CoEnzyme Q10: New approach in the treatment of corneal damage and glaucoma

Proceedings of the Symposium held on October 9th, 2017 at the ESCR Congress, Lisbon, Portugal

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Introduction

Dry eye is a multifactorial disease of the tears and ocular surface resulting in symptoms of discomfort, visual disturbance and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Dry eye can be acute or chronic, it can be caused by either exogenous factors such as acute post-surgery trauma or endogenous triggers such as hormonal imbalance or autoimmune diseases. Symptom relief is normally achieved by lubrication of the ocular surface, while other strategies target the underlying inflammation and contribute to corneal wound healing. A recent approach is the use of cross-linked hyaluronic acid to ensure a maximum residence time on the ocular surface, in combination with Coenzyme Q10 (CoQ10), the latter regulating mitochondrial apoptosis by acting as antioxidant and support of energy production.

Glaucoma is one of the leading causes of irreversible blindness worldwide. It is recognized as a progressive neurodegenerative disorder, affecting the retinal ganglion cells (RGCs) and their axons. The death of RGCs ultimately leads to the loss of visual field. Recent evidence indicates that there is a link between the pathogenesis of glaucoma and mitochondrial dysfunction: As RGC axons are rich in mitochondria, an alteration of the functional status of these mitochondria will influence RGC survival and thus their functional contribution to the vision process. An endogenous molecule maintaining the mitochondrial function is CoQ10, potentially offering a complementary approach to IOP lowering therapy in glaucoma.

The newest findings on CoQ10 for both indications were presented during a symposium at the 2017 Meeting of the European Society of Cataract & Refractive Surgeons (ESCRS) in Lisbon, Portugal, chaired by Professor Leopold Schmetterer, Professor of Ophthalmology at the Singapore Eye Research Institute and Nanyang Technological University in Singapore.

Summary

- **Dry eye** is a multifactorial disease of the tears and ocular surface resulting in symptoms of discomfort, visual disturbance and tear film instability. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

- Corneal nerves appear to be very important in tear production and a decreased amount of such nerves after ocular surgery such as LASIK or cataract can be detected. Such interventions can lead to a vicious cycle of ocular surface disease (OSD).

- CoQ10 targets mitochondria. It appears to reach the residence time on the ocular surface, in combination with cross-linked hyaluronic acid to ensure a maximum residence time on the ocular surface with lower concentrations, a formulation with cross-linked HA (XLHA) can be used. Its high molecular weight and size results in an increased resistance to hyaluronidase degradation.

- A wide combination of XLHA and CoQ10 is very useful in the treatment of dry eye induced ocular surface damage. While XLHA is a well-tolerated, high molecular weight HA showing all the characteristics of HA, CoQ10 acts as a potent antioxidant.

- An addition of CoQ10 to the preoperative and postoperative standard of care, may accelerate full patient recovery and decrease sequelae such as dry eye and neuropathic pain. The beneficial effect of CoQ10 should be further investigated by conducting well-defined longer-term clinical trials to help better understand the mechanism of action of this promising new approach.

- Glaucoma is one of the leading causes of irreversible blindness worldwide. It is currently recognized as a progressive neurodegenerative disorder, affecting the retinal ganglion cells (RGCs) and their axons. The death of RGCs ultimately leads to the loss of visual field.

- There is a clear unmet need in glaucoma. When looking at landmark glaucoma trials such as OHTS, EMGT and CNTGS, one will find that successful IOP reduction does not necessarily prevent loss of vision and this is where the concept of neuroprotection comes in.

- Recent evidence indicates there is a link between the pathogenesis of glaucoma and mitochondrial dysfunction: As RGC axons are rich in mitochondria, an alteration of the functional status of these mitochondria will influence RGC survival and thus their functional contribution to the vision process.

- An endogenous molecule maintaining the mitochondrial function is Coenzyme Q10 (CoQ10), potentially offering a complementary approach to IOP lowering therapy in glaucoma.

