Universität Rostock Traditio et Innovatio

Universitätsmedizin Rostock

Innovative Therapieansätze für Trockenes Auge und Glaukom

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3. Oktober 2021

Disclosures

- Alcon (Vorträge)
- Santen (Vorträge)
- Shire (Advisory Board)
- Visufarma (Vorträge)
- Ursapharm (Vorträge)

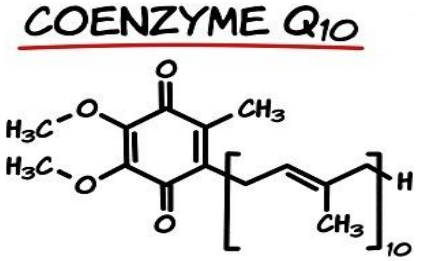
Übersicht

- Coenzym Q10
- quervernetzte Hyaluronsäure
- Vitamin D-Supplementation bei Trockenem Auge
- Phospholipide und Citicolin und Glaukom

Coenzym Q10, CoQ10

- CoQ10

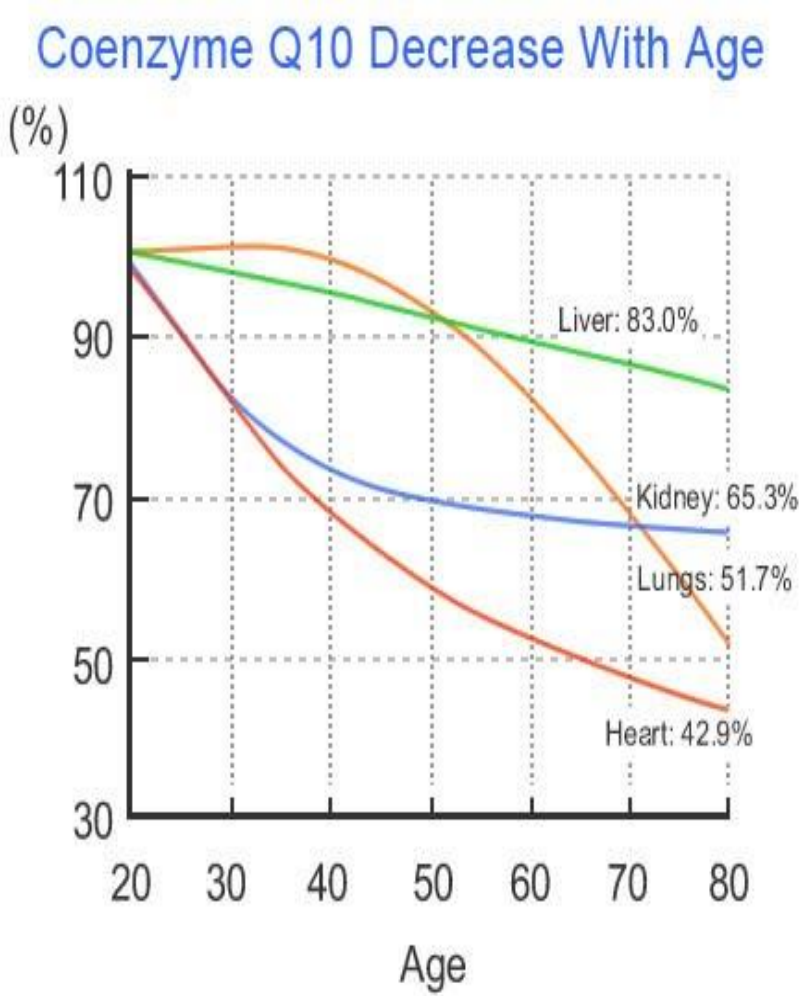
  = Ubichinon (engl. Ubiquinone) / Ubidecarenon
- Lipophiles Molekül – natürlich vorhanden in allen eukaryotischen Spezies, in jeder Zelle
- gefunden in Plasmamembran und anderen Endomembran-Systemen (wie Mitochondrien)



Coenzyme Q10, CoQ10

- CoQ10-Spiegel sind hoch in Zellen mit hoher Aktivität
- CoQ10-Spiegel sinken mit dem Alter

➢ *„Mitochondriale Dysfunktion“*



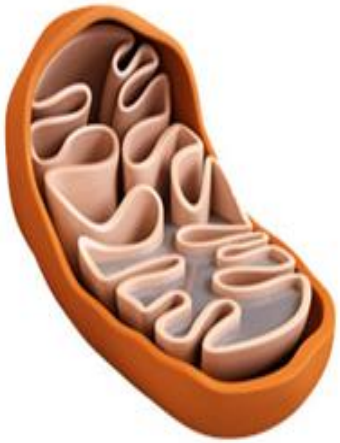
Coenzyme Q10, CoQ10

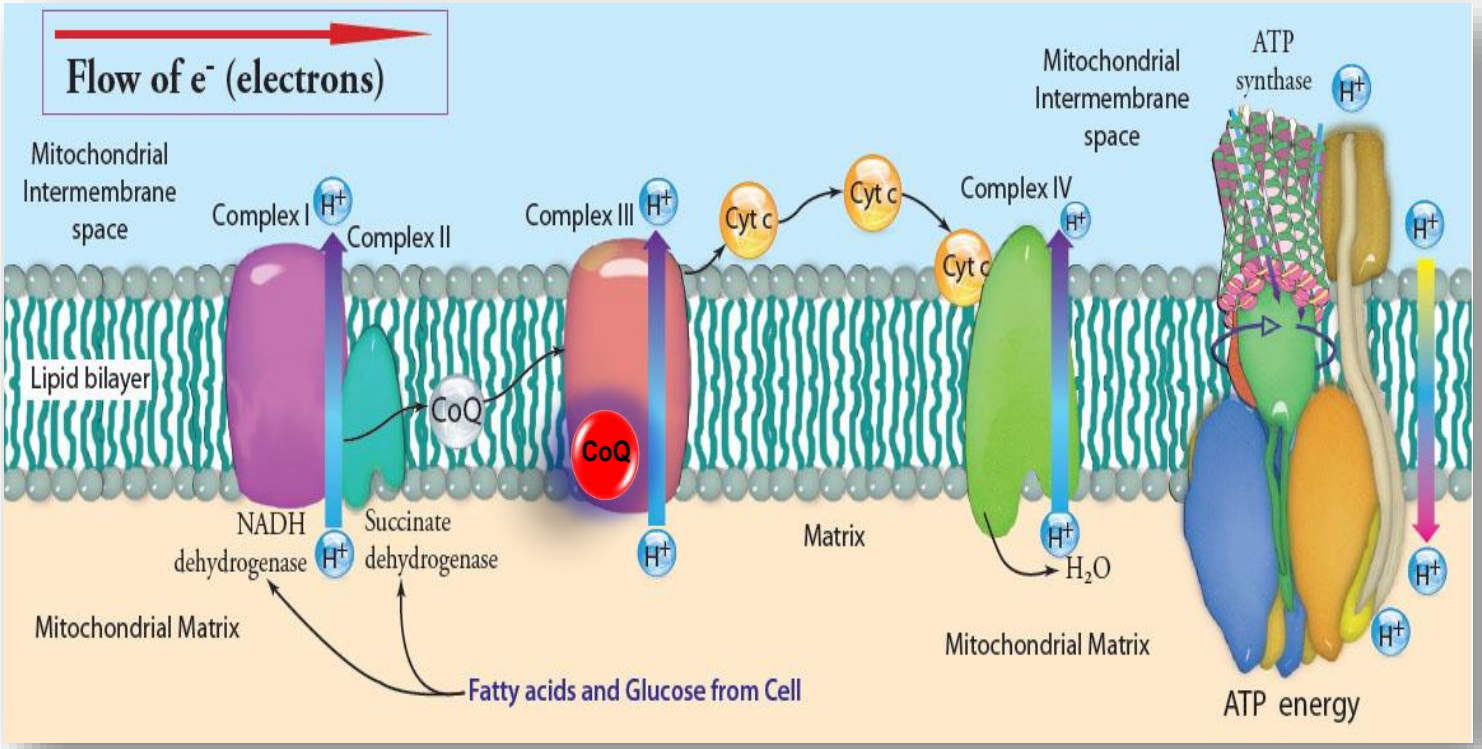
- Spielt eine Rolle in
  - Mitochondriale Energie: **Herstellung von ATP** (Adenosintriphosphat, Energiequelle, die von allen Zellen verwendbar ist)
  - Effektives **Antioxidans / Radikalfänger:**
    - Schutz der mitochondrialen und lipiden Membranen gegen oxidative Schäden
  - **Regulierung der Apoptose:**
    - Direkt über die mitochondriale Wirkung und indirekt als Radikalfänger (*reduziert die mitochondriale Depolarisation, Wirkung auf Caspasen …*)
  - Regulation von **Entzündungsprozessen**
    - Wirkung auf den Transkriptionsfaktor NF_KB

Rolle von CoQ10 bei der Produktion von ATP

CoQ10 *ist essentiell in der mitochondrialen Atmungskette (Elektronentransportkette), die zur Produktion von ATP führt*

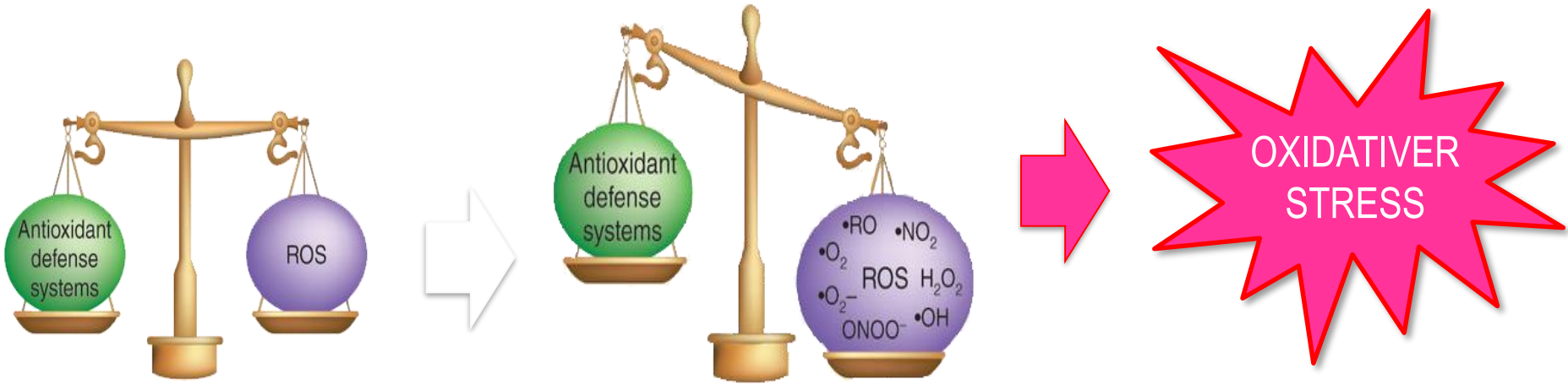
Dient als ***Elektronentransporter*** *in den Komplexen I, II und III*





