AMWC CHINA

2024 10/18–20

ANTI-AGING OF OUR OPTIC NERVE – DREAM OR REALITY?

Dr.Sylvia Paulig, Martin Krause
PAULIG EYE & HEALTH, Berlin, Germany

PURPOSE

Over the last 15 years we have examined over 12 000 patients, experiencing a reduction in nerve fiber thickness, suspected to suffering from Low (or normal) Tension Glaucoma.
Current treatment options for this type of glaucoma are limited and the mechanism of it is not fully understood.

BASICS TO KNOW and some definitions around the background

1. Anti-aging medicine – is a branch of medical science and their application.
Goal is to treat underlying causes of aging to extend healthy lifespan of humans and their organs.

2. Regenerative medicine – deals with the healing of various diseases by restoring dysfunctional cells or organs through biological replacement or/and stimulating body's own regeneration and repair processes.

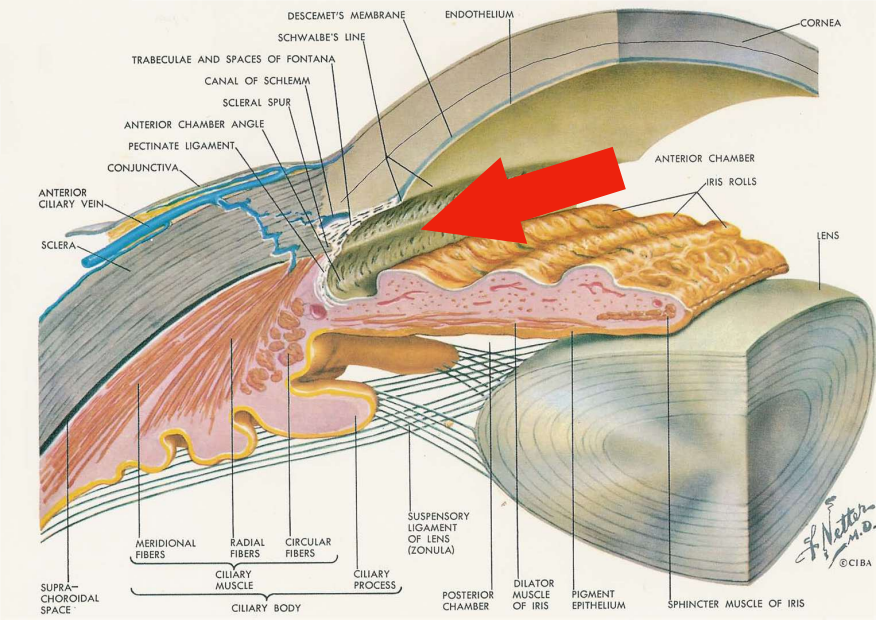
3, Glaucoma – is a set of eye diseases that cause damage to the optic nerve and leads to vision loss. Some types are characterized by high eye pressure, some not.

4. SLT (Selective Laser Trabeculoplasty) – is a noninvasive and painless procedure to lower intraocular eye pressure.
It is a safe and repeatable procedure. Newer studies show, that there are additional advantages as well.
SLT is not limited to lower eye pressure by lowering outflow resistance but activate macrophages and clean the trabecular meshwork.

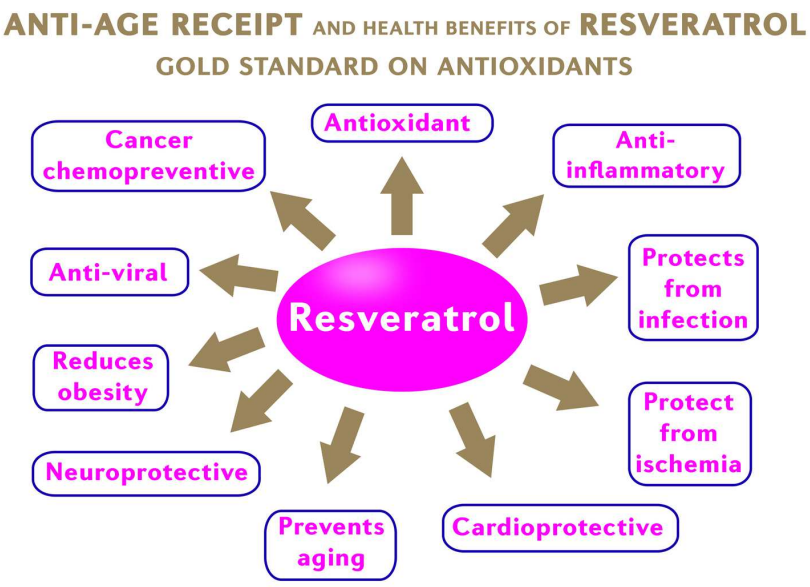
Our SLT Laser is a Neodymium–YAG–Laser.
Wavelength: 532 nm
Spot size: 400 micron
Energy: 0,2 – 2 mJ / pulse
Treatment time: 3 ns / pulse