- CoQ10 targets mitochondria. It appears to reach the back of the eye and this suggests potential utility as neuroprotective therapy in glaucoma through preventing RGC apoptosis and functional loss. CoQ10 may also counteract reperfusion damage.

- In vitro and in vivo data shows that application of CoQ10 prior to exposure to apoptotic stimuli reduces apoptosis by a direct inhibition of mitochondrial depolarization.

- In clinical study CoQ10 has been shown to have an effect on electrophysiological parameters such as VEP and PERG in patients with glaucoma.

- Further proof-of-concept studies with strong endpoints are needed to determine the effect of CoQ10 on visual field function.
A group of Italian researchers was also able to show an additional function of CoQ10 within mitochondria. The coenzyme is able to protect mitochondria from oxidative stress and apoptosis. CoQ10 is known as an endogenous antioxidant and is also a crucial component of the electron transport chain, which drives ATP synthesis. CoQ10 deficiencies can be manifest as 5 clinical subtypes, including CNS, muscular and renal involvement. According to literature, the response to CoQ10 supplementation is variable.5

“Before looking at its clinical application, it is important to initially understand the basic science of CoQ10 such as its characteristics and functions in the cell”, Dr. Sajjad Ahmad, Consultant Ophthalmic Surgeon at Moorfields Eye Hospital in London, introduced the topic to the audience.

Coenzyme Q10 consists of a quinone and 10 isoprenyl subunits. It is present in most bacteria and mainly in the mitochondria of animal cells. It is endogenously produced mainly by the liver and thus nutritionally non-essential, although approximately 25% of CoQ10 is obtained via dietary sources. CoQ10 levels decline with age.8

CoQ10 has two important functions. It is a key component for the generation of ATP in the mitochondria and it has direct antioxidant effects by neutralizing reactive oxygen species (ROS) indirectly inhibiting cell apoptosis. In the inner membrane of the mitochondria proton (H+)-gradient derived energy is used to neutralize reactive oxygen species (ROS). CoQ10 is an antioxidant that reduces the expression of pro-apoptotic factors and prevents mitochondrial membrane depolarization.10 Neurons and neuronal cells exposed to hydrogen peroxide.11 In the back of the eye, CoQ10 has been shown to prevent apoptosis in retinal ganglion cells and retinal pigment epithelial cells exposed to hydrogen peroxide.12 A reduced oxidative damage was observed in retinal ganglion cells and retinal pigment epithelial cells exposed in vitro to radiation, hypoxia and growth factor deprivation. Furthermore topical CoQ10 had an anti-apoptotic effect on retinal ganglion cells in a mouse model of induced retinal degeneration.13 CoQ10 exposure was shown to inhibit oxidative stress and increase mitochondrial mass in hydrogen peroxide treated optic nerve head cells and astrocytes.14 It reduced oxidative stress induced mitochondrial alterations as a result of transient ischemia in mouse model.15

As a corneal and ocular surface disease specialist, Dr. Ahmad noted that: “Clinical data has now also become available on the efficacy of CoQ10 in two challenging corneal endothelial diseases. Authors of a case series reported joint use of CoQ10 in corneal ulcers, where it enhanced corneal healing, while another research group found it to be an effective supportive measure in recovery of the cornea in patients suffering from Fuchs endothelial corneal dystrophy.”15,16

Dr Ahmad summarized that “CoQ10 is important in the production of ATP, as an anti-oxidant for ROS and a direct anti-apoptotic agent. While systemic use of CoQ10 has been shown to have some effect on diseases of the central nervous system, there is also significant pre-clinical evidence for a protective activity of CoQ10 in several ocular cell types. Currently, clinical evidence is becoming available to support the beneficial role of CoQ10 in several ocular pathologies.”