Oxidativer Stress

ROS = reaktive oxygen species = freie Radikale

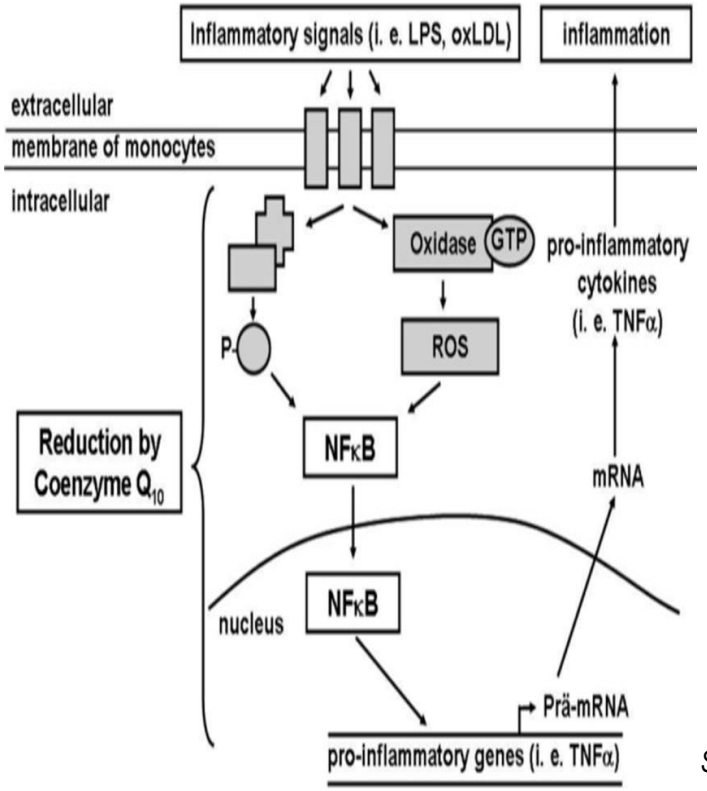


✓ Eine unterbrochene Balance zwischen antioxidativen Abwehrsystemen und dem Niveau von ROS führt zu **oxidativem Stress** und kann zu **oxidativen Schäden** führen

CoQ10 und Entzündung

Die Produktion freier Radikale stimuliert die Entzündung über den NFKB Weg.

CoQ10 kann eine Rolle bei der Entzündung durch seine *Antioxidans- / Radikalfänger-Eigenschaften* haben.



Schmelzer et al. BioFactors 32 (2008) 179–183

Coenzym Q10, CoQ10

- Spielt eine Rolle in
  - Mitochondriale Energetik: **Herstellung von ATP**
  - Schutz der Mitochondrien- und Lipidmembranen gegen oxidative Schäden: wirksames **Antioxidans** / Radikalfänger
  - **Regulierung der Apoptose** als Radikalfänger und und durch mitochondriale Wirkung

- Es wird angenommen, dass CoQ10 die Hornhautheilung durch dieselben Mechanismen beeinflusst
  - **Produktion von ATP / Energie**
  - Reduktion der Keratocyten-Apoptose
  - Fähigkeit, freie Radikale zu fangen

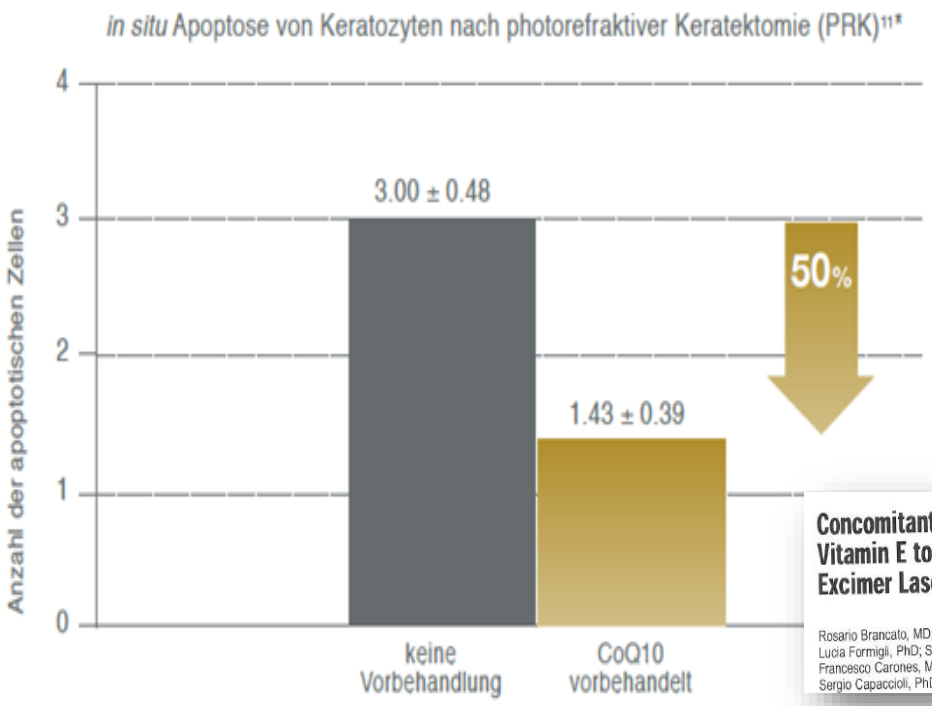
Mencucci et al. IOVS 2014, 55, 7266-7271
Papucci et al. JBC 2003;278(30):28220-8

Coenzym Q 10, CoQ10 – ausgewählte Studien

Vorbehandlung mit CoQ10 + Vitamin E reduziert die Apoptose der Keratozyten post-PRK um 50%[11]

* *in vivo* Kaninchenmodell.

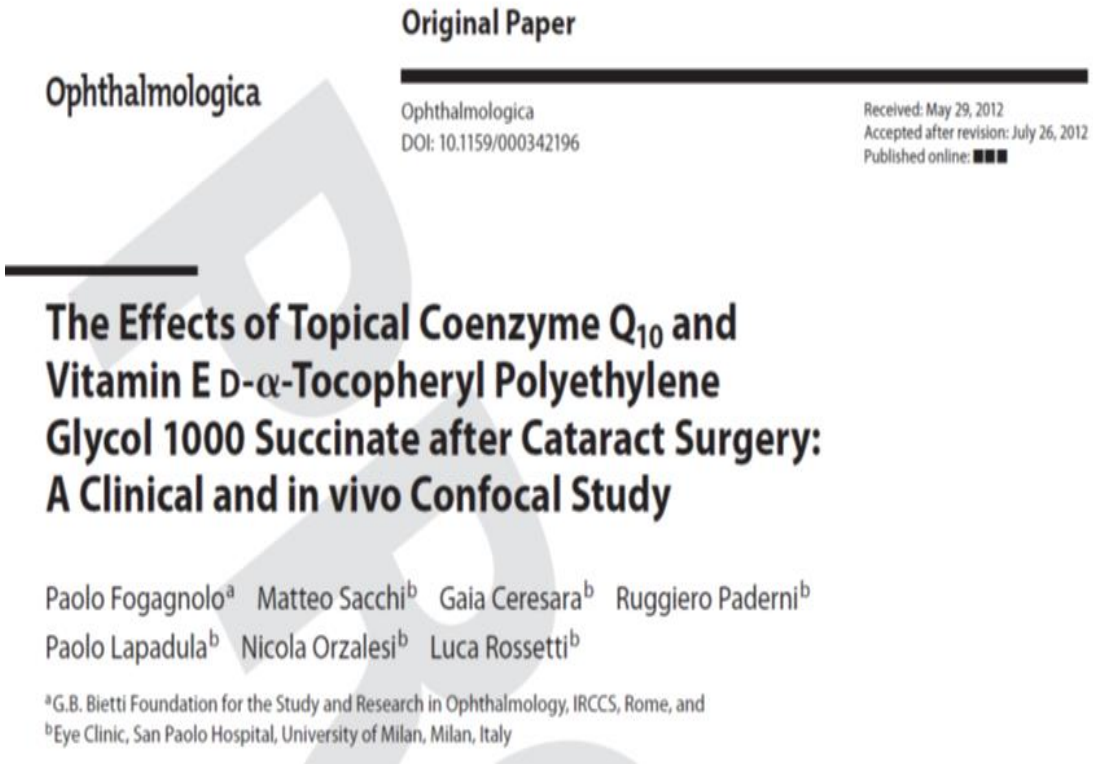
Behandlungsgruppe: jedes rechte Kaninchenauge mit CoQ10 4x täglich. Kontrollgruppe: jedes linke Kaninchenauge unbehandelt.



Concomitant Effect of Topical Ubiquinone Q10 and Vitamin E to Prevent Keratocyte Apoptosis After Excimer Laser Photoablation in Rabbits

Rosario Brancato, MD; Tito Fiore, MD; Laura Papucci, PhD, Nicola Schiavone, PhD; Lucia Formigli, PhD; Sandra Zecchi Orlandini, PhD; Pier Giorgio Gobbi, PhD; Francesco Carones, MD; Martino Donnini, PhD; Andrea Lapucci, PhD; Sergio Capaccioli, PhD

Coenzym Q 10, CoQ10 – ausgewählte Studien



Original Paper

Ophthalmologica

Ophthalmologica
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Received: May 29, 2012
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Published online: ■■■

The Effects of Topical Coenzyme Q_{10} and Vitamin E D-α-Tocopheryl Polyethylene Glycol 1000 Succinate after Cataract Surgery: A Clinical and in vivo Confocal Study

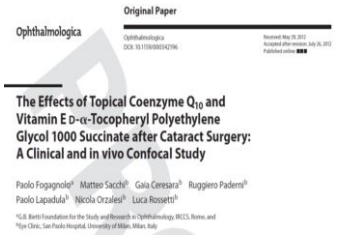
Paolo Fogagnolo[a] Matteo Sacchi[b] Gaia Ceresara[b] Ruggiero Paderni[b]
Paolo Lapadula[b] Nicola Orzalesi[b] Luca Rossetti[b]

[a]G.B. Bietti Foundation for the Study and Research in Ophthalmology, IRCCS, Rome, and
[b]Eye Clinic, San Paolo Hospital, University of Milan, Milan, Italy

