No Blindness In Low Tension Glaucoma Anymore? New Treatment Option.

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Purpose

We did study the effect of Resveratrol in combination with SLT treatment on more than 2,000 of our Low Tension Glaucoma patients. Our main point of view was an activation of macrophages / cleaning and detoxication of trabecular meshwork / role and increase of mitochondria in retinal ganglion cells / improving of nerve fiber thickness, showing in OCT / GDX by application of Resveratrol, additional to SLT.

Basics to know:

1. SLT (Selective Laser Trabeculoplasty)

SLT Laser Optotek YAG / SLT M

- Frequency doubled Q-switched pulsed Nd: YAG laser
- Wavelength 532 nm
- Spot size: 400 micron
- Energy: 0.2 – 2.0 mJ/puls
- Treatment time: 3 ns/puls
- Two treatment sessions per eye (superior / inferior)

2. Resveratrol

Resveratrol is a Phytoalexin, belongs to Polyphenols. It is an ingredient of red grapes or different plants.

Ophthalmologische Nachrichten
Resveratrol im Fokus des
3. Eye Nutrition Meeting in Barcelona
HO
OH
OH
Resveratrol
C14H12O3

Our micronutrition pills with Resveratrol.

Ingredients:

Resveratrol 100,0 mg

Vitamin B2 (Riboflavin) 1,4 mg
Vitamin B3 (Niacin) 16,0 mg
Vitamin B6 Pyridoxin) 1,4 mg
Vitamin B7 (Biotin) 0,05 mg
Vitamin C 240,0 mg

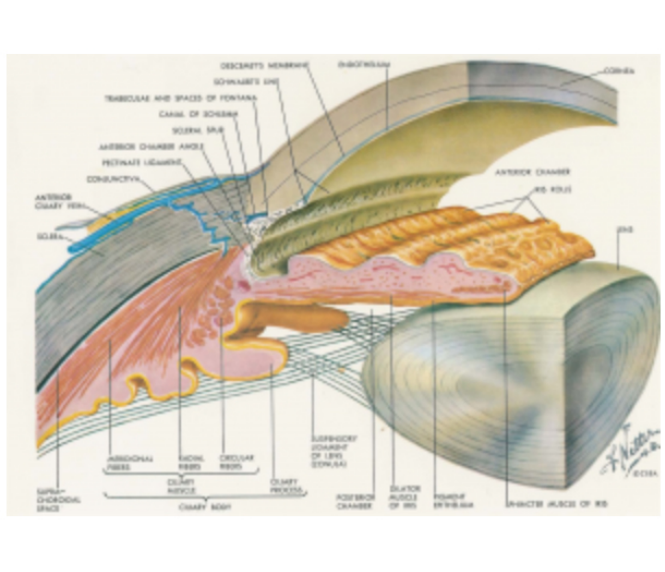
Iron 14,0 mg
Copper 1,0 mg
Zinc 10,0 mg

Methods

More than 2,000 of our Low Tension Glaucoma patients were treated with Selective Laser Trabeculoplasty (SLT) in the last 4 years.

SLT means glaucoma treatment in a physiological, natural manner without inducing damage to the trabecular meshwork. Because of the very good absorption of the SLT laser beam in pigmented, melanin containing, trabecular cells, a selective irritation of the pigmented trabecular cells develops. This induces an increased release of different cytokines, which significantly improve the function of the endothelial cells of Schlemm's canal. The cytokines have a chemotactic effect. It increases the concentration and formation of macrophages in the trabecular meshwork without tissue damage, resulting in a higher permeability and an improvement of the aqueous humor flow.

Illustration of the treatment area



Laser parameter:

- Frequency doubled Q-switched pulsed Nd: YAG laser
- Wavelength 532 nm
- Spot size: 400 micron
- Energy: 0.2 – 2.0 mJ/puls
- Treatment time: 3 ns/puls

We started with a whole examination:

- Visual Acuity
- Refraction
- Tension
- Fundus (excavation)
- Optic Field
- GDX / OCT
- Pachymetry

Our study includes patients with Low Tension Glaucoma, some of them in early stages.

We did perform two laser treatments per eye, superior area and inferior area in separate sessions. Between each session was a recovery time of at least 22 days.

We did perform the final examination 3 months after the last SLT session.

Like before SLT, we performed a complete eye check, including OCT, after the four laser sessions.

In most cases worldwide SLT is a treatment to lower intraocular eye pressure. This was not what we were looking for.
Our interest of view was to find out, what happens with nerve fibers, is there any recovery possible?

To improve the results of SLT treatment we did recommend our patients, to take every day one tablet of micronutritions, containing 100mg Resveratrol, during the whole laser treatment period until final examination 9 – 12 months after treatment start.