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20 days after photorefractive keratectomy (PKR).** HA has also been shown to improve migration of epithelial cells.**

The ocular surface expresses the hyaluronate receptor (CD44). When CD44 is overexpressed in corneal and conjunctival cells - in the course of ocular surface damage - it promotes the interaction of the inflammatory marker ICAM-1 with cytoskeletal proteins. These findings suggest a role for hyaluronate in cell adhesion and motility.**

HA has also displayed healing properties in superficial punctate keratopathy. When the corneal epithelium was stained with fluorescein dye before and during treatment with HA eye drops, a discernible improvement was detected after 2 and 4 weeks of treatment.**

Longer term use of artificial tears containing HA has also been shown to promote epithelial healing in patients with more severe dry eye.** In severe dry eye treatment the use of hypertonic HA formulations appear to be more effective. This was demonstrated during a 3 month study treating patients with Sjogren syndrome with either hypertonic or isotonic artificial tears containing HA.**

"To allow an eye drop to achieve an increased residence time on the ocular surface with lower concentrations, a formulation with cross-linked HA (XLHA) can be used. Its very high molecular weight and size results in an increased resistance to hyaluronidase degradation", knows Dr. Aragona. "This is why XLHA is for example used as a dermal filler and synergetic fluid substitute."

The way to produce XLHA is a relatively simple one. HA is immersed in a polymerisation mixture and cross-linked. Recent studies on XLHA have also shown it to unfold positive properties on the ocular surface. An improved tear film quality was detected in Sjogren’s patients**, as were reduced clinical signs in patients suffering from keratoconjunctivitis Sicca (KCS)**. Non-healing corneal ulcers were resolved when treated with XLHA.**

Another interesting new approach for treatment of OSD is the use of the lipid soluble CoQ10, also known as ubiquinone. As already described above, it plays a role in several cellular functions and is widely distributed in mitochondria, but also in microsomes, and the Golgi apparatus of cells. It is a key player in the oxidative metabolism, supporting biosynthesis of ATP in the mitochondria and, in its reduced form, acting as a lipid antioxidant.**

While the usefulness of CoQ10 in improving ocular surface damage has already been demonstrated in studies on UVB-induced corneal damage** and corneal edema in Kearns-Sayre dystrophy**; a most recent study looked at the efficacy of eyedrops containing cross linked HA and CoQ10 in treating patients with mild to moderate dry eye. This randomized, single-masked, parallel-group, comparative study compared an unpreserved formulation of XLHA in combination with CoQ10 (VisuXL®, VISUfarma, Rome, Italy) to an unpreserved 0.15% linear HA eyedrop (Ocuylat, Schalcon, Rome, Italy). To qualify for inclusion adult patients had to have a history of at least 3 months of dry eye symptoms categorized as moderate (stage 2-3 of DEWS classification). Patients with other ocular diseases, ocular contact lenses or topical treatments other than tear substitutes were excluded, as were patients with systemic diseases, hypersensitivity to the active substance or to excipients. After 1 week of saline use, patients were treated with either medication four times a day for 12 weeks. Evaluations carried out at baseline and after 15, 30 and 90 days were the OSDI (Ocular Surface Disease Index) assessment, BUT, ocular surface staining, corneal sensitivity, MGD assessment and in vivo confocal microscopy. Primary outcome parameters were the OSDI as well as corneal and conjunctival fluorescein staining. In this comparable patient population the OSDI score improved significantly in both groups at day 30 and 90 compared to baseline and day 15. Additionally the score was significantly better for patients treated with XLHA at day 90 compared to those receiving HA. Conjunctival staining was significantly less in XLHA patients compared to HA at day 90, while corneal staining showed to be significantly less in XLHA patients compared to HA at day 30 and 90, and compared to baseline and day 15. These findings were also confirmed by in vivo confocal microscopy findings, showing an improvement in proliferation, keratocytes and stromal matrix. All these were reduced from day 30 in the XLHA group versus baseline and patients in the HA group over time.