We did perform 2 sessions per eye
(each session 2 quadrants and between 20 to 50 pulses).
We did only treat the cells in trabecular meshwork,
which contain melanin.

Illustration of the treatment area



5. Resveratrol – is a type of polyphenol, produced by several plants in response to injury or when the plant is under attack by pathogens.
It has many effects in body, in Ophthalmology most interesting is the neuroprotective effect on retinal ganglion cells and improvement of mitochondrial biogenesis. Mitochondria play a key role in health and disease and their function is not limited to energy production.



6. What did we examine in the eye?

- Visual acuity
- Refraction
- Tonometry (eye pressure)
- Slit lamp examination anterior and posterior segment of the eye
- Optic field
- Pachymetry
- OCT (optical coherence tomography)

7. Regenerative medicine approach – utilization of body's own cells to activate healing processes and involve removal of metabolic waste.
Our strategy aimed to activate macrophages and enhance phagocytosis and autophagy.
Our goal was to protect healthy and regenerate the damaged nerve fibers.

8. Pathways of SLT in trabecular meshwork

Laser effect

Development of macrophages

Macrophages at work

„Cleaned" trabecular meshwork

(Courtesy of R. Peschke and S.Paulig)

OBJECTIVE

The goal was to determine whether reducing metabolic waste can promote regeneration of damaged nerve fibers and protect against blindness in patients with normal eye pressure.
This research is highly relevant in cases such as normal tension glaucoma (NTG), where patients experience optic nerve damage despite having normal intraocular pressure.

Estimates of 60 - 80% of glaucoma patients may not benefit from traditional IOP-lowering treatments.
Instead the focus must shift toward understanding and addressing other underlying factors, such as vascular dysregulation, oxidative stress and metabolic waste.
a) **Methodology** – For our study we used Optical Coherence Tomography (OCT) to measure the thickness of retinal nerve fiber layer (RNFL) before (Baseline) and after Selective Laser Trabeculoplasty (SLT). This follow ups were repeated yearly to monitor changes in RNFL thickness.

b) **Resveratrol supplementation** – We initiated a regimen of 100 mg Resveratrol supplementation, integrating cutting-edge insights from ophthalmology with the latest advancements in anti-aging and regenerative medicine.
Resveratrol is renowned for its potent neuroprotective effects and its remarkable ability to promote the regeneration of nerve fibers.
By enhancing mitochondrial energy production and stimulating macrophage activity, Resveratrol shows significant promise in supporting neural repair and overall cellular rejuvenation.