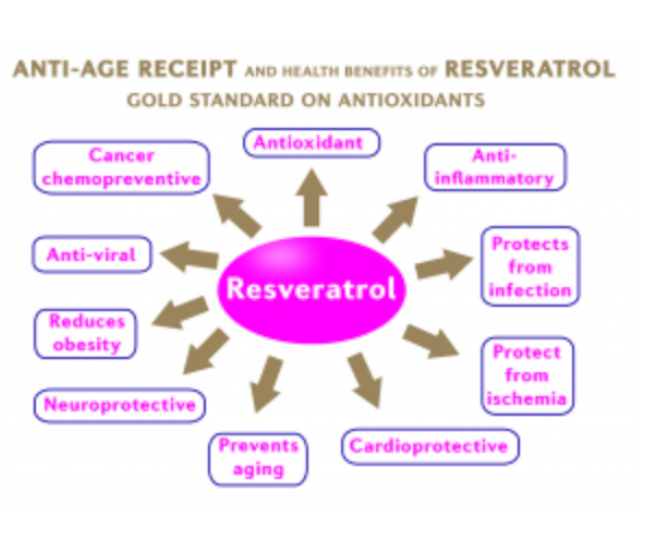
We recommended an intake of the tablets either in the morning with breakfast or around noon together with the lunch.
We told the patients that a little fat would improve the bioavailability of Resveratrol.

Resveratrol has a neuroprotective effect on glaucoma. Increased intraocular pressure increases oxidative stress on the retina and trabecular meshwork. This leads to increased inflammatory markers such as interleukin-1α, interleukin-6, interleukin-8 and for faster cell aging by oxidative species such as lipofuscin in the cells of the trabecular meshwork and the optic nerve.

Resveratrol reduces the expression of these substances and therefore has an antioxidative and anti-apoptotic effect in the trabecular meshwork and in the neurons of the optic nerve.

Resveratrol increases expression of Sirtuin genes similar to caloric restriction and we will show later, what happens intracellular.

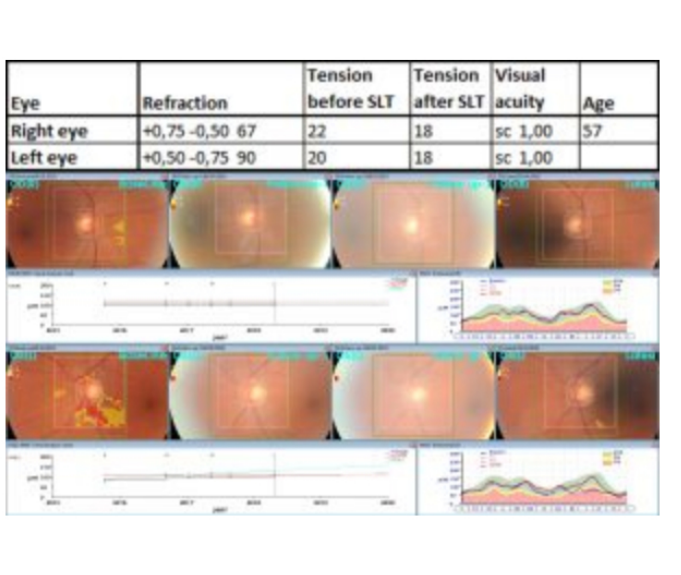
Resveratrol is multipotent and important for many diseases.



Results / Discussion

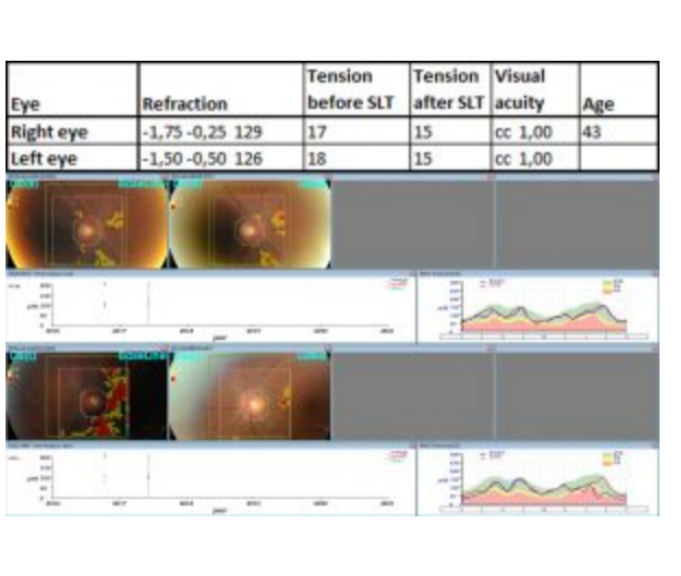
We would like to introduce 12 cases, 24 eyes, representing 2,000 patients. The patients were treated within the last four years. In all shown cases we corrected the intraocular eye pressure already, considering each patients pachymetry.