Dr. Aragona concluded that the "formulation containing a combination of XLHA and CoQ10 is very useful in the treatment of dry eye induced by keratitis, keratitis and, and ocular surgery."

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Coenzyme Q10 and surgery: Its benefit in corneal regeneration

Dr. José Manuel Benitez del Castillo Sánchez, Professor of Ophthalmology and Chairman Hospital Clínico San Carlos, Professor of Ophthalmology, University Complutense of Madrid, Spain

When discussing corneal surface disease, the consequences of corneal refractive and cataract surgery should also be kept in mind.

Dr. Benitez del Castillo reported from a study looking at tear secretion and corneal sensitivity after laser in situ keratomileusis (LASIK). There was a clear reduction of both 6 months after surgery. Tear secretion only returned to its preoperative values 9 months after the intervention.** Corneal sensitivity recovery, as measured by non-contact aesthesiometry was not reached in many cases until more than 4 years after surgery. Recovery rates were even slower after hypermetropic LASIK.

Dr. Benitez del Castillo concluded that "corneal nerves appear to be very important in tear production and a decreased amount of such nerves after LASIK can be detected. Additionally LASIK can lead to a vicious cycle of OSD. Existing hypotheses assume a reduced blink rate and decreased presence of goblet cells. The tear film of the ocular surface becomes unstable. In this environment Interferon γ inhibits mucin generation and cytokines Interleukin 1, 6, 8 and as well as TNF (tumor necrosis factor) alpha start kicking-off inflammatory processes, distorting sensitive information signalled to the brain. The brain in turn acts on the lacrimal gland initiating a cycle of its hypo- or hyperstimulation and neurogenic inflammation, prompting in neurotrophic keratopathy resulting in reduced tear clearance and production of Memboramin lipids and thus a tear film instability." (Graphic 3)

Graphic 3: Post-LASIK ocular surface disease

Another surgical intervention potentially compromising the tear film is cataract extraction. It is usually performed in patients in whom the ocular surface is already affected by age. Thus there are a lot of borderline patients with more DED, conjunctivochalasis and eye problems. These patients will also generally have a lower amount of nerves at the plexus with a decrease in corneal sensitivity and innervation.**

A study looking at the pathogenic factors in dry eye patients after cataract surgery found a decrease of the conjunctival epithelial cells and goblet cells by impression cytology at the lower conjunctiva covered by the lower lid. They concluded that DED after cataract surgery is related with drug toxicity.** Even if the eye was satisfactorily covered by tear film before surgery, any injury and environmental related to incisional trauma can also lead to tear film disturbances. Another group of researchers also detected changes in corneal sensitivity and tear physiology after phacoemulsification (Phaco). Using non-contact mechanical aesthesiometry on the central cornea they found a statistically significant decrease in corneal sensitivity until 3 months after surgery.**

"So how is DED triggered after phacoemulsification?" explained Dr. Benitez del Castillo. The consequence is a non-satisfied patient. A study evaluating symptoms and their underlying causes after multifocal lens implantation, multithreaded patients with age-related macular degeneration and patients with cataract surgery resulted in a reduction of ocular surface inflammation and dry eye signs and symptoms. This was assessed in 48 patients undergoing Phaco and receiving preservative free hydroxypropyl (HP)-guar eye drops in addition to the usual treatment scheme of corticosteroids. Inflammatory markers identified in flow cytometric analysis were reduced in patients receiving HP-guar eye drops.**

"As other mechanisms of action in dry eye treatment are being explored, the role of the mitochondria and effect of CoQ10 have increasingly been focused on. Mitochondria have a key role in the cell respiratory chain by producing energy using CoQ10. Following stress or damage, nerve, muscle and epithelium cells highly increase their O2 intake. During this activity CoQ10 increases the cell metabolism by exerting an anti-oxidant effect, producing energy and acting anti-apoptotic", Dr. Benitez del Castillo continued. In vitro models have shown that the addition of CoQ10 increases the fraction of surviving cells after apoptosis induced by irradiation or ethanol.**

