> "THE ENERGY OF THE MIND IS THE ESSENCE OF LIFE."—Aristotle

Age is the most common risk factor for glaucoma.[11,12] With normal aging, RGC metabolic capacity decreases in association with a concomitant increase in mitochondrial stress.[13] Elevated IOP conspires with age to further compromise mitochondrial integrity.

Emerging research suggests that a systemic vulnerability to metabolic compromise exists in patients with glaucoma. Genomic analysis has demonstrated increased mitochondrial DNA content and a spectrum of mitochondrial DNA mutations in glaucomatous eyes.[14-16] Population studies and gene association studies have identified an increased risk of glaucoma subtypes associated with metabolism.[17-20] Gene and protein expression of these candidates has been shown in the retina and optic nerve, suggesting a local vulnerability to metabolic stress. Pathway analyses of gene candidates have implicated lipid metabolism and mitochondrial metabolism in glaucoma. These effects may not only be local to RGCs; defects in mitochondrial metabolism have been shown in the lymphoblasts of patients with glaucoma, indicating a systemic susceptibility to metabolic defects.[21] Metabolic dysfunction and mitochondrial abnormalities occur before neurodegeneration in glaucoma (ie, may exist already with age or as a consequence of early IOP changes). This has been demonstrated both in humans and in animal models of the disease, with a correlation shown between the two.[22,23]

"THE IDEA IS TO DIE YOUNG AS LATE AS POSSIBLE."—Ashley Montagu

Targeting metabolism does not mean trying to resurrect dead RGCs. Research on RGC axon regeneration is ongoing, but it is not yet possible for regenerating axons to be guided to their terminal thalami in the brain, a key step in restoring functional vision. Dogma in glaucoma once maintained that cells are alive or dead, with little grey area in between. However, it has since been established that RGCs are not alive or dead but are, in fact, a heterogenous mix of alive, stressed, dysfunctional, dying, and dead, with a lot of grey area in between. Part of this may be due to subtypes of RGCs with different inputs,[24] sizes of dendritic fields, calibers of axons, and thus different metabolic requirements.

In glaucoma, evidence supports that RGCs enter a comatose-like state in which they go through a period of dysfunction and low activity before degeneration.[25] This cellular activity can be partially recovered by reducing the IOP, but more information is needed on how this occurs. What methods can be developed to promote positive changes in metabolism to keep RGCs from falling off this metabolic cliff? Changing or reducing metabolic load appears to support RGCs subjected to IOP insults, and this seemingly can be accomplished simply by targeting diet and exercise.[26]

"EVERYTHING IS ENERGY AND THAT'S ALL THERE IS TO IT."—Albert Einstein

RGCs are highly bioenergetic, yet they exist in a Goldilocks state of not too little and not too much. As such, these cells are highly sensitive to fluctuations in metabolic demand and to metabolic or mitochondrial defects. The mechanisms by which mitochondrial defects influence neuronal metabolism, leading to RGC dysfunction and degeneration, are being studied. Metabolic dysfunction and mitochondrial abnormalities were shown to occur before neurodegeneration in multiple experimental models of glaucoma and in human postmortem tissue.[22,23,27] Targeting mitochondria and metabolism via dietary intervention, exercise, and drug or gene therapy has shown promise in animal models of glaucoma.[26,28] Many of the changes discovered in animal models sensitized RGCs, leaving them vulnerable to the insults of elevated IOP.

One molecule that aids metabolism is the essential metabolite nicotinamide adenine dinucleotide (NAD), commonly referred to as the *longevity molecule*. NAD acts as a cofactor to hundreds of enzymatic reactions in the cell and is an important regulator of neurodegeneration. Ongoing studies have shown that the body's capacity to maintain NAD levels in the retina and optic nerve declines with age, rendering RGCs susceptible to pressure-related stress and promoting dysfunction and degeneration.[22] Preventing age-related NAD depletion via the administration of nicotinamide (the amide of vitamin B3 and an NAD precursor) or through gene therapy (targeting terminal enzymes for NAD production) has been shown to provide robust protection against age-related metabolic decline and prevent neurodegeneration in animal models of glaucoma.[22]

NAD-generating capacity is low in peripheral blood mononuclear cells from patients with glaucoma[29] and in the sera of patients with POAG.[30] Elevating NAD levels through nicotinamide supplementation can improve visual function in patients with glaucoma.[31] Further, defective gluconeogenesis/glycolysis (the process by which cells make different sugar molecules) has been identified in animal models of glaucoma. Treatment with nicotinamide and/or pyruvate (a simple sugar in these pathways) has been found to provide robust protection against these effects in animal models.[22,32,33] In humans, a small phase 2 trial showed that a combination treatment of nicotinamide and pyruvate improved vision/visual recovery in glaucomatous eyes.[34] These data suggest that glaucoma has a strong metabolic component and that it is possible to correct these bioenergetic insufficiencies to provide neuroprotection in animal models and improve the vision of at least some patients with glaucoma.