Case 1



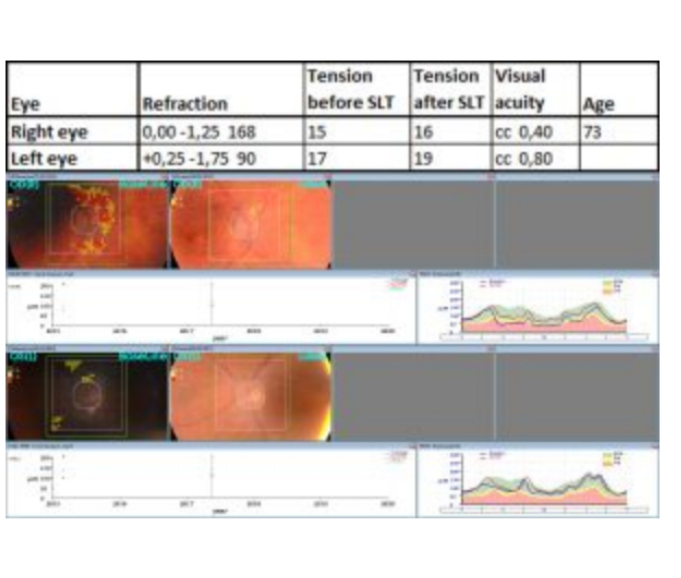
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	+0,75 -0,50 67	22	18	sc 1,00	57
Left eye	+0,50 -0,75 90	20	18	sc 1,00	

Case 2



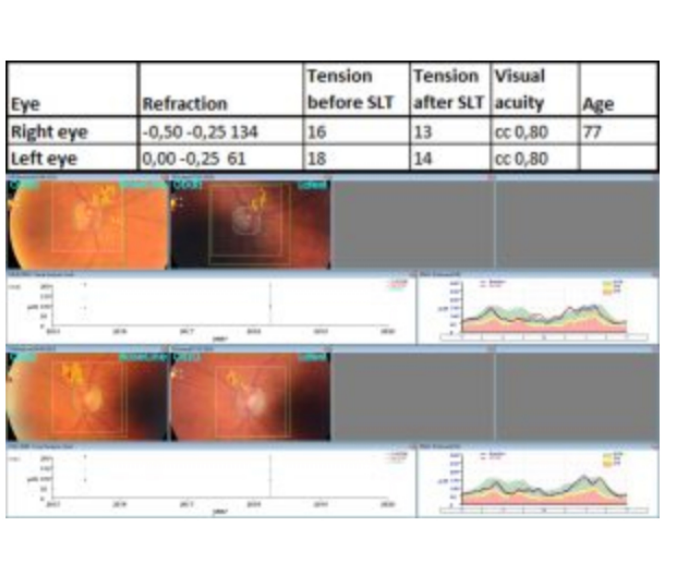
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-1,75 -0,25 129	17	15	cc 1,00	43
Left eye	-1,50 -0,50 126	18	15	cc 1,00	

Case 3



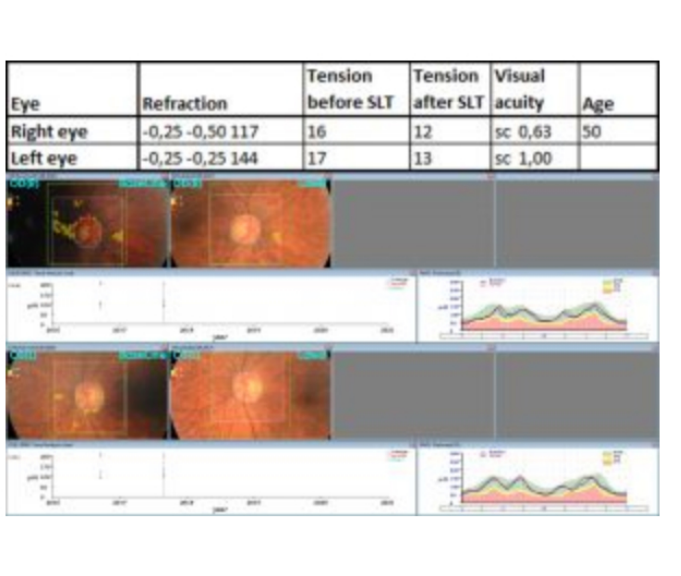
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	0,00 -1,25 168	15	16	cc 0,40	73
Left eye	+0,25 -1,75 90	17	19	cc 0,80	