A group of Italian researchers was able to show that use of topical ubiquinone Q10 and vitamin E prevents keratocyte apoptosis after photorefractive keratectomy.
Clinical studies have shown that CoQ10 administration in patients after cataract surgery is also available. A study in 40 patients undergoing uneventful cataract surgery and receiving either topical CoQ10 + vitamin E eye drops or saline solution were followed up for 9 months after the intervention. At day 14 and months 3, 6 and 9 patients were examined for signs and symptoms of OSD. In all groups, the group receiving CoQ10 displayed an accelerated nerve regeneration and better recovery from signs and symptoms of OSD. At day 14, patients treated with CoQ10, already showed a physiological recovery of CFD that was comparable to 9 months of physiological recovery under saline solution. After 9 months the full SBP at the central cornea was recovered in 95% of patients using CoQ10 compared to only 80% treated with saline solution. After about 3 months of CoQ10 treatment, the SBP of the temporal cornea was fully recovered in 75% of patients using CoQ10. This result was comparable with the values after 9 months of saline treatment. (Graphic 4)

No relevant side effects were found, apart from an occasional burning sensation reported by 10% of CoQ10 patients. Findings show that changes of the corneal nerves occurring after cataract surgery may influence the integrity of the ocular surface and that topical treatment with CoQ10 combined with vitamin E has a positive effect on nerve regeneration and anatomy and ocular surface stability by restoring the SBP.

Data from a mouse model also showed that CoQ10 prevents peripheral neuropathy and attenuates neuron loss in a type 2 diabetes mouse model. Apparently, reactive oxygen species and reduced PLCβ3 expression may contribute to sensory deficits in late-stage diabetic db/db− mice, and early long-term administration of the antioxidant CoQ10 could represent a promising therapeutic strategy for neuropathy in type 2 diabetes.

A recent systematic review and meta-analysis of existing data reported that CoQ10 supplementation has an impact on inflammatory markers and may therefore help downregulate the inflammation process.

Dr. Benitez del Castillo concluded that overall the addition of CoQ10 to the preoperative and postoperative standard of care, should reduce surgical damage, accelerate full patient recovery and decrease sequelae such as dry eye and neuropathic pain. The beneficial effect of CoQ10 should be further investigated by conducting well-defined long-term clinical trials to help better understand the mechanism of action of this promising new approach.

NEUROPROTECTION IN GLAUCOMA

Coenzyme Q10 and glaucoma: evidence and effects in the preservation of Retinal Ganglion Cells

Dr. Francesca Cordeiro, Professor of Ophthalmology, Imperial College London; Professor of Glaucoma and Retinal Neurodegeneration, UCL, London, UK

I would like to share with you the available evidence on use of CoQ10 in glaucoma”, Dr. Cordeiro introduced her presentation and continued that “there is a clear unmet need in glaucoma. If you look at landmark glaucoma trials such as OHTS, EMGT and CNTGS you will find that successful IOP reduction does not necessarily prevent loss of vision and this is where the concept of neuroprotection comes in.”

A better understanding of neurological or neuro-ophthalmological strategies for various ocular diseases involves taking a closer look at cell biology. There are various strategies targeting different causes of cell and tissue disorders such as inflammation, oxidative stress, protein misfolding and mitochondrial dysfunction. All of them have been put forward to help understand the nature of and to develop a cure for neurodegenerative diseases such as Alzheimer’s disease or glaucoma. In glaucoma, only 2 medications acting as potential neuroprotectants so far reached the stage of a randomized controlled trial in humans. In this plethora of possible strategies mitochondrial dysfunction appears to be a most interesting target.