- Offene, klinische Studie mit 40 Patienten, die nach einer Kataraktoperation entweder Kochsalz oder eine CoQ10 Lösung 2xtägl. über 9 Monate getropft haben
- Messpunkte nach 14 Tagen, 3, 6 und 9 Monaten nach OP
- *U.a. in vivo confocal microscopy* zur Bestimmung der Nervenfaserdichte im sub-basalen Plexus (SBP), zentral und temporal (HRT Rostock Modul)

Coenzym Q 10, CoQ10 – ausgewählte Studien

ZENTRALE Faserdichte (CFD)


Original Paper

Ophthalmologica

The Effects of Topical Coenzyme Q_{10} and Vitamin E D-α-Tocopheryl Polyethylene Glycol 1000 Succinate after Cataract Surgery: A Clinical and in vivo Confocal Study

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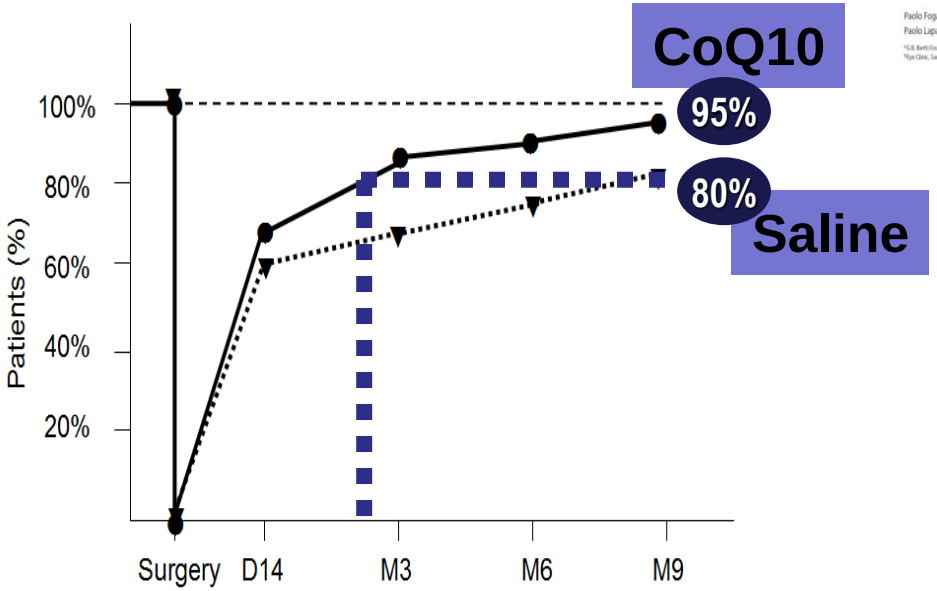
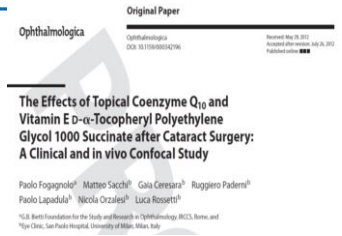
[a]G.B. Bietti Foundation for the Study and Research in Ophthalmology, IRCCS, Rome, and [b]Eye Clinic, San Paolo Hospital, University of Milan, Milan, Italy

Wieviel % der Patienten erreichen den Ausgangswert vor OP?



Nach weniger als 3 Monaten CoQ10 Therapie ist die CFD vergleichbar mit der nach 9 Monaten Erholung.

Coenzym Q 10, CoQ10 – ausgewählte Studien


Original Paper

Ophthalmologica

The Effects of Topical Coenzyme Q_{10} and Vitamin E D-α-Tocopheryl Polyethylene Glycol 1000 Succinate after Cataract Surgery: A Clinical and in vivo Confocal Study

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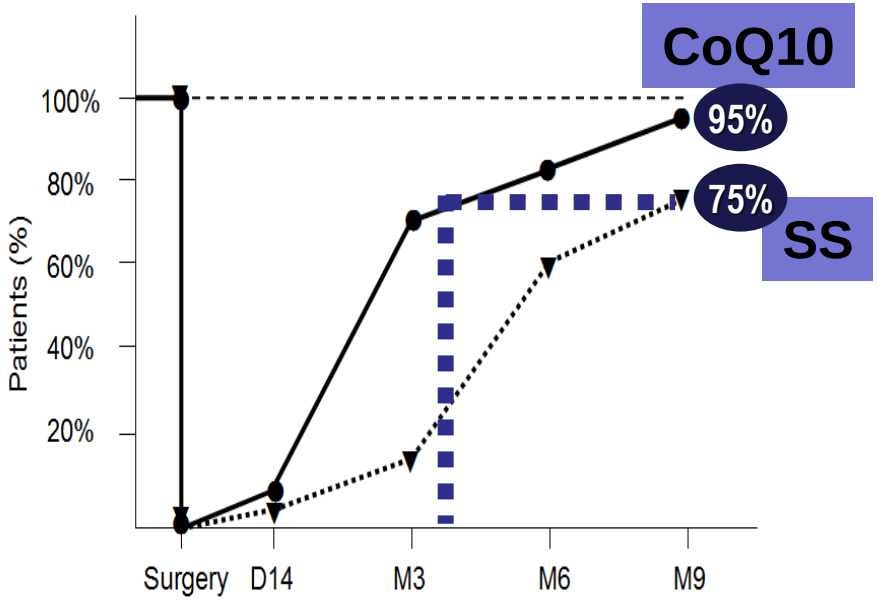
[a]G.B. Bietti Foundation for the Study and Research in Ophthalmology, IRCCS, Rome, and [b]Eye Clinic, San Paolo Hospital, University of Milan, Milan, Italy

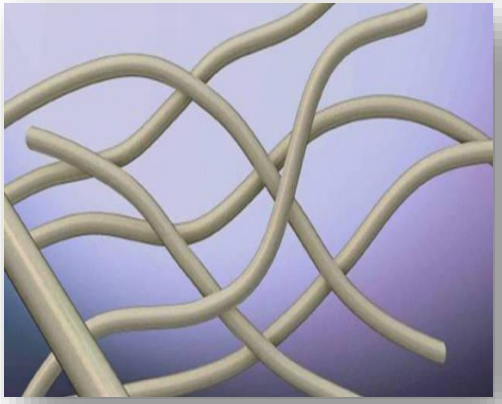
Temporale Faserdichte (TFD)

Wieviel % der Patienten erreichen den Ausgangswert vor OP?

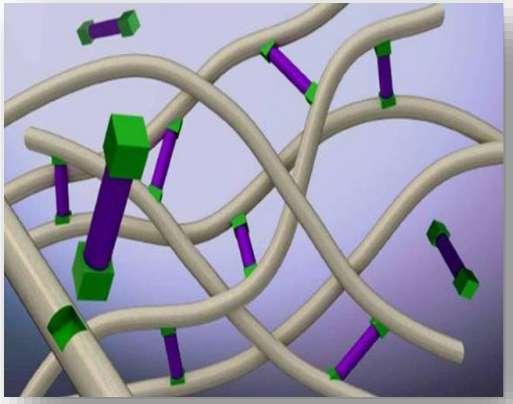


Nach ca.3 Monaten CoQ10 Therapie ist die TFD vergleichbar mit der nach 9 Monaten Erholung.

Coenzym Q 10, CoQ10 - Quervernetzung



Lineare Hyaluronsäure



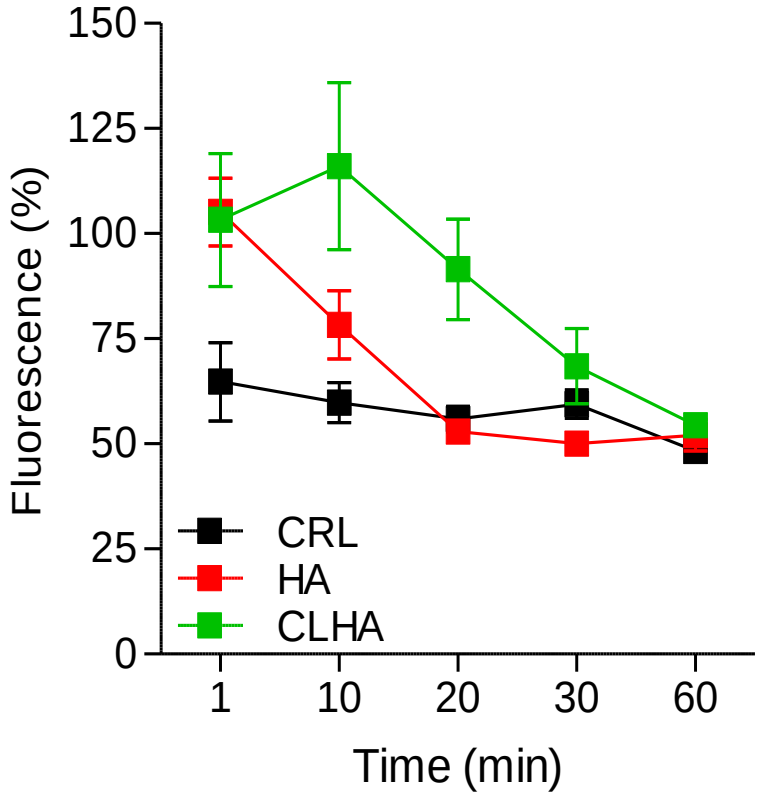
Quervernetzte Hyaluronsäure

Quervernetzte HA ist das Resultat einer chemischen Reaktion zwischen den OH und den COOH Gruppen der linearen Ketten. Diese chemischen Brücken bilden eine 3-dimensionale Struktur = «flüssiges Segel»

Coenzym Q 10, CoQ10 - Quervernetzung

In vivo comparison of the residence time of cross-linked compared to linear hyaluronic acid in rabbit eye.

Mirko Muzzi 1, Rita Mencucci 2
1 Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Italy.
2 Ophthalmology Unit, Careggi University Hospital, Florence, Italy.