Case 4



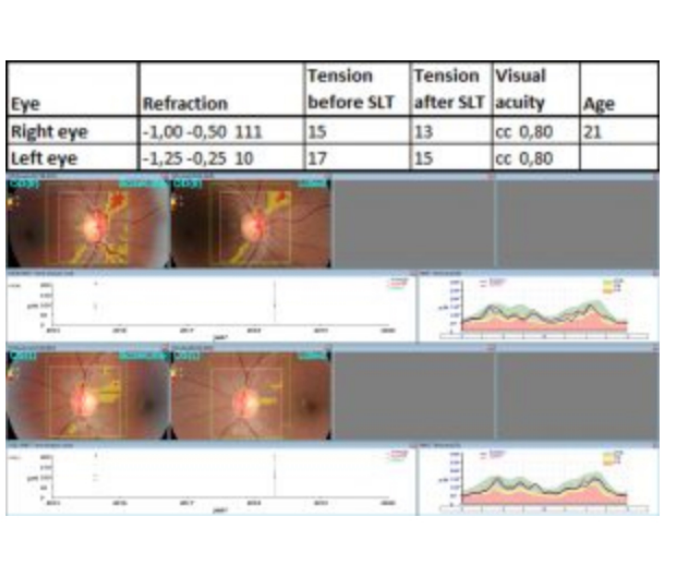
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-0,50 -0,25 134	16	13	cc 0,80	77
Left eye	0,00 -0,25 61	18	14	cc 0,80	

Case 5



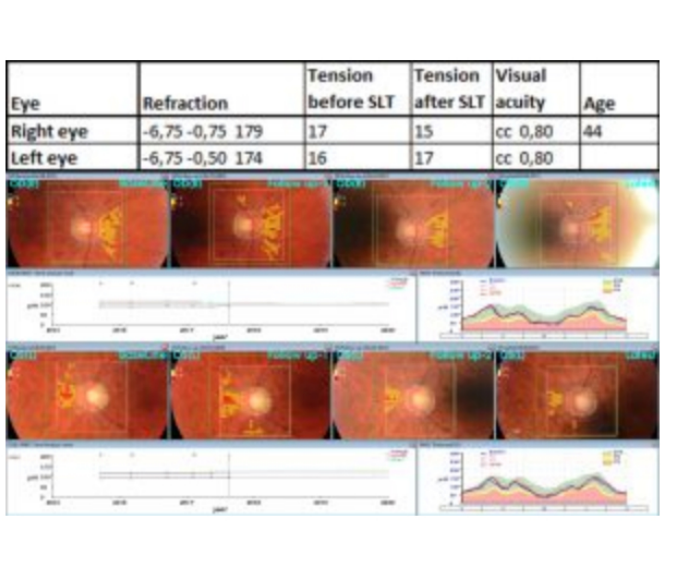
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-0,25 -0,50 117	16	12	sc 0,63	50
Left eye	-0,25 -0,25 144	17	13	sc 1,00	

Case 6



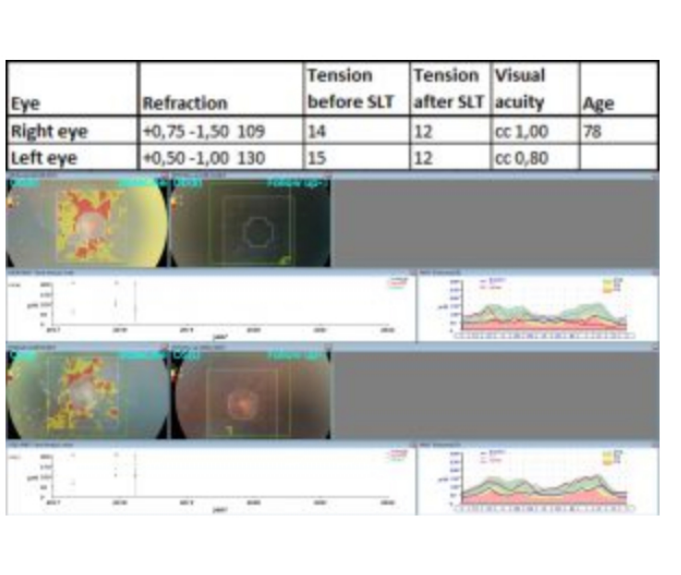
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-1,00 -0,50 111	15	13	cc 0,80	21
Left eye	-1,25 -0,25 10	17	15	cc 0,80	