The mitochondria are the powerhouse of the cell, where energy in the form of adenosine triphosphate (ATP) is produced in the intermembrane space. The cell’s life cycle is accompanied by regulatory mechanisms acting on the mitochondria. Within the mitochondrial respiratory chain Coenzyme Q10 (CoQ10) is essential for the production of ATP, where it serves as an electron transporter in complexes I, II and III. It also inhibits NF-B, a factor responsible for inflammation, autoimmune disease, virus infections and linked with aging. CoQ10 also inhibits the opening of permeability transition pores (PTP) of the cell. CoQ10 derives its antioxidant nature from an electron carrier function, this means it continuously goes through a cycle of oxidation and reduction (redox cycle), by accepting electrons in its oxidized form and conversely giving up electrons in its reduced form. In the latter state, CoQ10 holds electrons rather loosely and thus may easily give up electrons, thereby acting as an antioxidant. Endogenous CoQ10 is present everywhere in the body. Levels decrease with age as demonstrated by measurements in liver, heart, kidneys and lungs.

“So what value can topical application of Coenzyme Q10 add in ophthalmology?”, Dr. Cordeiro wants to know. She is aware that “this option has only recently become available. There is no comparison between topical and oral use yet, however, CoQ10 was detected in vitreous samples after eye drop application, demonstrating that it reaches the back of the eye. These findings are assuring to ophthalmologists, who prefer a topical route of administration in their patients”.

The indications for use of CoQ10 would include ocular surface as well as retinal diseases, since underlying mechanisms involve dysfunction of neurons. As already mentioned by Dr. Ahmad, CoQ10 has an effect on corneal keratocytes of rabbits, after cells had been exposed to apoptotic stimuli such as UV radiation, antimycin A and serum starvation. Application of CoQ10 prior to exposure, reduced apoptosis by a direct inhibition of mitochondrial depolarization.

Additionally, data recently published by Dr. Cordeiro and her team has shown that cultured retinal ganglion cells (RGCs), having been exposed to the anti-mitochondrial toxin, dimethyl sulfoxide (DMSO), and consequently having suffered from an insult to the electron transport and oxidation chain can be protected by the use of topical CoQ10. Furthermore an in vivo glaucoma study in rats with unilateral surgically induced ocular hypertension (OHT) which reduces the absolute number and density of RGCs demonstrated that treatment with CoQ10 combined with Vitamin E (TPGS) or Vitamin E alone, twice a day for 3 weeks reversed RGC loss, both in vivo using dARC (detection of apoptotic retinal cells) and histologically. (Graphic 5)

Graph 5: DARC analysis showing an increased amount of spots (apoptotic retinal cells) in OHT eyes compared to the respective contralateral eyes. Amount of DARC spots are lower on the group treated with CoQ10/TPGS compared to TPGS only.

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Dr. Cordeiro summarized for the audience that “mitochondria play an important role in neurodegeneration. Mitochondria mitochondrial dysfunction, appears to reach back of the eye and seems to be an effective therapy to reverse mitochondrial dysfunction in glaucoma by preventing ROC apoptosis and functional loss. Apart from ischaemic damage, CoQ10 can also counter peripapillary damage, as the level of apoptosis and ability to reverse this has an influence on muscle injury. CoQ10 also has its role in treating OSD. Further research is needed.”

Outlook

The use of CoQ10 for dry eye treatment needs to be further investigated. Some patients with persistent epithelial defects have experienced a positive effect. An ideal treatment will need to be further explored. In general, CoQ10 can improve the ocular surface by counteracting processes related to apoptosis. The optimal instillation frequency and length of treatment will also need to be further specified in long-term clinical studies, keeping in mind that this depends very much on the individual needs of the patient. Data relative to treatments targeting the inflammatory process in more severe cases of dry eye (DED accompanied by severe keratitis) such as cicatricial have also recently become available. Future studies on the use of CoQ10 in glaucoma should be further specified. Some patients with persistent corneal edema have also recently become available. CoQ10 can improve the ocular surface by counteracting processes related to apoptosis. 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