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NEWSLETTER
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Finding Positives in Delay: RRF Funded Researcher Studies Resilience to Diabetic Retinopathy (RDR)

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Delays aren't usually seen as good, but in the case of the body's response to diabetes and the development of diabetic retinopathy (DR), there may be a silver lining. Dr. Andrius Kazlauskas' team at the University of Illinois at Chicago is studying how the human retina can resist damage from high blood sugar, a condition caused by diabetes.

About one-third of people with diabetes have DR, a complication that can lead to blindness. DR usually appears many years after the onset of diabetes, eventually developing in 80% of people with either type 1 or type 2 diabetes. This is concerning, especially since DR is a major cause of blindness in working-age people, and thereby impacts productivity and increases healthcare costs. The number of people afflicted with DR is expected to rise with the ever-increasing number of individuals who develop diabetes.

In a recent conference call with RRF, Dr. Kazlauskas shared that resilience to DR (RDR), which is the long delay from the onset of DM to the development of DR, is a well-known clinical phenomenon and exciting research opportunity because RDR is not well understood.

To explore the RDR phenomenon, Dr. Kazlauskas created mouse and human cell models of RDR. Using the mouse RDR model he found that diabetes instructs retinal blood vessels to engage a defense system against diabetes-driven death. As the duration of diabetes increases, this defense deteriorates and cells within the vasculature of the retina begin to die. Such blood vessels are dysfunctional and therefore unable to support the needs of the neural retina. The collective consequence of these changes is DR, progressive accumulation of damage to the retina.

Dr. Kazlauskas proceeded to use the cell-based model of RDR to investigate the nature of this defense system. His group discovered that elevated glucose (the hallmark of diabetes) not only damages cells within blood vessels, but also boosts their capacity to repair such damage. As long as the rate of repair exceeds the rate a damage, cells remain healthy in the face of high glucose. Ongoing research is focused on why the defense eventually fails. Such information will enable development of new therapeutic approaches to indefinitely delay the onset of DR.

Image credit: Dr. Kazlauskas. Dysfunction of retinal blood vessels in diabetic retinopathy causes them to leak and proliferate, and thereby compromise vision.

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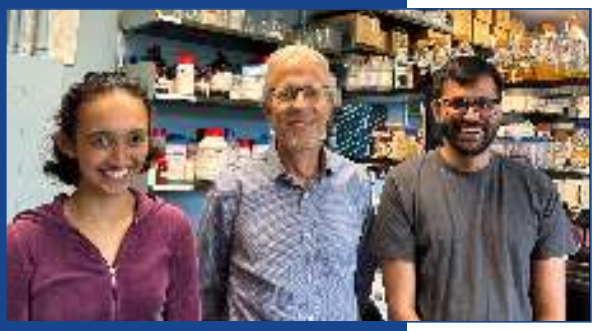

RRF has funded Dr. Kazlauskas' research since 2021. The latest findings from his team were published in the May 2024 issue of the journal *Progress in Retinal and Eye Research* in an article titled "Resilience To Diabetic Retinopathy." Visit retinaresearchfnd.org to learn more about Dr. Kazlauskas' work.

Members of the Kazlauskas Lab who are supported by RRF.
From left to right: Trupti Potdukhe, MS (PhD graduate student), Andrius Kazlauskas, PhD, Manav Gandhi, MS (PhD graduate student).

Tears Do More Than Just Meet the Eye

Tears of happiness? Tears of sadness? Tears of frustration? Complex emotions for sure, but surprisingly, your tears themselves are more complex than you might think, and they fulfill important functions in keeping your eyes healthy.

Tears of happiness?

Three Types of Tears

There are three types of tears: emotional tears that result from all our various feelings, basal tears that regularly protect our eyes, and reflex or irritant tears that remove things like dust or dirt from your eye.