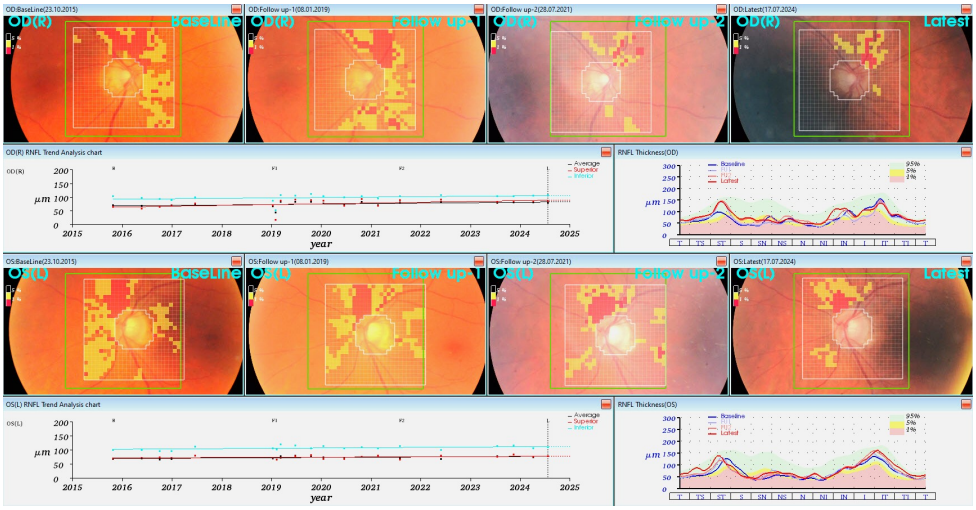
RESULTS

Since 2007, we have been utilizing Selective Laser Trabeculoplasty (SLT) as part of our treatment approach and since 2012, we've incorporated Resveratrol supplementation.
Over the years we have treated approximately 12,000 patients.
This extensive experience highlights the efficacy of SLT alongside the neuroprotective and regenerative properties of Resveratrol, offering a unique, integrative approach to patient care.

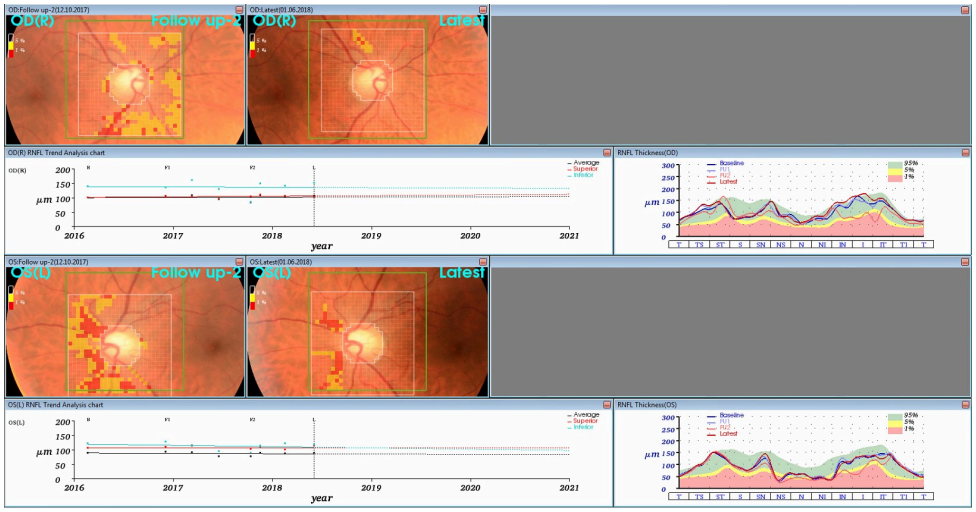
The intraocular pressure was either already well-controlled or consistently low due to the presence of low-tension glaucoma.

Please review the OCT images before and after SLT treatment, showcasing 6 representative patient cases, which reflect the overall outcomes.