3x längere Verweildauer
→ weniger Tropfen

Coenzym Q 10, CoQ10 – ausgewählte Studien

EJO

ISSN 1120-6721

Eur J Ophthalmol 2017; 00 (00): 000-000

DOI: 10.5301/ejo.5001011

ORIGINAL RESEARCH ARTICLE

Efficacy of eyedrops containing cross-linked hyaluronic acid and coenzyme Q10 in treating patients with mild to moderate dry eye

Elisa I. Postorino[1], Laura Rania[1], Emanuela Aragona[1], Carmen Mannucci[2], Angela Alibrandi[3], Gioacchino Calapai[2], Domenico Puzzolo[2], Pasquale Aragona[1]

[1] Department of Biomedical Sciences, Regional Referral Centre for the Ocular Surface Diseases, University of Messina, Messina - Italy
[2] Department of Biomedical Sciences, University of Messina, Messina - Italy
[3] Department of Economics, Unit of Statistical and Mathematical Sciences, University of Messina, Messina - Italy

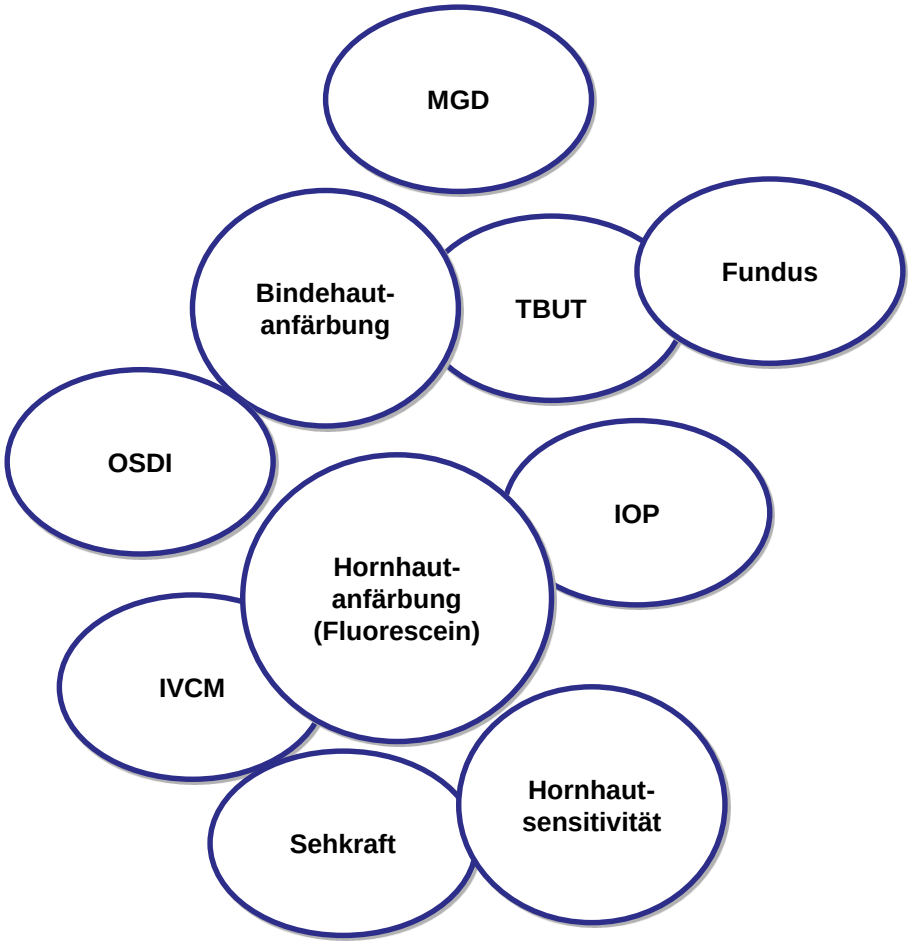
Coenzym Q 10, CoQ10 – ausgewählte Studien

40 Patienten
5 M / 35 F
40-79 Jahre alt
mind. seit 3 Monaten moderates TA
(2-3 DEWS classification)
7 Tage run-in mit 4xtägl. Hyabak, Théa
Therapiedauer 12 Wochen
Untersuchungszeitpunkte: 0, 15, 30, 90 Tagen

Gruppe A
20 Patienten
XLHA+CoQ10
(VisuXL)
4 x täglich

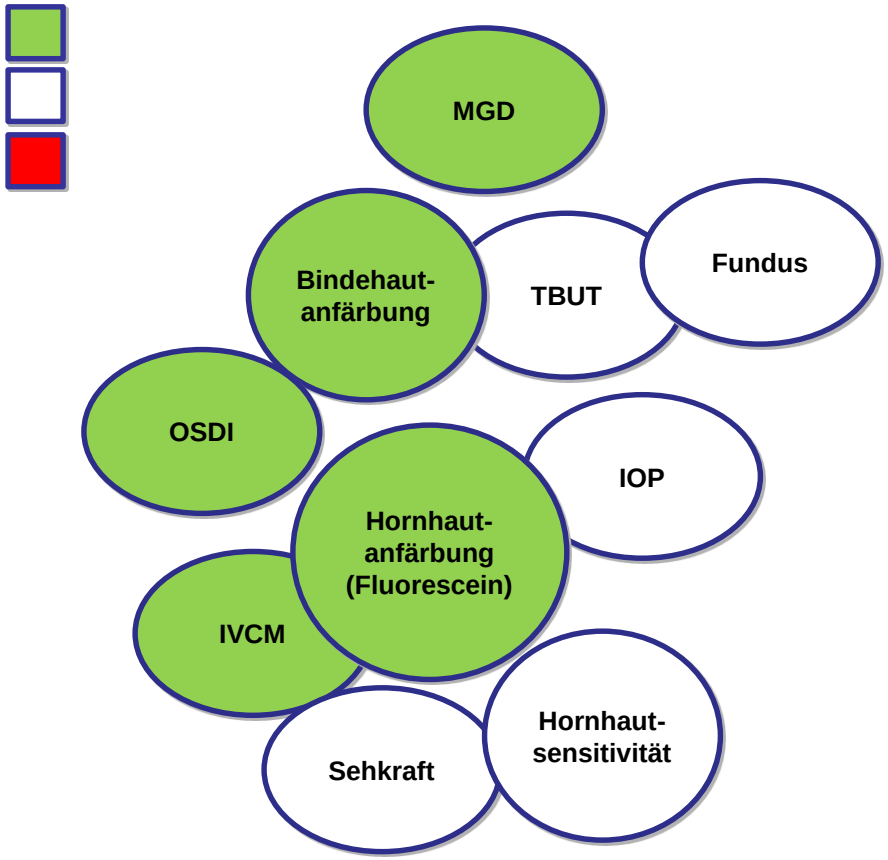
Gruppe B
20 Patienten
0,15 lineare %HA
(Ocuyal)
4 x täglich

Was wurde gemessen ?



Coenzym Q 10, CoQ10 – ausgewählte Studien

Wo war gecrosslinkte Hyalronsäure besser ?



„Furthermore, XLHA increases the stability, adhesiveness, and permanency on ocular surface of CoQ10, allowing a long-lasting effect.“

„This study showed an overall greater effectiveness of the XLHA + CoQ10 combination compared with HA alone.“

„[...] it can be hypothesized that the crosslinked hyaluronate molecule, together with the presence of CoQ10, has a greater effectiveness compared to HA alone.

Coenzym Q 10, CoQ10 – Glaukomstudien

- Das Glaukom ist eine fortschreitende neurodegenerative Erkrankung, die zum irreversiblen Tod der retinalen Ganglienzellen (RGC) und zur Schädigung des Sehnervs (Struktur) sowie zum Verlust des Sehvermögens (Funktion) führt.

- Der häufigste Typ ist das primäre Weitwinkelglaukom mit weniger häufigen Typen, einschließlich des Engwinkelglaukoms und des Normaldruckglaukoms.

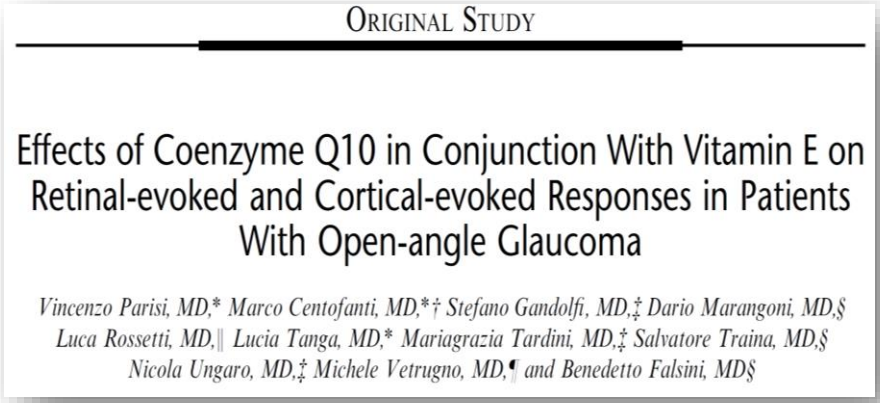
- Heutzutage ist der einzige kontrollierbare Risikofaktor der Augeninnendruck (IOD).

Parisi 2014: Effects of Coenzyme Q10 in Conjunction With Vitamin E on Retinal-evoked and Cortical-evoked Responses in Patients with Glaucoma

- 43 Glaukompatienten:
  - IOD <18 mmHg
  - nur mit β-Blockern behandelt
  - 8 Monate vor der Randomisierung

- Randomisierung:
  - 22 Patienten:
    - CoQun (2 AT pro Tag)
    - β-Blocker-Monotherapie
  - 21 OAG-Patienten:
    - nur β-Blocker-Monotherapie

  - Simultane Aufzeichnung des *visuell evozierten Potentials (VEP)* und des *Pattern ElectroRetinoGram (PERG)*
  - Messungen zu Studienbeginn und nach 6 und 12 Monaten


ORIGINAL STUDY

Effects of Coenzyme Q10 in Conjunction With Vitamin E on Retinal-evoked and Cortical-evoked Responses in Patients With Open-angle Glaucoma

Vincenzo Parisi, MD, Marco Centofanti, MD,*† Stefano Gandolfi, MD,‡ Dario Marangoni, MD,§ Luca Rossetti, MD,‖ Lucia Tanga, MD,* Mariagrazia Tardini, MD,‡ Salvatore Traina, MD,§ Nicola Ungaro, MD,‡ Michele Vetrugno, MD,¶ and Benedetto Falsini, MD§*