Case 7



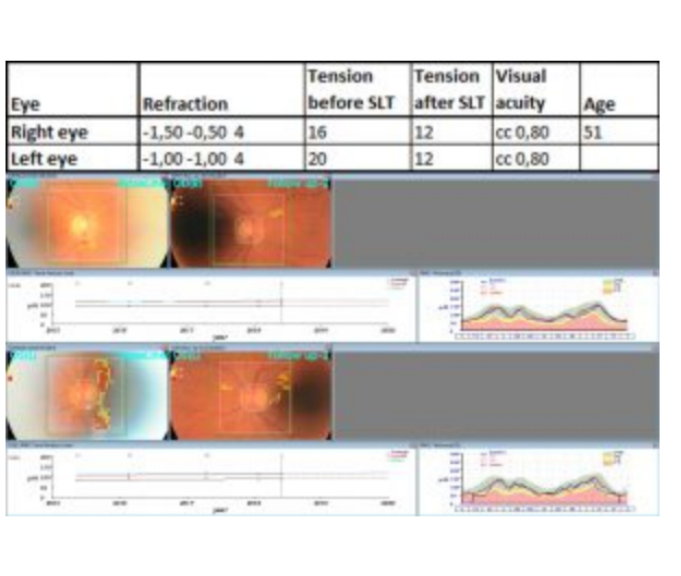
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-6,75 -0,75 179	17	15	cc 0,80	44
Left eye	-6,75 -0,50 174	18	17	cc 0,80	

Case 8



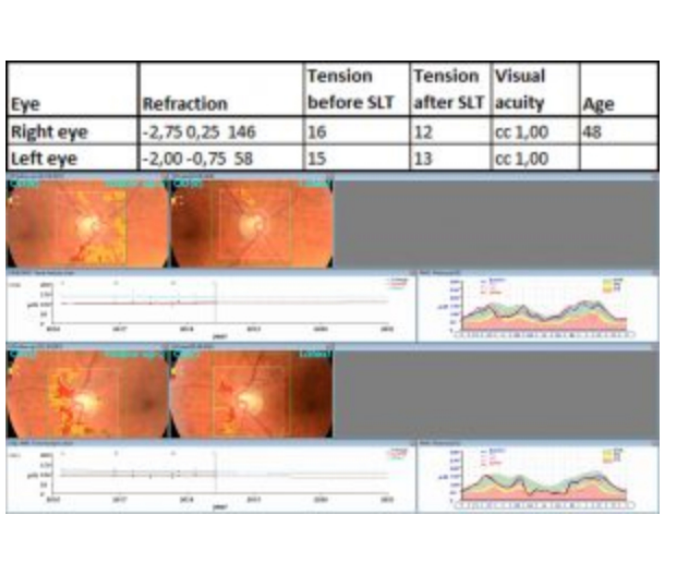
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	+0,75 -1,50 109	14	12	cc 1,00	78
Left eye	+0,50 -1,00 130	15	12	cc 0,80	

Case 9



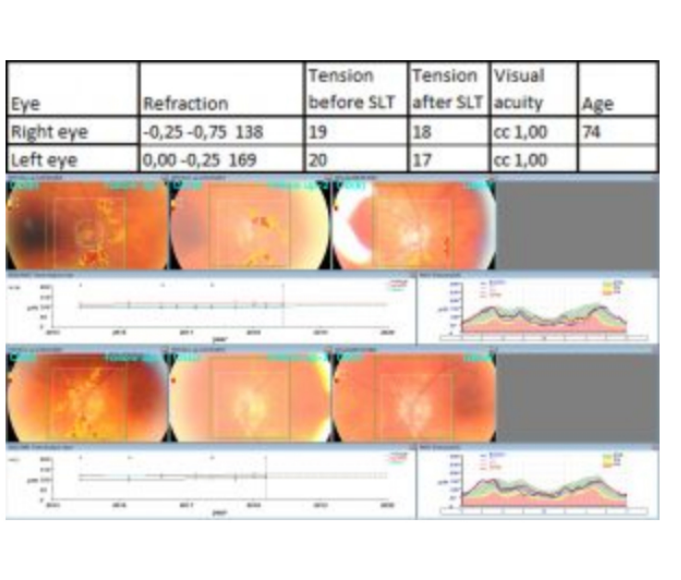
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-1,50 -0,50 4	16	12	cc 0,80	51
Left eye	-1,00 -1,00 4	20	12	cc 0,80	

Case 10



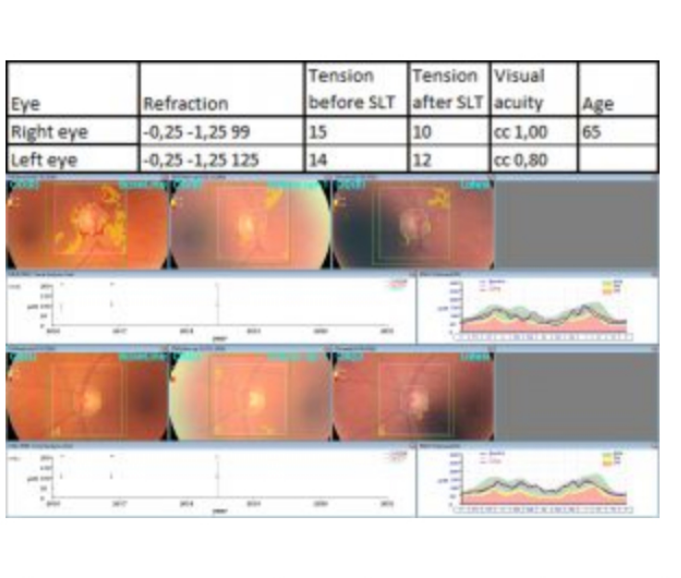
Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-2,75 0,25 146	16	12	cc 1,00	48
Left eye	-2,00 -0,75 58	15	13	cc 1,00	