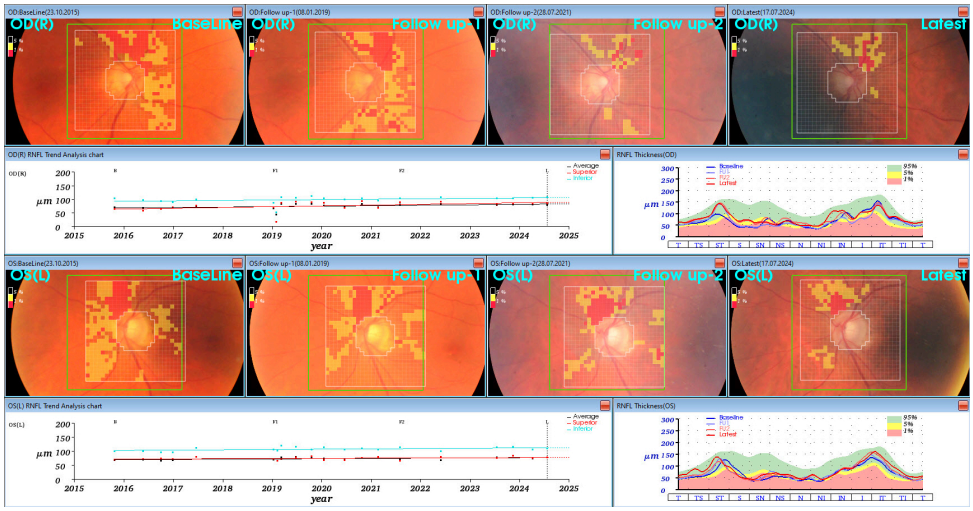
Patient 1



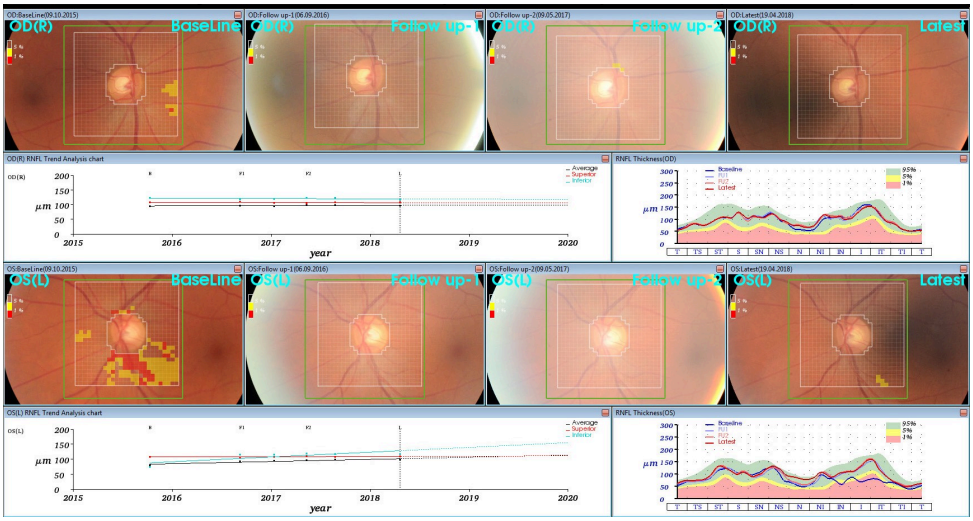
Patient 2



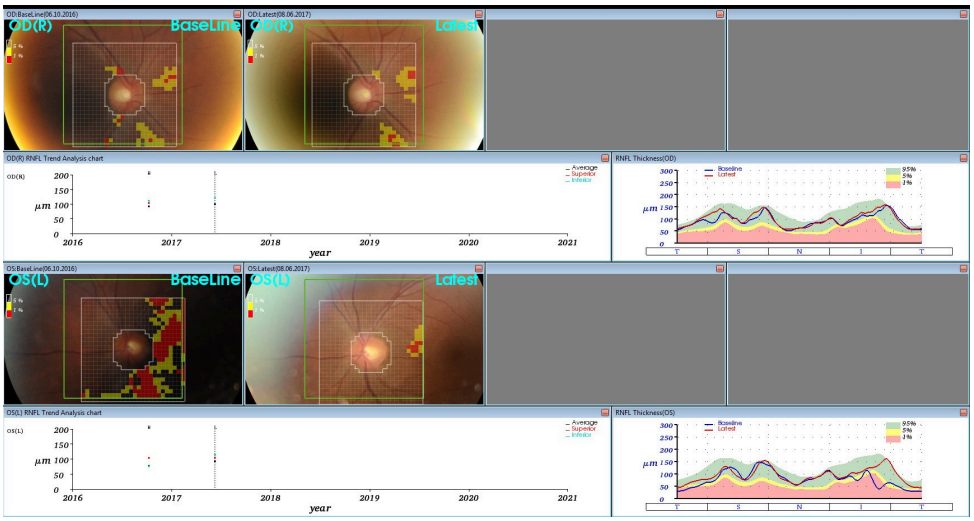
Patient 3



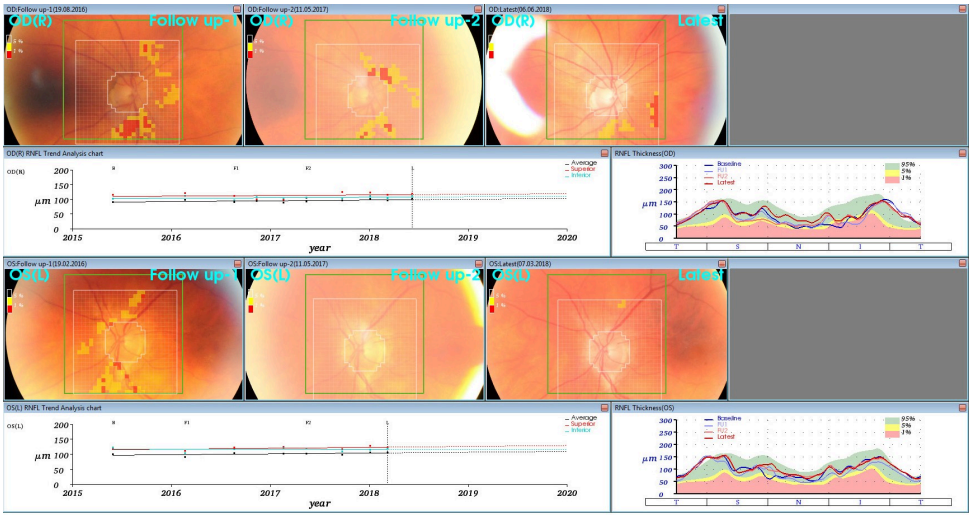
Patient 4



Patient 5



Patient 6



DISCUSSION

Glaucoma is a complex neurodegenerative disease and leading cause of blindness worldwide.
It is characterized by progressive visual dysfunction and degeneration of retinal ganglion cells and axons, that carry visual information from eye to brain.

Aging and low energy is significant for glaucoma because metabolism slows with aging but vision is a highly energetic process.
Axons require a great deal of energy. Up to 70% of all energy is used by neurons, just to maintain the resting membrane potential.
Energy and so axonal energy is generated in the mitochondria.

Our central nervous system prefers glucose as it's substrate, glucose enters the brain, retina and optic nerve.
Axon degeneration and mitochondrial dysfunction are energy related pathologies.

Different authors did examine the relation between energy deficit and axon disease
(Campbell et al. 2014, Rawson et al. 2014, Zhou et al. 2016).
It was demonstrated, that ATP homeostasis is important to axon survival and mitochondria / axon protection.

Mitochondrial dysfunction is one of important factors, responsible for many diseases such as age related macular degeneration and glaucoma in eye.

„IF THE MITOCHONDRIA ARE HEALTHY, THE PERSON IS HEALTHY".