Tears are produced as part of the body's autonomic nervous system that involuntarily controls functions like breathing and blinking. Every time you blink, a thin layer of basal tears, called "tear film" spreads across the surface of your cornea, the clear outer layer of the eye. Tears come from glands above your eyes, and lipids and mucus come from glands inside the upper and lower lids. Tears then drain into your tear ducts, the small holes in the inner corners of your eyes and down through your nose.

Three Tear Layers

Basal "tear film" has three different layers:

- The inner mucus layer covering the cornea helps the tear film stick to the surface of the eye,
- The watery "aqueous" middle layer keeps the eye wet and nourishes the eye tissue. It consists of many different components such as proteins, electrolytes and antimicrobial and anti-inflammatory agents,
- The oily outer layer made up of lipids keeps the watery layer of tears from drying up or evaporating too quickly and makes the eye surface smooth.

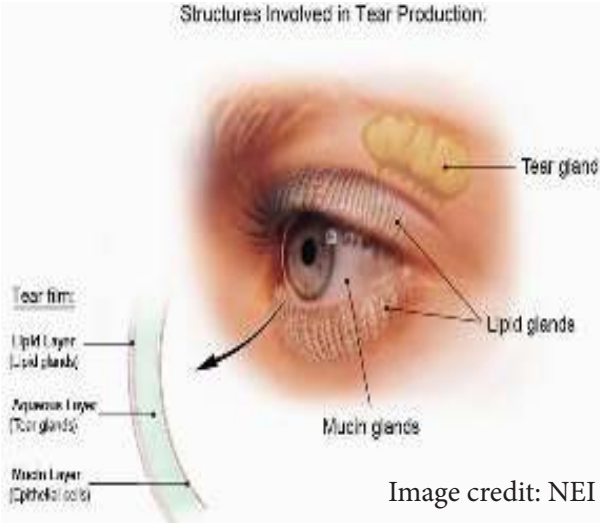

Image credit: NEI

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Basal tears keep your eyes wet and smooth, and help focus light so you can see clearly. They protect your eyes from infection and irritating things, and are a first line of defense against the effect of heat on your eyes. High summer temperatures can cause the eye tear film to evaporate more quickly, resulting in dry eye symptoms, including redness, irritation or a burning sensation. When it is hot outside, staying hydrated will support your body's ability to produce an adequate volume of tears.

Reflex tears are the body's response to having something in your eye or perhaps when you are cutting an onion. They are involuntary and formed when your eyes need to wash away harmful irritants. The eyes release them in larger amounts than basal tears, and these tears may contain more antibodies to help fight bacteria.

Like reflex tears, **emotional tears** also are produced in higher quantities than basal tears. However, unlike basal and reflex tears, emotional tears can be held back voluntarily, and they can stop when you want them to.

Tear Facts:

- Tears are normally present in the eyes from birth and throughout life,
- Humans produce 30 gallons of tears a year,
- The main function of tears is to clean, protect and lubricate the eyes,
- Tears have antibacterial properties,
- Tear production tends to decrease as a part of the aging process,
- Tears are essential to maintain healthy eyes.

As we age, there is a decline in tear film function, tear flow declines and the composition of tears changes, with the outer lipid layer loosing thickness, which allows evaporation. The structures that produce tears may become clogged and not work properly, causing your eyes not to make enough tears. Research shows that these changes, combined with environmental factors, such as air pollution, dust, smoke, medications, low humidity, screen time and eye surgeries may increase the risk of developing dry eye disease (DED), an ocular surface disorder. It is estimated that about 16 million people in the U.S. have dry eye, and it can be a complication of other health issues such as diabetes or allergies, or follow menopause.

The symptoms of dry eye are:

- Discomfort or pain,
- Feeling like there's something in your eye,
- Redness, stinging, burning or itching,
- Sensitivity to light,
- Blurry vision, including difficulty performing everyday activities, such as reading.

If you are experiencing symptoms, you may require medical attention. Visit your ophthalmologist to diagnose the cause and receive appropriate treatment, because left untreated, severe dry eyes may lead to eye inflammation, abrasion of the corneal surface, corneal ulcers and possibly vision loss due to corneal scarring.