"I PREFER TO BE ALIVE, SO I'M CAUTIOUS ABOUT TAKING RISKS."—Werner Herzog

It has been shown clinically that some patients respond well to IOP-lowering treatment and experience minimal vision loss due to glaucoma, whereas others experience rapid or continued disease progression despite treatment. In one retrospective study, the probability of glaucoma-related blindness in at least one eye over a person's lifetime was greater than 40%.[7] More can be done to identify who is most at risk of progression and requires intensive treatment and monitoring.

Currently, adequate clinical measures, whether with perimetry or OCT, exist to diagnose vision loss and structural damage in glaucoma, but these modalities can detect only losses that have already occurred. Medeiros et al found that glaucomatous eyes had an average RGC loss of 28.4% before an early visual field defect could be detected; in 20% of patients with early defects, more than 40% of RGCs had been lost.[35] In contrast, Harwerth et al demonstrated a linear relationship between structure and function when utilizing a pointwise analysis of the visual field.[36] Research on different types of perimetry have delved into identifying earlier signs of RGC loss with various stimuli, including short-wavelength automated perimetry and frequency doubling technology.[37,38] Despite those modalities' potential to detect earlier functional loss,[39-41] standard automated perimetry remains the gold standard. Prior research suggests that altering the visual field stimulus size and/or contrast in perimetry can help to detect earlier defects,[42,43] although these settings are largely fixed in commercially available devices. OCT can detect the early loss of retinal nerve fiber layer thickness, even in preperimetric glaucoma.[44-46] However, OCT may be prone to imaging artifacts and false segmentation, particularly in the presence of an epiretinal membrane and high myopia, which could lead to a false interpretation.[47-50]

Although the diagnosis of glaucoma has improved, current methods of disease monitoring do not provide direct insight into an individual's risk of progression or the health of the remaining RGCs. This information is essential if a precision medicine approach to glaucoma is to be adopted. The landmark United Kingdom Glaucoma Treatment Study (UKGTS) used a rigorous visual field testing protocol consisting of 11 visits in 24 months, with clustering of tests at baseline, 18 months, and 24 months for a total of 16 visual field tests. With this protocol, far beyond what is clinically feasible, it still took a year to detect visual field progression reliably.[4] Tan et al recently demonstrated that front-loading Swedish interactive thresholding algorithm-faster visual field tests may increase testing frequency while maintaining reliability.[51] Although the method holds promise, future implementation studies must be conducted for it to be deployed in clinical settings. Home monitoring of visual fields may have a role in the future as a potentially cost-effective solution for stringent monitoring.[52-54] Patients could also perform clustering of visual fields or frequent testing themselves, which could detect changes earlier.[53,55]

AI and deep learning are also being applied (with some success) to retinal fundus photographs and OCT images to aid in diagnosis and the detection of disease progression.[56-59] Although AI image screening could be useful for detecting glaucomatous progression, some obstacles must be overcome before clinical implementation can occur.[60,61] These include establishing a proper ground truth for glaucomatous progression as well as developing standardized AI strategies to accommodate input data from different sources.

An individual's risk of glaucoma could also be assessed using genetics and metabolomics. The latter studies the metabolites in the body. Genome-wide association studies can be used to calculate polygenic risk scores (PRSs) for patients with glaucoma,[10,62-64] and they offer a potential new tool for stratifying patients based on their risk of progression using a blood or saliva sample. Craig et al demonstrated that PRSs could accurately identify people with early glaucoma who were at increased risk of progression and the likelihood of surgical intervention being required in people with advanced glaucoma.[10] In another study, patients with a high polygenic risk were 2.5-fold more likely to develop glaucoma.[64] Although promising, PRS studies are still in the trial phase and must be applied to different populations and in longitudinal studies to determine whether the predictive power of PRSs can facilitate the timely treatment of high-risk patients.