(Prof.Huber and Prof. Metka Vienna 2023)

The reason for mitochondrial dysfunction is an imbalance between development of energy and the amount of free radicals, ROS (Reactive Oxygen Species).

The lack of energy in our eyes is leading to different diseases, glaucoma is one of them.
The level of oxidative stress in eyes is increased as a result of energy deficit, so mitochondrial dysfunction arises ((Erb / Konieczka 2018).

Not only the lack of energy but unstabil delivery of oxygen damages optic nerves.
When mitochondria function poorly they trigger inflammatory responses, leading to various diseases, including neurodegenerative conditions.

Let's talk about macrophages, existing in various tissues and can be activated in eye by SLT laser procedure. I mentioned this already.

Macrophages play essential roles in cleaning by phagocytosis, in autophagy and aging of tissues.
The essential function of macrophages is to sanitize cellular fragments produced by tissue remodeling and apoptosis, leading to cell death.
Phagocytosis is an essential function (Chen 2023).

SLT targets pigment cells without causing thermal damage to adjunctive structures.
It stimulates the body's own healing response to lower eye pressure and activate autophagy.
After SLT several chemotactic and vasoactive agents like Interleukins are released.
This Cytokins recruit macrophages, which „eat up" the obstructive proteins and clear the trabecular meshwork channels.