Sources: NEI, umiamihealth.org, clevelandclinic.org

Online Vision Simulator Illustrates Vision Loss Caused by Retinal Diseases

It can be challenging to explain a change in your vision to others or even, to understand it yourself. Online tools may offer some help if you are experiencing vision changes and want to better understand the condition and to share what you are experiencing with your friends and family. Janssen, now Johnson & Johnson Innovative Medicine, has developed an online tool that shows retinal disease progression and vision loss simulations for diabetic macular edema, diabetic retinopathy, age-related macular degeneration (AMD), and inherited retinal diseases: X-linked retinitis pigmentosa (XLRP), and achromatopsia, a cone disease affecting one's ability to see color. The tool's elements provide an introduction to these retinal diseases using visuals and everyday language that help to explain these complex conditions to patients and their families.

The Vision Simulator, which can be found online at: https://www.retina.janssen.com/vision-simulator provides for each disease: a short video that summarizes the condition, an interactive patient perspective of healthy vision and vision affected by the disease, a cellular view, and an example of the diagnostic imaging tool physicians use, an optical coherence tomography (OCT) scan. For some of the diseases, there is also an interactive 3D model feature to use to explore the inside of the eye to better see exactly where the disease is affecting the eye's tissues. While Janssen's simulator focuses on retinal diseases, there are also simulators that cover other eye conditions like myopia, commonly called nearsightedness and glaucoma that you will find if you search online for "vision simulator."

The Vision Simulator is an interactive virtual experience that explores retinal eye diseases and their effects—seen from everyday life to the cellular level inside the eye.

Sources: Janssen Vision Simulator, https://www.retina.janssen.com/vision-simulator; Adapted from article by Sydney M. Crago, Modern Retina, April 23, 2024.

Two New RRF Appointments at McPherson Eye Research Institute

As part of the RRF research program, RRF supports physician scientists in academic positions at the McPherson Eye Research Institute, University of Wisconsin-Madison. Recently, two new three-year appointments effective July 1, 2024, were announced:

Appointment to the RRF Daniel M. Albert Chair

Bikash Pattnaik, PhD
Associate Professor
Department of Pediatrics
Department of Ophthalmology & Visual Sciences

Dr. Bikash Pattnaik is a world-renowned retinal electrophysiologist with expertise in ion channelopathies that lead to severe, childhood-onset blinding disorders. His highly collaborative and productive research team has had great impact on the fields of retinal pigment epithelium (RPE) cell biology, mouse models of inherited blindness, retinal gene therapy, and novel therapeutic delivery systems. He has received numerous honors, fellowships and awards, including his recent induction as a Silver Fellow of the Association for Research in Vision and Ophthalmology (ARVO). Dr. Pattnaik has previously held both the RRF Rebecca Meyer Brown Professorship and the M.D. Matthews Research Professorship, and has been a member of the University of Wisconsin-Madison faculty since 2008.

Appointment to the RRF M.D. Matthews Research Professorship

Timothy Gomez, PhD
Professor
Department of Neuroscience

Professor Gomez is a pioneer and leader in the study of mechanisms of neuronal axon guidance and growth cone dynamics related to autism, development and regeneration of the retina, and tuberous sclerosis complex (TSC), a disease that affects the brain, retina, and optic nerve. His laboratory uses a diverse array of model systems to understand molecular mechanisms of normal neural circuit development and defects that occur in these disorders. A relatively new goal of the Gomez lab, is to understand how retinal circuits develop and how photoreceptor connections with bipolar cells may be restored after damage or loss due to outer retina injury or diseases such as macular degeneration and retinitis pigmentosa.

Dr. Gomez became a faculty member at the University of Wisconsin-Madison in 2000.

A Reader's Question…

Following publishing of the cover article in the last newsletter, RRF received a question about a diabetic medication, metformin, and whether it impacts the retina and might cause vision complications. The short answer is that metformin may have protective effects on some retinal diseases.