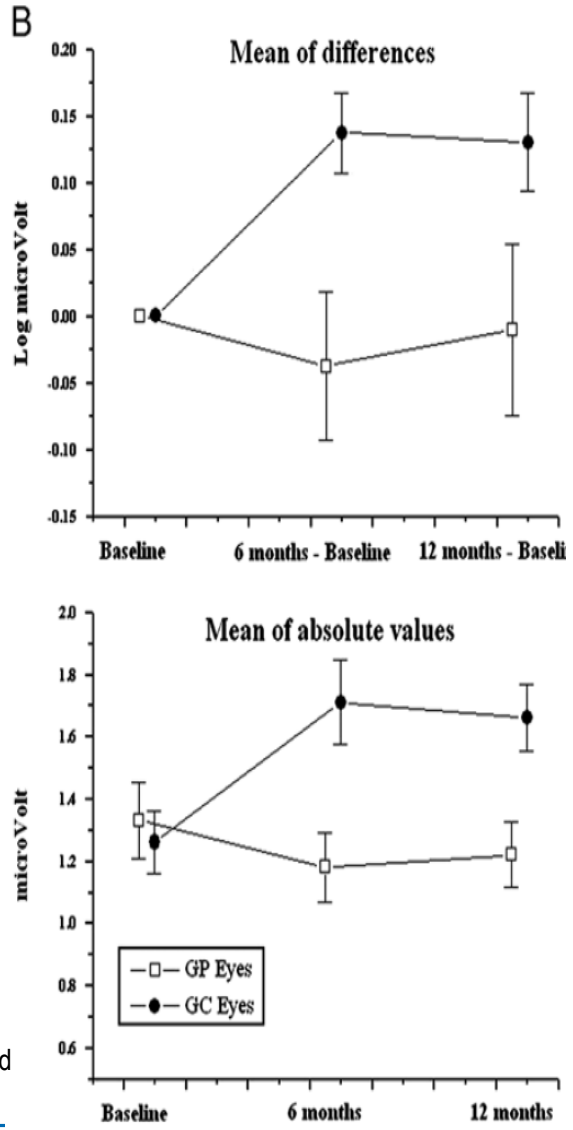
- Elektrophysiologische Methoden VEP & PERG zur Beurteilung, ob CoQ10 einen Einfluss hat auf:

1. Netzhautfunktion
2. visuelle kortikale Reaktionen (Amplitude)
3. neuronales Leitvermögen entlang des postretinalen visuellen Pfades (Geschwindigkeit)

Parisi 2014: PERG-Ergebnisse

Study results (I):

- Changes in PERG **increased amplitude** were found in CoQ10/Vitamin E patients.
  - After 6 months of follow-up of the GC group, the mean values of PERG P50-N95 amplitudes were significantly (P<0.01) increased when compared with those observed at baseline.
  - After 12 months of follow-up of GC eyes, the mean values of PERG P50-N95 amplitudes were significantly (P<0.01) increased when compared to those at baseline.

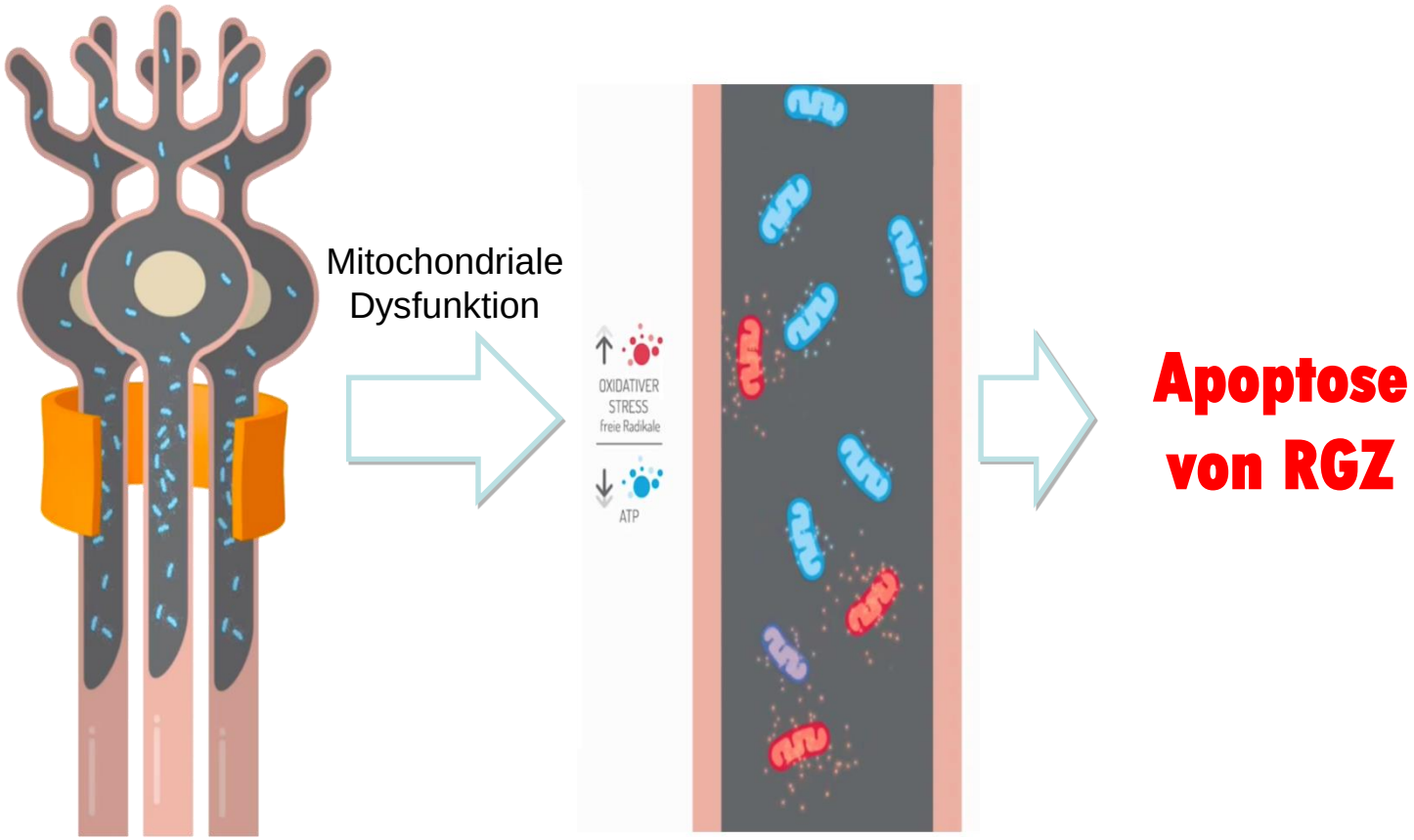


PERG P50 N95 Amplitude

Parisi V, Centofanti M et al. Effects of Coenzyme Q10 in conjunction with vitamin E on retinal-evoked and cortical-evoked responses in patients with open-angle glaucoma. J. Glaucoma 2014;23:391-404

Glaukom – Risikofaktor
Mitochondriale Dysfunktion

Mitochondriale Dysfunktion ist an der **Apoptose von retinalen Ganglienzellen (RGZ)** beteiligt, die zum **Fortschreiten des Glaukoms** führt.



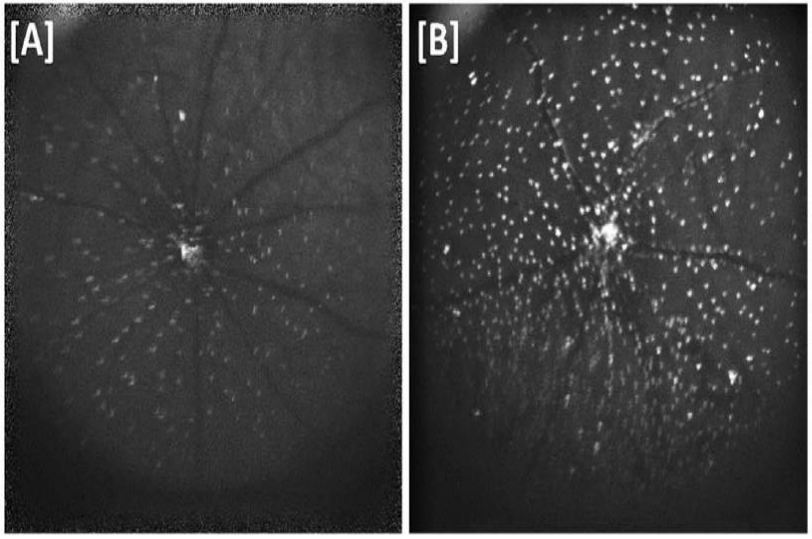
Coenzym Q 10, CoQ10 – Anti-apoptotische Wirkung

CoQ10 reduziert signifikant die Apoptose von RGZ im okulären Hypertensionsmodell im Vergleich zur Kontrollgruppe (Rattenmodell n=20)

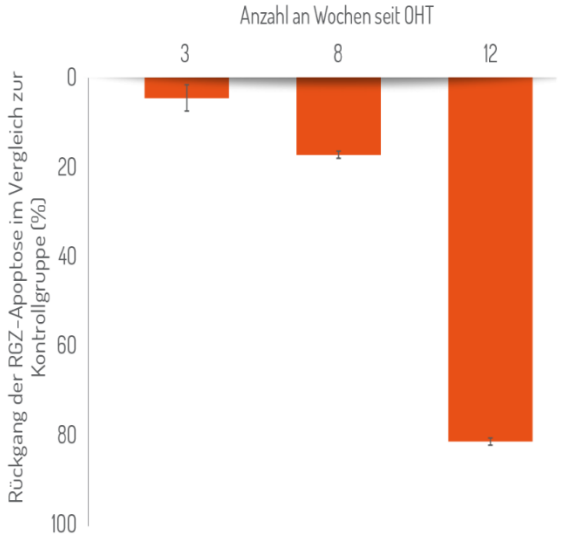
Nachweis apoptotischer retinaler Zellen (DARC)

Behandlung mit CoQ10
3 Wochen post OHT

Behandlung mit Vehicle
3 Wochen post OHT



Die Tiere (Morrison-OHT-Modell) erhielten 2x täglich CoQ10- bzw. Vehicle-Tropfen (A, B). Der Nachweis von apoptotischen Zellen erfolgte *in vivo* mittels DARC-Tomografie (HRT; Annexin A5, Brn3a). Davis *et al*., 2017 [OHT=okuläre Hypertension]



Die Tiere (n=10) erhielten 2x täglich CoQ10- bzw. Vehicle-Tropfen. Der Nachweis von apoptotischen Zellen erfolgte *in vivo* mittels DARC-Tomografie über einen Zeitraum von 12 Wochen. Codeiro *et al*., 2007

Ausblick: Prospektive Studie

Adv Ther
https://doi.org/10.1007/s12325-019-01023-3

STUDY PROTOCOL

Evaluating the Effects of an Ophthalmic Solution of Coenzyme Q10 and Vitamin E in Open-Angle Glaucoma Patients: A Study Protocol

Luciano Quaranta · Ivano Riva · Elena Biagioli · Erica Rulli · Eliana Rulli · Davide Poli · Lorenzo Legramandi · The CoQun® Study Group

Received: April 4, 2019

ABSTRACT

Introduction: The CoQun® study is a multicenter, controlled trial aimed to evaluate the neuroprotective effects of Coqun®, an ophthalmic solution of Coenzyme q10 (CoQ10) and Vitamin E (VitE), in patients affected by primary open-angle glaucoma (POAG). Pre-clinical studies and small non-controlled clinical trials have previously shown a potential role of CoQ10 and VitE in glaucoma neuroprotection, both in vitro and in vivo.