And how do macrophages know, which cells to eat?
Dead cells send out what scientists call „eat me" signal, they release chemicals that attract macrophages.

Healthy cells do not expose Phosphotidylserine on their surface to induce phagocytes to „eat“ them.

Contradictory AMPK (adenosinmonophosphate-activated protein kinase) - curse and blessing

AMPK is an energy sensor, activated when energy is low, organisms responding by slowing aging and increasing resistance to diverse age related pathologies, including neurodegenerative diseases.
AMPK plays a vital role in regulating mitochondrial activity.

There is an impaired ability of AMPK to generate new mitochondria in aged organisms but in the same time ROS are increased.
Result is unstable oxygen delivery with chronic hypoxia and oxidative stress with cells problems to hold their biological activity.

IF ATP AND NUTRIENTS PROVIDING IS LOW - AMPK LEVEL IS HIGH.

So the trigger signal for AMPK is the absence of energy, leading to reduced biosynthetic pathways.

The opponent of AMPK is mTOR (mammalian Target of Rapamycin) , it’s active when energy has a higher level and nutritients are available.
AMPK is responsible for removing toxins, autophagy of damaged proteins, regeneration and mTOR is building up new tissues when energy is high and nutrients are available.
Both are indicator for energy and nutrition in cells and both are influencing each other, working like a metabolic „one way“.

Imbalance of AMPK and mTOR increases chronic and degenerative diseases.

Bottom line: GROW AND REST !

Japanese Oshumi 2016 : „Autophagy must be activated regularly in order to keep cells clean and functioning well“.
Recycling is essential for life otherwise we face senescence, a complex phenomenon associated with cell loss and dysfunction as well as decrease in ability of cells to respond to stress.

D. Shukal 2022 : „AMPK is a potential therapeutic target for treatment of various diseases, including eye disorders. AMPK plays a precise role as a master regulator of cellular energy homeostasis“.

M.Otsubo 2024: „Protective effects of Brimonidine may be at least partially associated with AMPK activation“.

Metformin is an activator of AMPK and promotes axonal regrown of sensory axons.
„Metformin activates AMPK pathways“. (Li 2014)

AMPK enhances the destruction of dying cells and removal of intrazellularem waste, so it slows and reverses aging of organs.

Reznich 2007: „Mitochondria activation declines in age and Reactive Oxygen Species are increased because of AMPK impaired ability to generate new mitochondria.

🤔 **So if AMPK has a protective effect we need to work on this fact.** 🤷‍♀️

But there are some other voices as well: „AMPK hyper activation promotes neuronal dysfunction“. (Belforte 2021)

„AMPK activation decreases axonal retrograde mitochondrial transport.
Inhibition of AMPK promotes axonal growth of sensory axons.“ (Waters 2020)

And Autophagy?

Autophagy in the optic nerve refers to the process by which cells within the optic nerve degrade and recycle damaged or unnecessary cellular components.
This mechanism is crucial for maintaining cellular health, particularly in the context of neurodegenerative conditions and injuries affecting the optic nerve.

It can potentially play a role in protecting against or slowing down diseases like glaucoma, optic neuropathy and other conditions involving retinal ganglion cell death.
Autophagy also aids in reducing inflammation and promoting cellular repair, making it a key area of interest in optic nerve research.

Impairment of autophagy leads to the accumulation of misfolded proteins, dysfunctional mitochondria and ultimately results in axonal degeneration.

This disruption in cellular maintenance hampers the optic nerve's ability to clear damaged components, contributing to neurodegenerative processes and worsening conditions such as glaucoma and optic neuropathy.

Osborn 2016: „Glaucoma is a neurodegenerative disease associated with increased eye pressure, impairment of vascularization, oxidative stress, aging, axonal flow and mitochondrial function“.

BUT

After regulation/lowering eye pressure the disease and progression continues in many cases (Weinreb 2016) and axon degeneration and loss of retinal ganglion cells continues as well.