Metabolomics can enable the identification of potential systemic biomarkers and assist in drug discovery for glaucoma. Previous work identified a series of metabolites that are increased or decreased in concentration in patients with POAG.[65,66] In particular, investigators identified reduced levels of nicotinamide as an important feature in POAG, supporting its potential as a therapeutic agent for glaucoma. Previous studies have also found that the metabolomic signature of POAG points to mitochondrial dysfunction.[67] Such studies support their further investigation as potential therapeutic targets in the diagnosis and treatment of POAG.

"THAT THOUGH THE RADIANCE WHICH WAS ONCE SO BRIGHT BE NOW FOREVER TAKEN FROM MY SIGHT. THOUGH NOTHING CAN BRING BACK THE HOUR OF SPLENDOUR IN THE GRASS, GLORY IN THE FLOWER. WE WILL GRIEVE NOT, RATHER FIND STRENGTH IN WHAT REMAINS BEHIND."—William Wordsworth

While it is known that RGCs are compromised in glaucoma, there is no strong clinical evidence for any neuroprotective therapies to support RGC health and function. A range of additional neuroprotective therapies have been proposed, including brimonidine, citicoline, coenzyme Q10, and gingko biloba.[68-70] Some preclinical studies have suggested that these compounds have neuroprotective properties. Brimonidine was once touted as a potential neuroprotective agent but failed to demonstrate a significant effect in clinical trials.[71] The potential neuroprotective properties of citicoline have been shown in multiple experimental models of glaucoma.[72,73] Coenzyme Q10 has been demonstrated as a mitochondrial-targeted antioxidant that could prevent RGC degeneration in rodent models,[74-77] and clinical trials are underway.[78] Gingko biloba extract has been suggested to improve blood flow around the optic nerve head,[79] and some small studies suggest that it may have potential clinical utility.[68,80]

One promising therapy is high-dose nicotinamide supplementation. Oral supplementation with the metabolite provided robust neuroprotection in rodent models of glaucoma.[22,32] Follow-up studies have shown the potential of high-dose nicotinamide (3 g/day) to support RGC function in patients with glaucoma.[81] In a 6-month, placebo-controlled crossover study, patients with glaucoma were randomly assigned to high-dose nicotinamide or placebo for 12 weeks,[31] after which they crossed over to the other treatment without a washout period. After 12 weeks of nicotinamide treatment, a significant improvement in RGC function, as measured by the photopic negative response on electroretinography (ERG), was observed in approximately 25% of patients. Patients treated with nicotinamide also showed a tendency for improved visual field parameters compared to those who received placebo. Larger and longer-term clinical trials are required to show the clinical utility of high-dose nicotinamide supplementation in glaucoma.

Large-scale clinical trials of neuroprotection in glaucoma are limited by their inherent difficulty. Glaucoma clinical trial endpoints depend on a range of clinical tools, including perimetry, that require at least 12 months to detect changes in vision reliably,[82] making neuroprotection studies lengthy and expensive to run. One of the most recent large-scale clinical trials testing neuroprotection by memantine failed to reach its primary endpoint of visual field progression after 2 years.[83]

Another issue is determining whom to target in clinical trials. Theoretically, at any disease stage, a retina will have a population of healthy, sick, and dying or dead RGCs. However, if only patients with early disease are recruited for a trial, then it may be too hard to detect clinical signs of change. If patients with advanced disease are recruited, then it may be too late for intervention to be useful. Patients with moderate glaucoma represent a spectrum of disease status, so large sample sizes are required to achieve the statistical power needed to find significant changes.

Yet another issue is which clinical parameters should be used to classify what is early, moderate, or advanced glaucoma. Does this classification, moreover, truly reflect the RGC health status of each patient? Herein lies the conundrum faced in glaucoma clinical trials.