Case 11



Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-0,25 -0,75 138	19	18	cc 1,00	74
Left eye	0,00 -0,25 169	20	17	cc 1,00	

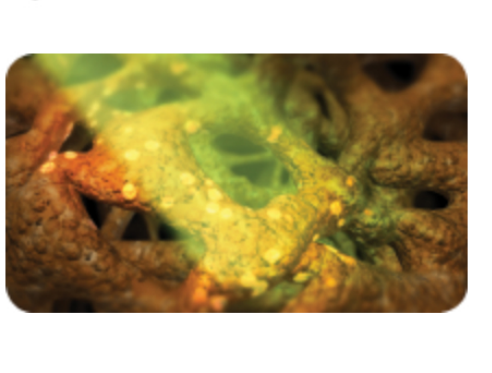
Case 12



Eye	Refraction	Tension before SLT	Tension after SLT	Visual acuity	Age
Right eye	-0,25 -1,25 99	15	10	cc 1,00	65
Left eye	-0,25 -1,25 125	14	12	cc 0,80	

In all cases the optic field was without pathological symptoms before and also after treatment.

Pathways of SLT in trabecular meshwork



SLT laser effect

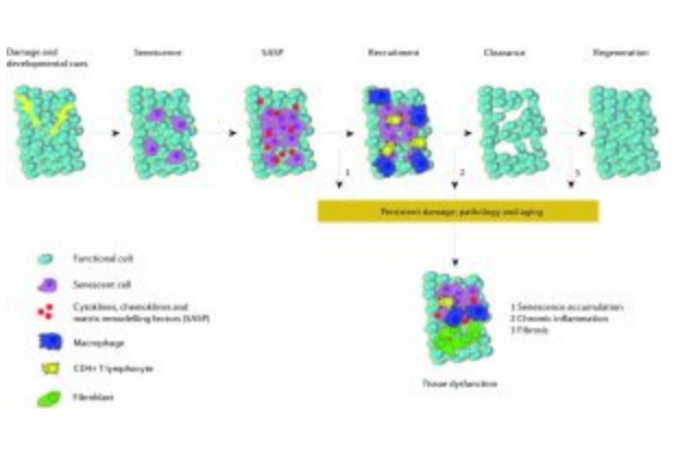
Development of macrophages

Macrophages at work

„Cleaned" trabecular meshwork

What happens in the cell?

In the following overview it is visible, that induction of macrophages flow can reverse the damaging process. Using macrophages the cells are able to follow the way of clearance and regeneration instead of tissue dysfunction.



This is what we are inducing by using Selective Laser Trabeculoplasty. The concentration of macrophages in trabecular meshwork is increased after the treatment. Phagocytose, clearance and regeneration of cells can be improved.

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

Aging and low energy is significant for glaucoma because metabolism slows with aging, vision is a highly energetic process.

Axons require a great deal of energy, up to 70% of all energy used by a neuron, just to maintain the resting membrane potential.

Axonal energy (ATP) is generated in the mitochondria. The central nervous system prefers glucose as its substrate, glucose enters the brain and optic nerve (the retina as well).

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 to be the site of axon protection (Avery et al., 2012) though preventing mitochondrial transport into axons.

Retinal ganglien cells are the primary affected neuronal population with a critical insult damaging their axons in the optic nerve had. This insult is typically secondary to harmfully high levels of intraocular pressure.

Mitochondrial homeostasis is linked to multiple pathways known to modulate aging.

Mitochondria play diverse roles in processes as disparate as apoptosis, intermediary metabolism.