Resveratrol possesses a wide range of beneficial properties, including antioxidant, anti-inflammatory, and neuroprotective effects.
It promotes cellular health by enhancing mitochondrial function, supporting autophagy, and combating oxidative stress.

Additionally, Resveratrol is known for its potential to improve cardiovascular health, protect against neurodegenerative diseases, and may even play a role in extending lifespan by activating certain longevity pathways such as SIRT1.
Its multifaceted benefits make it a promising compound in the fields of anti-aging and regenerative medicine.

Resveratrol helps prevent the accumulation of homocysteine in the blood and inhibits the formation of new homocysteine.

By regulating homocysteine levels, Resveratrol may reduce the risk of cardiovascular diseases, as elevated homocysteine is a known factor contributing to vascular inflammation, endothelial dysfunction, and increased oxidative stress.
This property adds to Resveratrol's broad protective effects on cardiovascular and overall health and it supports cellular resilience and longevity.

Lee 2017: „Aqueous humor puncture shows increased level of homocysteine“.

Resveratrol mimics the effects of caloric restriction by activating similar biological pathways, particularly the SIRT1 pathway, which is associated with longevity and improved metabolic function.

NAD+ dependent SIRT 1 plays a crucial role in cellular regulation, particularly in aging metabolism and stress resistance.
Like caloric restriction, Resveratrol enhances mitochondrial function, reduces oxidative stress and promotes autophagy, all of which contribute to cellular health and longevity.

This "caloric restriction mimetic" effect makes Resveratrol a promising compound for extending lifespan and improving health span and protection against age–related diseases without the need for significant reductions in caloric intake.

SIRT 1 – Autophagy axis as a neuroprotective pathway was demonstrated in 2023 by Lee and Yu.

Resveratrol activates AMPK and plays a key role in this energy regulating pathway.
By stimulating AMPK, Resveratrol enhances cellular energy balance, promoting processes like glucose uptake, fatty acid oxidation and mitochondrial biogenesis.

This activation not only boosts energy metabolism but also helps reduce oxidative stress, inflammation and supports longevity.
So Resveratrol is a powerful agent in metabolic regulation and overall cellular health.

CONCLUSION

After performing over 12,000 SLT treatments for glaucoma and supplementing a significant percentage of patients with Resveratrol we have observed, that glaucoma is indeed a multifactorial condition.

Our findings underscore the complexity of glaucoma, highlighting that it involves a range of contributing factors beyond intraocular pressure, including neurodegenerative, vascular, and cellular mechanisms.
That means, we need to examine different locations that are interconnected with each other and relevant to the treatment.

- SLT
- Macrophages
- Phagocytosis
- Autophagy
- Mitochondria
- Energy level
- AMPK
- Apoptosis
- Resveratrol
- SIRT 1
- Homocysteine
- Inflammation
- Age
- Lifestyle (whole epigenetic mechanisms)

WHAT WE LEARNED
IT IS ALL ABOUT HOMEOSTASIS OF ENERGY AND EPIGENETIC PATHWAYS, CLEANING AND REMOVING OR REBUILDING OF DESTROYED CELLS,AND REDUCING INFLAMMATION.

Even our genes are influenced by epigenetic factors and healthy lifestyle, all parameters, influencing our optic nerve and so glaucoma and of course every organ, healthy aging and so longevity.

We observed an improvement in optic nerve fiber thickness reflectively transitioning from degeneration to regeneration of optic nerves.