"HOPE IS BEING ABLE TO SEE THAT THERE IS LIGHT DESPITE ALL OF THE DARKNESS."—Desmond Tutu

DIAGNOSTIC TESTING

ERG has been used to detect short-term changes in retinal function over as little as 3 months after a change in glaucoma treatment.[84] ERG was also used in the short-term nicotinamide randomized controlled trial to demonstrate improved retinal function.[31] Moreover, as mentioned earlier, home monitoring of visual fields may play a role. In a recent study, patients with glaucoma were amenable to at-home

testing of visual fields over 12 months with high retention rates.[54]

A longitudinal 2-year randomized controlled trial of nicotinamide in glaucoma (NCT05275738, NCT05405868) will explore the ability of methods beyond perimetry, including ERG, OCT, and metabolomics, to detect changes due to nicotinamide supplementation. The research is a global collaboration designed to provide substantial clinical evidence showing whether nicotinamide should be incorporated into glaucoma management. Clinical trials are also underway to investigate the effects of nicotinamide and pyruvate (NCT05695027) and nicotinamide riboside (ChiCTR 1900021998).[85]

DIET

Current evidence suggests that a ketogenic diet—a diet high in fat and low in carbohydrates—may be neuroprotective. This diet has been shown to be beneficial in other diseases, including epilepsy, Alzheimer disease,[86-88] and Parkinson disease,[89,90] potentially by reducing reactive oxygen species and preventing the loss of mitochondria.[26,91] In a mouse model of glaucoma, a ketogenic diet produced a robust antioxidant response and significantly improved RGC survival.[92] One study examining food frequency questionnaires showed that, although low-carbohydrate diets were not associated with a risk of POAG, a high-fat and high-protein diet (obtained from vegetables) was associated with about a 20% reduced risk of POAG with paracentral visual field loss.[93] Although this diet has been shown to improve quality of life in patients with multiple sclerosis and Alzheimer disease, evidence of its neuroprotective effect is limited.[94] Further, the regimen is difficult to maintain and can cause gastrointestinal side effects.

LOOKING AHEAD

Targeting bioenergetic insufficiency and metabolic dysfunction has the potential to be translated rapidly to the clinic. In addition to these strategies, several exciting therapeutic avenues are showing strong promise preclinically. As a result, the future of patients with glaucoma looks bright.

Identifying the right patients for the right therapies. More comprehensive screening of patients might be beneficial (although the cost might outweigh the benefit), and the use of PRSs might help define who is at risk and who is most likely to benefit from certain treatments. The integration of biopsies or blood work (where candidate biomarkers have been identified) could provide an additional benefit.

Predicting progression. Although there are valuable tools for diagnosing glaucoma, predicting its progression is a different story. The typical spacing of clinic visits also limits the clinician's ability to gain a rapid understanding of a given patient's disease progression. Home monitoring might provide additional data points without requiring an office visit.

Accelerating clinical trials. Glaucoma clinical trials are arduous, which slows the translation from bench to bedside. The landmark UKGTS showed that, by increasing the number of clinic visits, a treatment effect could be observed in less than 12 months. Current research suggests that ERG may have a similar role in decreasing clinical trial time, with the photopic negative response showing a nicotinamide treatment–related change within 12 weeks.[31,84]

Stem cell therapy. Stem cell therapy has shown potential for the treatment of select retinal diseases. Stem cell therapy for glaucoma is advancing, but many hurdles remain, including integrating RGCs into diseased tissue, reconnecting synaptic connections (or making new ones), and facilitating the long-range projection of RGC axons to the brain.[95]

Optic nerve regeneration. Despite major advances in the field and achievements in long-range axon regeneration, several obstacles still must be overcome. These include facilitating axon regeneration beyond the optic chiasm and into the brain and the reintegration of lost synaptic connections.[96]

Gene therapy. Gene therapy has been successful for monogenic eye diseases. One example is voretigene neparvovecrzyl (Luxturna, Spark Therapeutics), which targets *RPE65* in retinitis pigmentosa. Although most glaucoma cases are polygenic, several targets have been identified for gene therapy. These include tropomyosin receptor kinase B/brain-derived neurotrophic factor[97] and nicotinamide mononucleotide adenylyltransferases.[22,98] Numerous regulatory hurdles must be cleared before gene therapy for polygenic glaucoma can enter the clinic. However, clinical trials are being planned that may yield the first gene therapy treatment for glaucoma in the coming years.

CONCLUSION

Although IOP lowering is still the mainstay of glaucoma management, it is promising to see a wealth of new research and resources for patient diagnosis and stratification, glaucoma biomarkers, and novel neuroprotective therapies on the horizon. Work in other fields, especially in other neurologic and ophthalmic diseases, is informative and provides a platform of technology for further scientific exploration in the glaucoma space.

Given the surge in glaucoma research in recent years—both clinical and experimental—there is light at the end of the tunnel. ■

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