Methods: Randomized, parallel arm, multicenter, double-blind study. POAG patients with an IOP ranging from 17 to 21 mm Hg on monotherapy with a prostaglandin analogue (PGA) will be considered for study enrollment. Inclusion criteria will be visual field (VF) mean deviation between − 4 and − 10 dB and VF Pattern Standard Deviation between 4 and 10 dB. Eligible patients will be randomized to receive CoQun® (Arm A) or placebo (Arm B), in addition to PGA monotherapy.

Planned Outcomes: Primary outcome will be time to progression, defined as the time between the baseline visit and the visit with confirmed VF progression. A total of 612 patients are planned to be enrolled, to detect a hazard ratio of 0.65, with a power of 80% and an alpha error of 0.05 (two-sided). For study power calculation, 10% non-evaluable patients are assumed. This is the first study investigating, in a randomized, double-blind and controlled fashion, the neuroprotective effects of CoQ10 and VitE in POAG patients.

Trial Registration: ClinicalTrials.gov identifier, NCT03611530.

Keywords: Coenzyme Q10; Open-angle glaucoma; Ophthalmology; Prostaglandin analogue; Randomized clinical trial; Vitamin E

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.8306330.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-019-01023-3) contains supplementary material, which is available to authorized users.

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Zusammenfassung

- CoQ10 kommt in allen Zellen vor (u.a. Mitochondrien)
- CoQ10-Spiegel nimmt mit dem Alter ab
- CoQ10 wirkt
  - positiv auf die Zellenergiegewinnung,
  - ist antioxidativ und
  - reguliert die Apoptose

- positiver Effekt auf die **Regeneration von Nervenfasern in der Cornea**

- *quervernetzte* Hyaluronsäure hat ggü. einer linearen HA zeigen können,
  - dass es eine **Regeneration geschädigter Hornhautzellen** unterstützt,
  - dass dieser Unterschied für Patienten relevant ist

- positiver, neuroprotektiver Effekt bei **Glaukom**patienten

  - positiver Effekt auf die retinalen Ganglienzellen bei Glaukompatienten
  - gross angelegte, prospektive Studie rekrutiert bereits Patienten

Publikationen

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Vol. 278, No. 30, Issue of July 25, pp. 28220–28228, 2003
Printed in U.S.A.

Coenzyme Q_{10} Prevents Apoptosis by Inhibiting Mitochondrial Depolarization Independently of Its Free Radical Scavenging Property*

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A Ubiquinone-binding Site Regulates the Mitochondrial Permeability Transition Pore*

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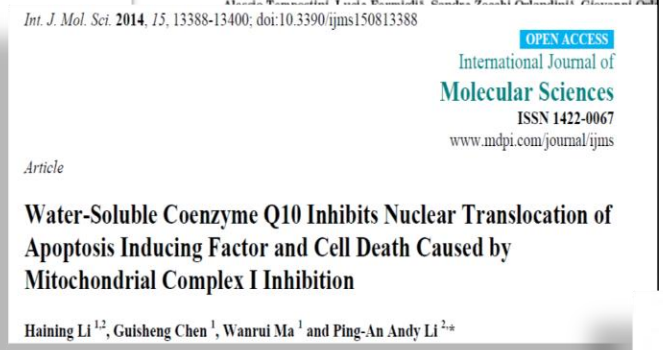

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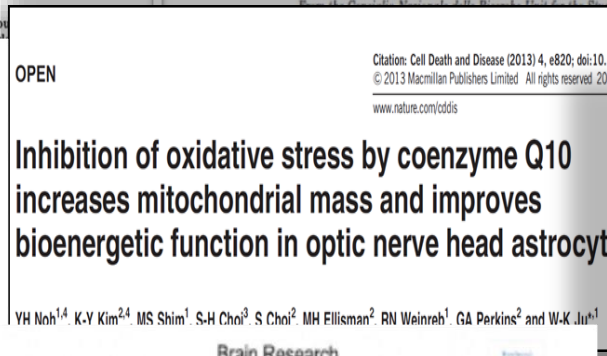
Article

Water-Soluble Coenzyme Q10 Inhibits Nuclear Translocation of Apoptosis Inducing Factor and Cell Death Caused by Mitochondrial Complex I Inhibition

Haining Li [1,2], Guisheng Chen [1], Wanrui Ma [1] and Ping-An Andy Li [2,*]



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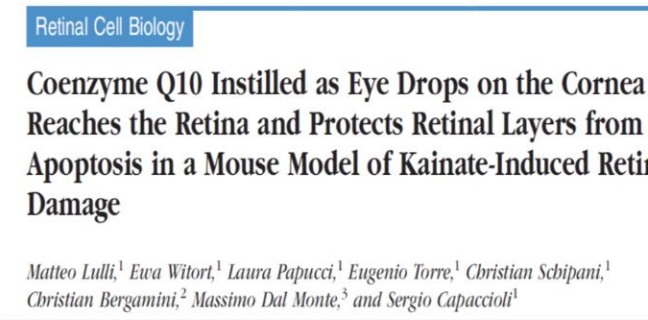
Inhibition of oxidative stress by coenzyme Q10 increases mitochondrial mass and improves bioenergetic function in optic nerve head astrocyt

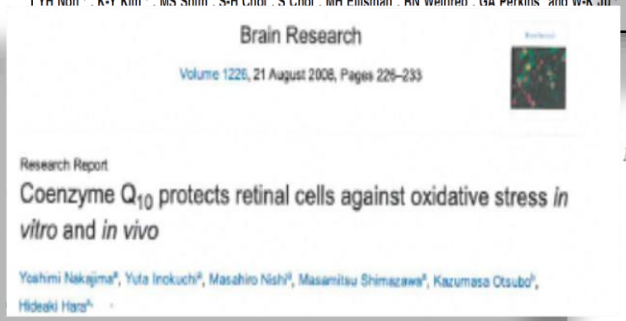
YH Noh[1,4], K-Y Kim[2,4], MS Shim[1], S-H Choi[3], S Choi[2], MH Ellisman[2], RN Weinreb[1], GA Perkins[2] and W-K Ju[*,1]



Retinal Cell Biology

Coenzyme Q10 Instilled as Eye Drops on the Cornea Reaches the Retina and Protects Retinal Layers from Apoptosis in a Mouse Model of Kainate-Induced Reti Damage

Matteo Lulli,[1] Ewa Witort,[1] Laura Papucci,[1] Eugenio Torre,[1] Christian Schipani,[1] Christian Bergamini,[2] Massimo Dal Monte,[3] and Sergio Capaccioli[1]



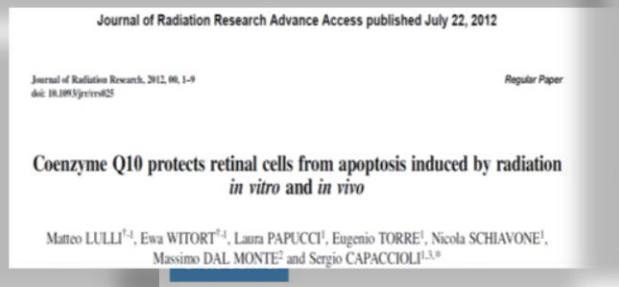
Brain Research

Volume 1226, 21 August 2008, Pages 225–233

Research Report

Coenzyme Q_{10} protects retinal cells against oxidative stress *in vitro* and *in vivo*

Yoshimi Nakajima[a], Yuta Inokuchi[a], Masahiro Nishi[a], Masamitsu Shimazawa[a], Kazumasa Otsubo[b], Hideaki Hara[a,*]



Journal of Radiation Research Advance Access published July 22, 2012

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Regular Paper

Coenzyme Q10 protects retinal cells from apoptosis induced by radiation *in vitro* and *in vivo*

Matteo LULLI[†,1], Ewa WITORT[†,1], Laura PAPUCCI[1], Eugenio TORRE[1], Nicola SCHIAVONE[1], Massimo DAL MONTE[2] and Sergio CAPACCIOLI[1,3,*]

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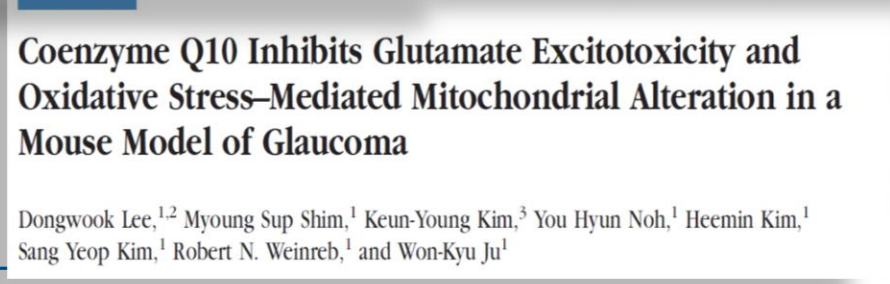
Article

Coenzyme Q10 Ameliorates Ultraviolet B Irradiation Induced Cell Death Through Inhibition of Mitochondrial Intrinsic Cell Death Pathway

Li Jing [1,2], Santosh Kumari [1], Natalia Mendelev [1] and P. Andy Li [1,*]



Coenzyme Q10 Inhibits Glutamate Excitotoxicity and Oxidative Stress–Mediated Mitochondrial Alteration in a Mouse Model of Glaucoma

Dongwook Lee,[1,2] Myoung Sup Shim,[1] Keun-Young Kim,[3] You Hyun Noh,[1] Heemin Kim,[1] Sang Yeop Kim,[1] Robert N. Weinreb,[1] and Won-Kyu Ju[1]

Vitamin D Supplementation bei Dry Eye

SCIENTIFIC REPORTS

OPEN

Vitamin D Supplementation for Patients with Dry Eye Syndrome Refractory to Conventional Treatment

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Vitamin D Supplementation bei Dry Eye

This study investigated the effect of vitamin D supplementation in patients with dry eye syndrome (DES) refractory to conventional treatment with vitamin D deficiency. A total of 105 patients with DES refractory to conventional treatment and vitamin D deficiency that was treated with an intramuscular injection of cholecalciferol (200,000 IU). Serum 25-hydroxyvitamin D (25(OH)D) levels were measured. Eye discomfort was assessed using ocular surface disease index (OSDI) and visual analogue pain score (VAS). Tear break-up time (TBUT), fluorescein staining score (FSS), eyelid margin hyperemia, and tear secretion test were measured before treatment, and 2, 6, and 10 weeks after vitamin D supplementation. Mean serum 25(OH)D level was 10.52 ± 4.61 ng/mL. TBUT, and tear secretion test showed an improvement at 2 and 6 weeks after vitamin D supplementation compared to pretreatment values ($p < 0.05$ for all, paired t-test). Eyelid margin hyperemia and the severity of symptoms showed improvement at 2, 6, and 10 weeks after vitamin D supplementation ($p < 0.05$ for all). Compared to pre-treatment values, FSS, OSDI and VAS were decreased at 2 weeks ($p < 0.05$ for all). In conclusion, vitamin D supplementation is effective and useful in the treatment of patients with DES refractory to conventional treatment and with vitamin D deficiency.