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

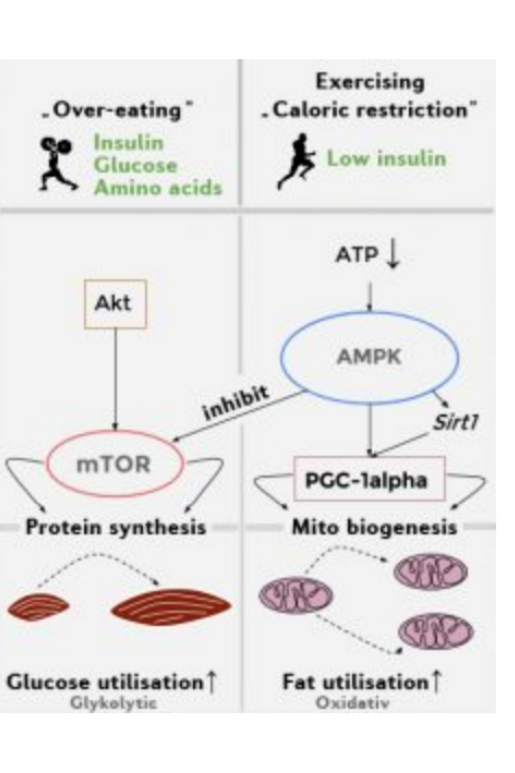
Reason for mitochondrial dysfunction is an imbalance between development of energy and the amount of free radicals, reactive oxygen species (ROS). Lack of energy and increased oxidative overcome in eyes is the result, leading to different eye diseases such as glaucoma. It seems to be the cause of the development of mitochondrial dysfunctions (Erb / Konieczka 2018). The level of oxidative stress in eyes increases as a result of energy deficit.

Not the lack of oxygen but instable delivery of oxygen damages the optic nerve. Result is oxidative stress, damaging mitochondries, responsible for delivery of energy in the cells.

Nitric oxide (NO) will be transformed into Peroxinitrit (INOO) in case of oxidative stress. It is neurotoxic and damages optic nerves. (Prof Flammer Uniklinik Basel).

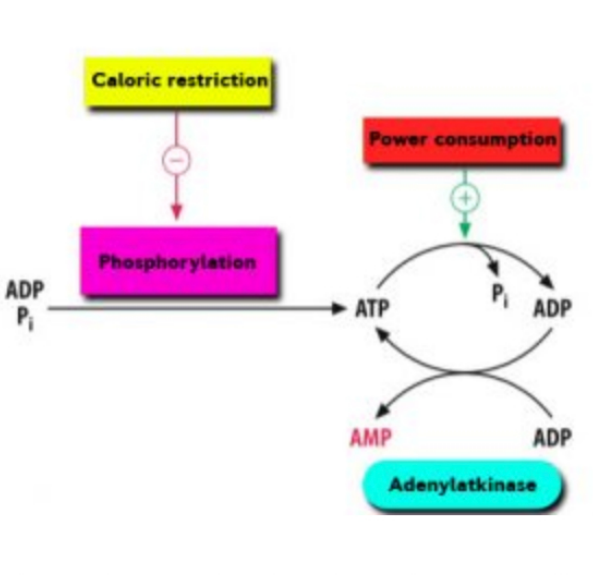
Early mitochondrial abnormalities within ganglion cells lead to neuronal dysfunction. Mitochondries are responsible for delivering of energy.

Let's talk about AMPK.



AMPK is an energy sensor, it becomes activated when energy is low. When energy supply is low, organisms respond by slowing aging and increasing resistance to diverse age related pathologies, including neurodegenerative diseases / glaucoma (Masoro 2002).

Lack of nutrients results in a slowing of ATP delivery via oxidative phosphorylation. As the energy-consuming processes continue to run down, however, the ATP levels are lowered. The adenylate kinase in all cells can improve ATP deficiency. All cells have a regulatory mechanism that, in the absence of energy, reduces the biosynthetic pathways at the same time as stimulating catabolic metabolic reactions. This is intended to restore the cellular ATP population. The triggering signal for this mechanism is AMP concentration and subsequent activation of AMP-dependent protein kinase (AMPK).

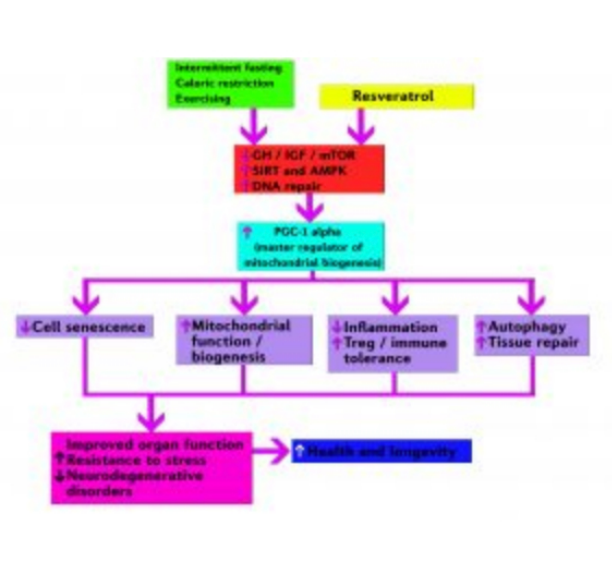


AMPK plays vital roles as both a sensor and regulator of mitochondrial function. Mitochondrial activity declines with age while production of potentially toxic reactive species (ROS) increases in part through the impaired ability of AMPK to generate new mitochondria in aged organisms (Reznick et al., 2007).