Metformin is a medication prescribed as a first-line treatment of Type 2 diabetes. It has been available in the U.S. since 1995, is taken orally and works differently than the semaglutides, like Ozempic, to lower blood glucose, sugar.

Robert Shmerling, MD, Senior Faculty Editor, Harvard Health Publishing, has referred to the medication as potentially a "wonder drug," helpful for conditions beyond diabetes. Metformin has been demonstrated to have protective effects in many different diseases, including stroke, cancer, dementia, glaucoma, and cardiovascular disease.[1] Its anti-inflammatory and antioxidant properties, reduction of blood glucose levels and improvement of blood vessel health and antiangiogenic properties, warrant continuing research to further understand whether metformin use influences the risk of age-related eye illnesses such as AMD and diabetic retinopathy.

The medication has been studied in both preclinical and clinical studies with evidence that there may be some favorable effect on retinal diseases. Scientists affiliated with the University of Chicago, in 2022 conducted a comprehensive review of key studies related to metformin and retinal diseases in order to provide a better understanding of research conducted to date and help stimulate future studies to better elucidate the role of metformin in retinal diseases.[2]

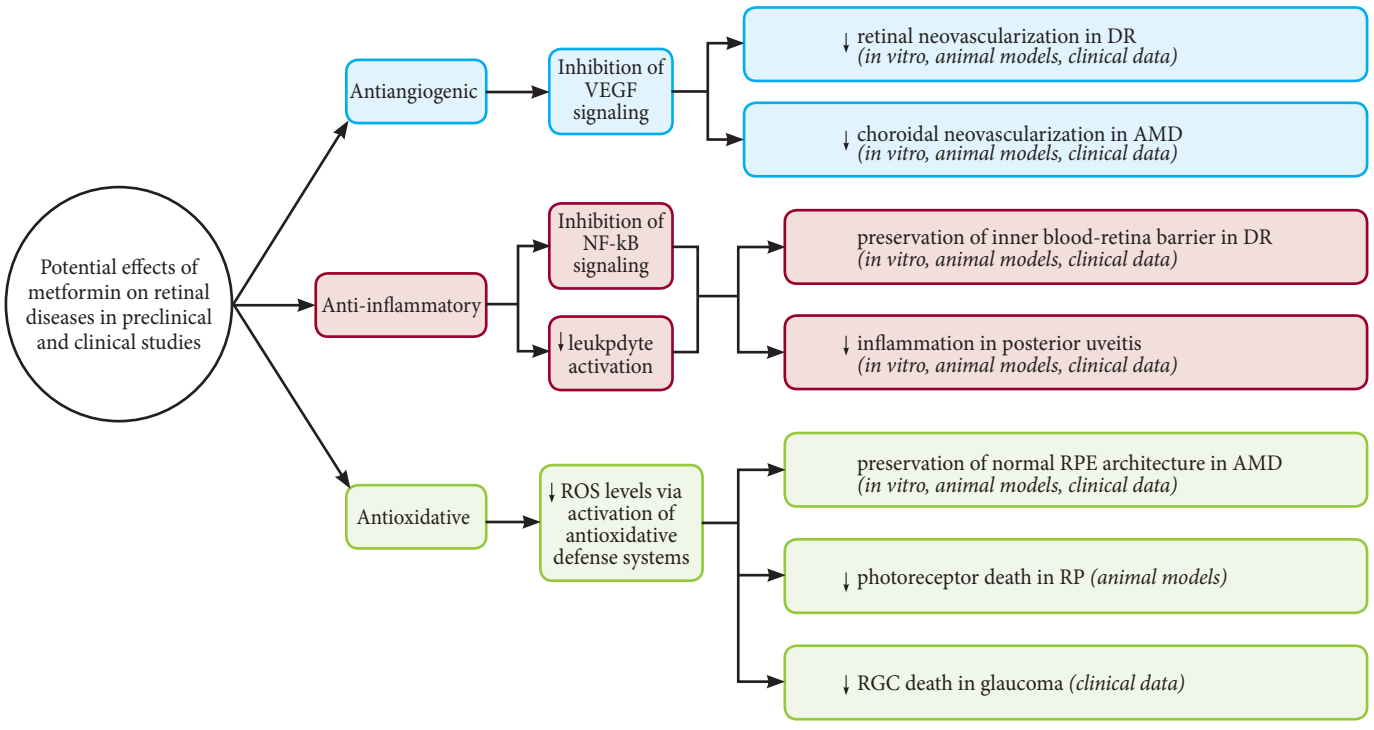

Figure 1. Potential effects of metformin on retinal diseases in preclinical and clinical studies.

Adapted from Amin, Experimental Biology and Medicine[2]

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Metformin as a Preventative Treatment for Diabetes Retinopathy (DR)
Data reviewed from a few large retrospective studies suggest that metformin is protective both against the development of DR in patients with diabetes and in reducing the severity of the disease, but it did not protect against progression to sight threatening DR in those who already had the disease. This suggests that earlier metformin use has a greater impact on manifestation of pathologic retinal disease, even before DR develops. The medication may represent a new therapeutic preventative and strategy for treatment of diabetes retinopathy, but further study through prospective clinical trials needs to be conducted.[2]

Metformin as a Preventative Treatment for Age-related Macular Degeneration (AMD)
A meta-analysis study published in June, 2024, aimed to determine the role of metformin as a prophylactic therapy against AMD. Authors reviewed 10 randomized, control clinical trials covering 1,447,470 patients. The pooled analysis showed no statistically significant role of metformin in decreasing AMD risk, and authors recommend that metformin should not be considered as a prophylactic treatment for AMD. They further concluded that more research is necessary to confirm these findings. [3]