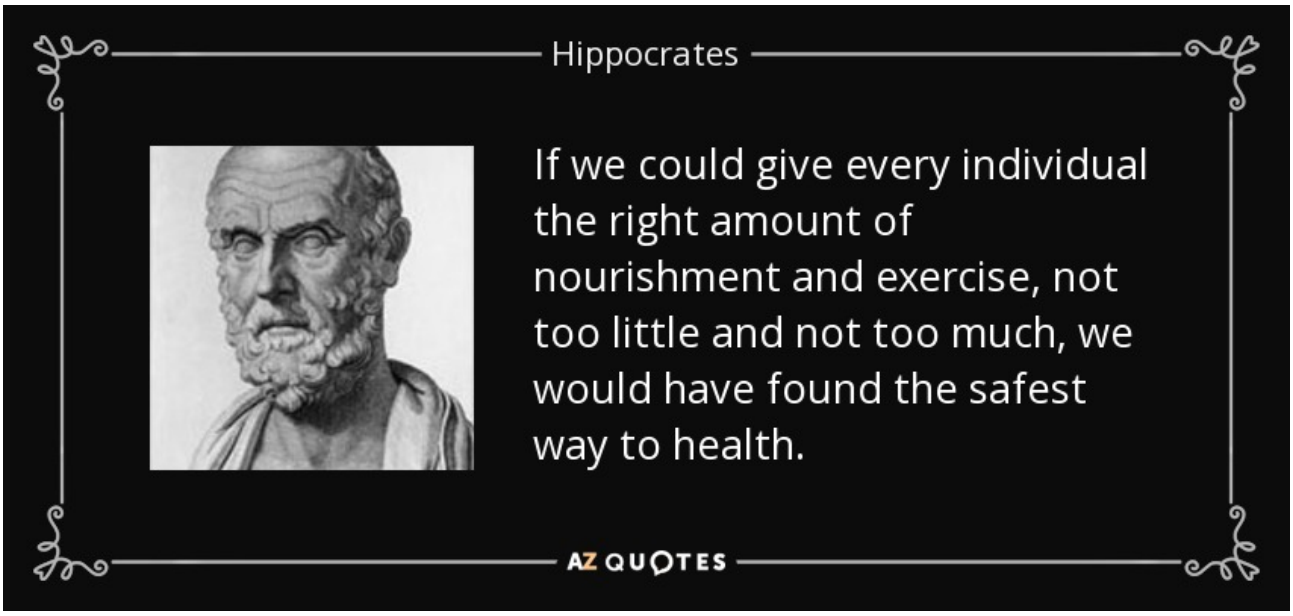
Our work highlights the importance of interdisciplinary medical treatment and offers valuable insights for longevity and anti-aging research supported by a substantial clinical database.

SLT Laser should not be limited for reducing intraocular pressure.
In low tension glaucoma it's possible to improve cell metabolism.

An important conclusion is increasing the amount of mitochondria and improving their activity by using different activators like Resveratrol (important is it's permeability of blood brain barrier) but also epigenetic factors such as caloric restriction, exercising and caring about balance of AMPK homeostasis and so of energy flow.

SLT with Resveratrol combined influences each other's effect in glaucoma treatment.

This treatment is not only healthy and without negative side effects but also very cost consuming and so interesting from economical and political point of view.



FUTURE DIRECTIONS

Our clinical work serves as an excellent foundation for further studies in glaucoma, longevity and anti-aging medicine, aligning with ongoing research, such as that by Professor David Sinclair and his group at Harvard University in United States.

Our findings contribute to the brother scientific understanding of reversing aging processes and improving health outcomes.

• Metabolic waste accumulates as a result of cellular processes and its buildup can contribute to oxidative stress and inflammation, both of which are harmful to nerve cells, including the optic nerve.
If reducing metabolic waste decreases oxidative stress and inflammation, it could create a healthier environment for nerve cells, potentially leading to the regeneration of damaged nerve fibers.

• Protecting the optic nerve from damage could prevent or slow the progression of glaucoma, even when eye pressure is normal. By reducing metabolic waste, we might help to maintain mitochondrial function and enhance the survival of neurons, potentially preserving vision.

• Therapeutic Avenues? Potential treatments could include antioxidants or agents that enhance the removal of metabolic waste, either through pharmacological / micronutrient means or lifestyle interventions, like diet and exercise.

This approach could be a novel and promising way to manage or even reverse neurodegenerative conditions affecting the eyes, particularly for patients whose symptoms are not linked to elevated eye pressure.

ANTI-AGING OF OUR OPTIC NERVE – DREAM OR REALITY?

Anti-aging of the optic nerve is no longer just a dream but a tangible reality. However, further studies are essential to better understand the pros and cons of AMPK homeostasis and how epigenetic lifestyle factors can be integrated into this research.