Vitamin D Supplementation bei Dry Eye

Materials and Methods

This observational study was performed in accordance with the tenets of the Declaration of Helsinki, and was reviewed and approved by the institutional review board/ethics committee of Hallym University Medical Center. The ethics committee/IRB waived the need for informed consent because this study is retrospective. We reviewed the medical charts from patients who had visited the Hallym University Kangnam Sacred Heart Hospital from June 2015 to March 2016. Patients with DES that was refractory to artificial tear treatment (hyaluronate sodium; New Hyaluni, Taejoon Pharm Co., Seoul) and liposic EDO (Bausch & Lomb, Gerhard Mann Gmbh) and with demonstrated vitamin D deficiency were included. Serum 25(OH)D concentration was measured. Patients with vitamin D deficiency or insufficiency were treated by an intramuscular injection of 200,000 IU cholecalciferol. Exclusion criteria were autoimmune diseases such as Sjogren's syndrome or lupus syndrome; corneal surgery such as penetrating keratoplasty, corneal limbal allo-transplantation or corneal laceration repair; corneal diseases such as recurrent corneal erosion syndrome or keratoconus; and corneal opacity. Data was obtained pre-treatment, 2 weeks, 6 weeks, and 10 weeks after vitamin D supplementation.

Vitamin D Supplementation bei Dry Eye

	Total subjects
N	105
Age	58.21 ± 12.94 years
Gender (male: female)	21:84
Serum 25 (OH)D levels	10.52 ± 4.61 ng/mL

Table 1. Demographic data of subjects.

Vitamin D Supplementation bei Dry Eye

	Pre-treatment (n = 105)	After vitamin D supplementation					
		2 weeks (n = 78)		6 weeks (n = 54)		10 weeks (n = 49)	
	Mean ± SD	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
TBUT (sec)	3.16 ± 2.27	5.58 ± 2.44	<0.001*	5.19 ± 2.34	<0.001*	4.49 ± 2.60	0.066
FSS (grade)	0.57 ± 0.75	0.36 ± 0.56	0.013*	0.32 ± 0.56	0.088	0.42 ± 0.59	0.826
Hyperemia of eyelid margin (grade)	2.05 ± 0.75	1.13 ± 0.89	<0.001*	1.18 ± 0.84	<0.001*	1.51 ± 0.80	0.006*
CCH (grade)	0.40 ± 0.77	0.36 ± 0.73	0.884	0.28 ± 0.74	0.537	0.31 ± 0.54	1.000
Schirmer tear secretion test (mm)	6.69 ± 3.92	8.64 ± 6.32	0.006*	8.92 ± 7.60	0.015*	8.40 ± 7.16	0.140
OSDI score	34.39 ± 24.88	29.25 ± 23.35	0.046*	29.20 ± 20.44	0.136	21.07 ± 16.52	0.004*
VAS score	2.80 ± 2.70	2.05 ± 2.43	0.005*	2.02 ± 2.38	0.059	1.42 ± 1.73	0.085
Severity of symptoms (grade)	2.09 ± 1.03	1.68 ± 1.02	0.008*	1.52 ± 0.91	0.001*	1.32 ± 1.01	0.045*
Duration of symptoms (grade)	2.14 ± 1.18	1.44 ± 0.91	0.005*	1.36 ± 0.87	0.001*	1.40 ± 1.22	0.389

Table 2. The effect of vitamin D supplementation on dry eye syndrome. TBUT = tear break-up time; FSS = fluorescein staining score; CCH = conjunctivochalasis; OSDI = ocular surface disease index; VAS = visual analogue scale; *$p < 0.05$ by paired t-test compared to pre-treatment.

Vitamin D Supplementation bei Dry Eye

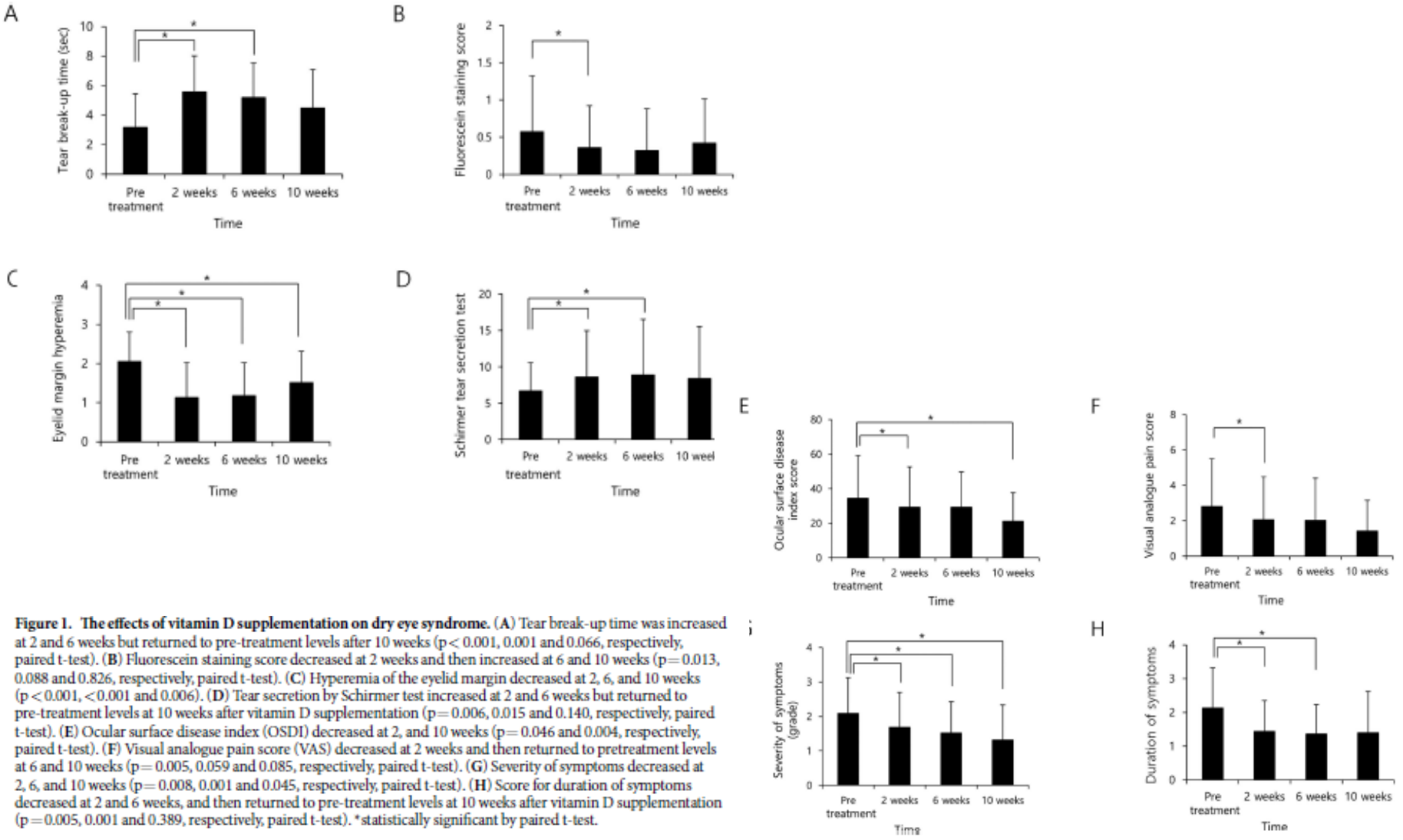

Figure 1. The effects of vitamin D supplementation on dry eye syndrome. (**A**) Tear break-up time was increased at 2 and 6 weeks but returned to pre-treatment levels after 10 weeks ($p < 0.001$, 0.001 and 0.066, respectively, paired t-test). (**B**) Fluorescein staining score decreased at 2 weeks and then increased at 6 and 10 weeks ($p = 0.013$, 0.088 and 0.826, respectively, paired t-test). (**C**) Hyperemia of the eyelid margin decreased at 2, 6, and 10 weeks ($p < 0.001$, < 0.001 and 0.006). (**D**) Tear secretion by Schirmer test increased at 2 and 6 weeks but returned to pre-treatment levels at 10 weeks after vitamin D supplementation ($p = 0.006$, 0.015 and 0.140, respectively, paired t-test). (**E**) Ocular surface disease index (OSDI) decreased at 2, and 10 weeks ($p = 0.046$ and 0.004, respectively, paired t-test). (**F**) Visual analogue pain score (VAS) decreased at 2 weeks and then returned to pretreatment levels at 6 and 10 weeks ($p = 0.005$, 0.059 and 0.085, respectively, paired t-test). (**G**) Severity of symptoms decreased at 2, 6, and 10 weeks ($p = 0.008$, 0.001 and 0.045, respectively, paired t-test). (**H**) Score for duration of symptoms decreased at 2 and 6 weeks, and then returned to pre-treatment levels at 10 weeks after vitamin D supplementation ($p = 0.005$, 0.001 and 0.389, respectively, paired t-test). *statistically significant by paired t-test.