As is sometimes the case when researching a topic using different approaches, scientists may offer differing conclusions. A study released in February, 2024, conducted by researchers at the University of Chicago, detailed findings of a case-controlled analysis of claims data of diabetic patients compared with diabetic patients newly diagnosed with neovascular age-related macular degeneration (nAMD). The study preliminarily found that people who take oral metformin have 5% lower odds of developing nAMD than people who do not use the diabetes drug. The effect increase correlates with dosage increase and the protective effect increases to 9% reduced odds of developing nAMD in diabetic patients who do not take insulin. Researchers concluded that metformin use was associated with reduced odds ratio of nAMD, particularly in patients without diabetic retinopathy. The protective effect was noted for 24-month cumulative doses below 1,080 g thus suggesting that metformin may be a novel preventive strategy for nAMD.[4] Since these findings show a result that may indicate a slight protective effect, more research is needed to try to further resolve the protective or prophylactic effect of metformin across various forms of this retinal disease.

Metformin's protective effects have also been evaluated for inherited retinal diseases such as retinitis pigmentosa, glaucoma, retinal vein occlusion and uveitis, and while retrospective clinical data is sparse, the review suggests that metformin may represent a new therapeutic preventative strategy for these retinal diseases as well. The caveat as Dr. Shmerling said, is that metformin's role in preventing or treating diseases beyond diabetes, and possibly even slowing aging and extending life expectancy, is still not definitively clear. While the research is promising, more evidence is needed before endorsing metformin's widespread use for people without diabetes.

If you are currently taking or considering taking metformin for diabetes management, research suggests that metformin does not have negative effects on the retina and the medication might even offer protective benefits for multiple retinal diseases. Make sure to share this medication information with your ophthalmologist at a future visit so that it is accurately noted in your medical record.

Sources:
1 Is metformin a wonder drug? Health.harvard.edu/blog.

2 Shivam V Amin, et al. Metformin and retinal diseases in preclinical and clinical studies: insights and review of literature. Ex.Bio.Med. 2022; 247:317-329.

3 Elhalag RH, et al. The role of oral metformin in preventing and treating age-related macular degeneration: A meta-analysis. Medicine 2024; 103:28(e38728).

4 Metformin Shows Potential to Prevent Neovascular AMD. Medscape.com.

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