Oxidative stress means overflow of aggressive chemical combinations, so called free radicals. It is also clear, that a variety of other factors like vascular conditions and oxygen flow is important in the pathogenesis of the glaucomatous opticopathy. Unstable oxygen delivery means chronic hypoxia. Unstable oxygen flow leads to local oxidative stress. The general pathomechanism in cells, suffering from hypoxia is always the same.

Even in nutritient-deficients cases cells have the problem to hold their biological activity. For this reason ATP providing is lower and AMPK becomes activated.

Another possibility to increase AMPK is Resveratrol.



Resveratrol is a polyphenol compound found in certain plants and in red wine that has antioxidant properties and has been investigated for possible anticarcinogenic, antiinflammatory, neuroprotective effects and much more.

It modulates life spam and metabolism and it is thought that these effects are largely mediated by activating the deacetylase enzyme SIRT1.

Resveratrol also activates the cell energy sensor AMPK. AMPK activators inhibit nitric oxide synthase, a key pro inflammatory mediator of insulin resistance in obesity.

Resveratrol blocks two key encymes for inflammation, Cyclooxigenase 2 (COX-2) and intrinsic nitric oxide Synthase (iNOS).

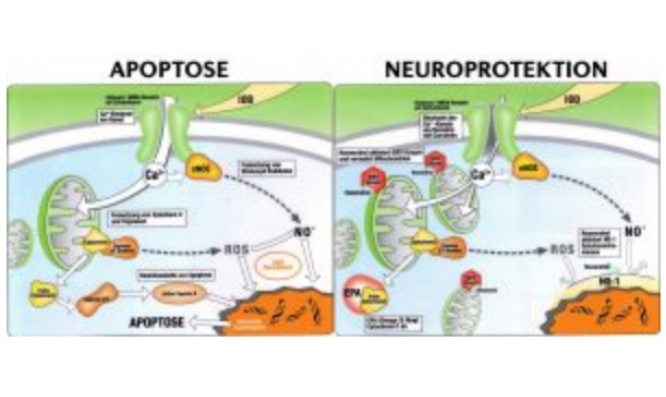
One reason, that Resveratrol seems to be effective in ocular conditions is, that it has the ability to cross the semi-permeable blood brain and blood eye tissue barriers.

Resveratrol has a neuroprotective effect. It protects the optic nerve from dangerous oxidation and inflammation and conteracts destructive symptoms of glaucoma.

Resveratrol activates two signal proteins: SIRT-1 delayes and reduces apoptose. PGC-1-alpha triggers dividing and proliferation of mitochondries and it enhances the activity of AMPK. We did show this pathway before.

AMPK activation helps to mimic the beneficial effects of caloric restriction, the best documented method of slowing and reversing degenerative aging processes.

AMPK activation enhances destruction of diseased or dying cells as well as removal of intracellular metabolic debris – a method to slow and reverse degenerative aging process of organs.



Conclusion

We believe, Selective Laser Trabecularplasty should not be limited for reducing intraocular pressure.

Even in cases of Low Tension Glaucoma it is possible, to improve cell metabolism for cleaning and regenerating of cells of the trabecular meshwork.

Another possibility – increasing the amount of mitichondries and improving their activity by using different activators like Resveratrol but also caloric restriction and exercising – is promising.

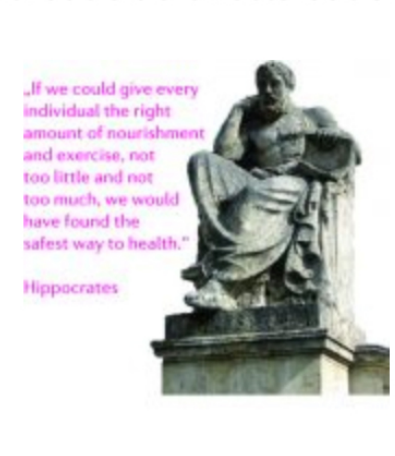
It should be one of the most important treatments since it reduces many of pathological mechanisms for better health in other organs too.

SLT in combination with Resveratrol increases each others effect in glaucoma treatment.

Our study, including more than 2,000 Low Tension Glaucoma cases, is highly representative. Additional to lower eye pressure in all cases patients did benefit from increasing of nerve fiber thickness.

Another study – SLT and caloric restriction would be very interesting too.

This treatment would be not only healthy and without side effects but also very cost consuming.


„If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health."
Hippocrates

Relax.
Eat less.
Move more.
A glass of red wine in the sun
with a good company
and a little bit of Resveratrol ...
It's that simple.