Vitamin D Supplementation bei Dry Eye

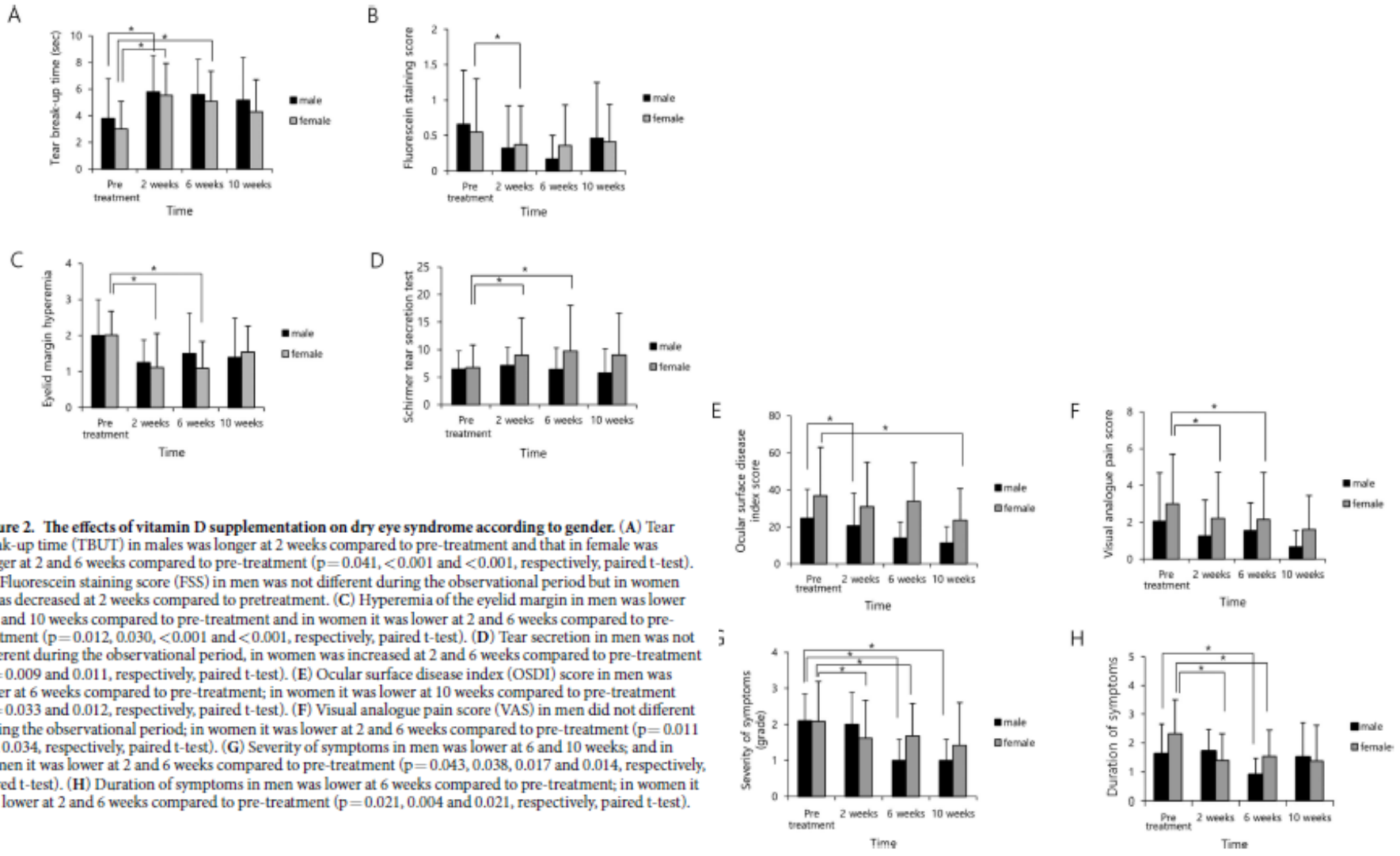

Figure 2. The effects of vitamin D supplementation on dry eye syndrome according to gender. (**A**) Tear break-up time (TBUT) in males was longer at 2 weeks compared to pre-treatment and that in female was longer at 2 and 6 weeks compared to pre-treatment ($p = 0.041$, < 0.001 and < 0.001, respectively, paired t-test). (**B**) Fluorescein staining score (FSS) in men was not different during the observational period but in women it was decreased at 2 weeks compared to pretreatment. (**C**) Hyperemia of the eyelid margin in men was lower at 6 and 10 weeks compared to pre-treatment and in women it was lower at 2 and 6 weeks compared to pre-treatment ($p = 0.012$, 0.030, < 0.001 and < 0.001, respectively, paired t-test). (**D**) Tear secretion in men was not different during the observational period, in women was increased at 2 and 6 weeks compared to pre-treatment ($p = 0.009$ and 0.011, respectively, paired t-test). (**E**) Ocular surface disease index (OSDI) score in men was lower at 6 weeks compared to pre-treatment; in women it was lower at 10 weeks compared to pre-treatment ($p = 0.033$ and 0.012, respectively, paired t-test). (**F**) Visual analogue pain score (VAS) in men did not different during the observational period; in women it was lower at 2 and 6 weeks compared to pre-treatment ($p = 0.011$ and 0.034, respectively, paired t-test). (**G**) Severity of symptoms in men was lower at 6 and 10 weeks; and in women it was lower at 2 and 6 weeks compared to pre-treatment ($p = 0.043$, 0.038, 0.017 and 0.014, respectively, paired t-test). (**H**) Duration of symptoms in men was lower at 6 weeks compared to pre-treatment; in women it was lower at 2 and 6 weeks compared to pre-treatment ($p = 0.021$, 0.004 and 0.021, respectively, paired t-test).

Vitamin D Supplementation bei Dry Eye

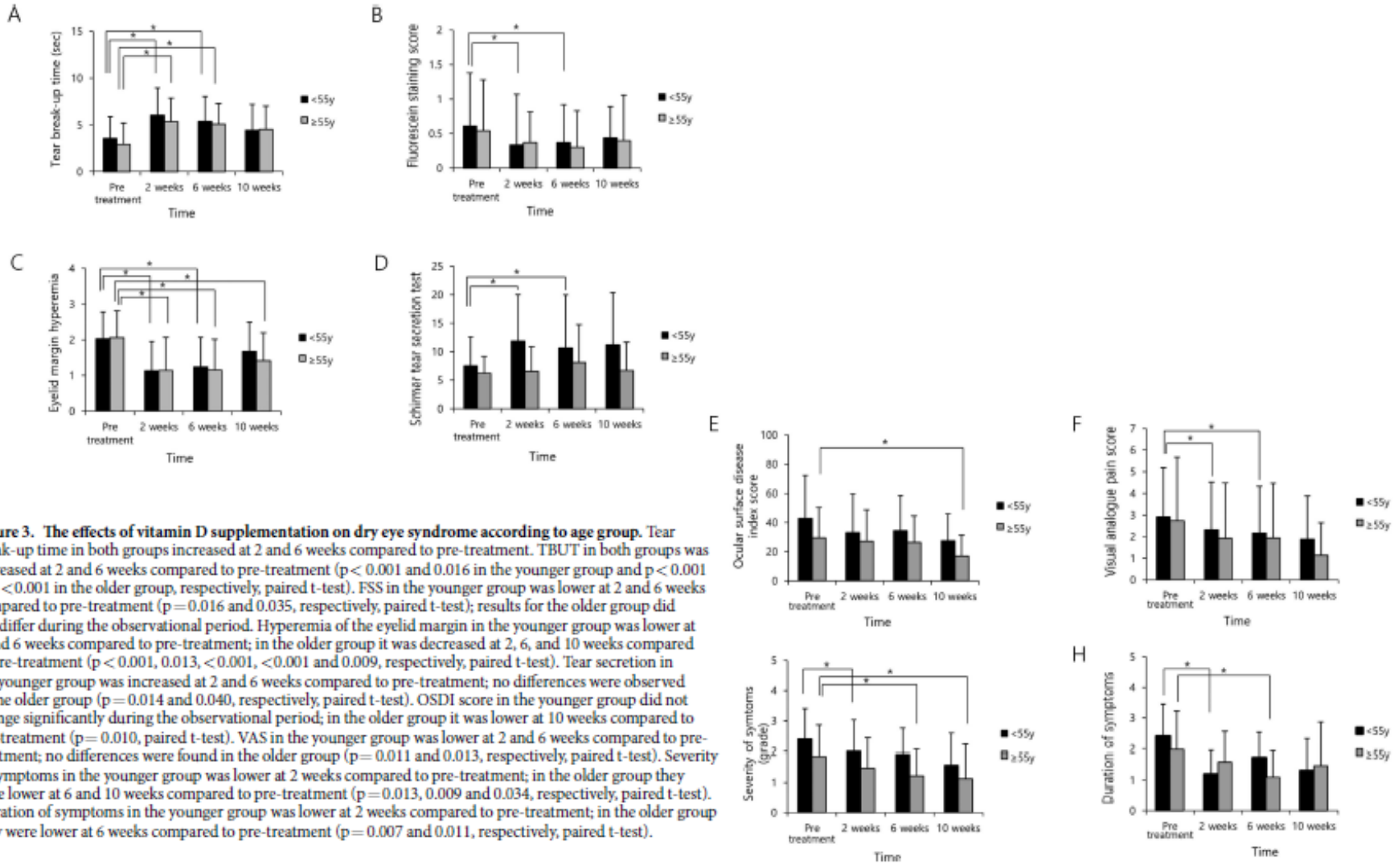

Figure 3. The effects of vitamin D supplementation on dry eye syndrome according to age group. Tear break-up time in both groups increased at 2 and 6 weeks compared to pre-treatment. TBUT in both groups was increased at 2 and 6 weeks compared to pre-treatment ($p < 0.001$ and 0.016 in the younger group and $p < 0.001$ and < 0.001 in the older group, respectively, paired t-test). FSS in the younger group was lower at 2 and 6 weeks compared to pre-treatment ($p = 0.016$ and 0.035, respectively, paired t-test); results for the older group did not differ during the observational period. Hyperemia of the eyelid margin in the younger group was lower at 2 and 6 weeks compared to pre-treatment; in the older group it was decreased at 2, 6, and 10 weeks compared to pre-treatment ($p < 0.001$, 0.013, < 0.001, < 0.001 and 0.009, respectively, paired t-test). Tear secretion in the younger group was increased at 2 and 6 weeks compared to pre-treatment; no differences were observed in the older group ($p = 0.014$ and 0.040, respectively, paired t-test). OSDI score in the younger group did not change significantly during the observational period; in the older group it was lower at 10 weeks compared to pre-treatment ($p = 0.010$, paired t-test). VAS in the younger group was lower at 2 and 6 weeks compared to pre-treatment; no differences were found in the older group ($p = 0.011$ and 0.013, respectively, paired t-test). Severity of symptoms in the younger group was lower at 2 weeks compared to pre-treatment; in the older group they were lower at 6 and 10 weeks compared to pre-treatment ($p = 0.013$, 0.009 and 0.034, respectively, paired t-test). Duration of symptoms in the younger group was lower at 2 weeks compared to pre-treatment; in the older group they were lower at 6 weeks compared to pre-treatment ($p = 0.007$ and 0.011, respectively, paired t-test).

Vitamin D Supplementation bei Dry Eye

Conclusions

In summary, vitamin D supplementation promoted tear secretion, reduced tear instability, and reduced inflammation at the ocular surface and eyelid margin. Furthermore, vitamin D supplementation improved the symptoms of DES. In conclusion, vitamin D supplementation is an effective and useful treatment for patients with DES that is refractory to conventional treatment.

Phospholipide und Citicolin

Der Ophthalmologe

Leitthema

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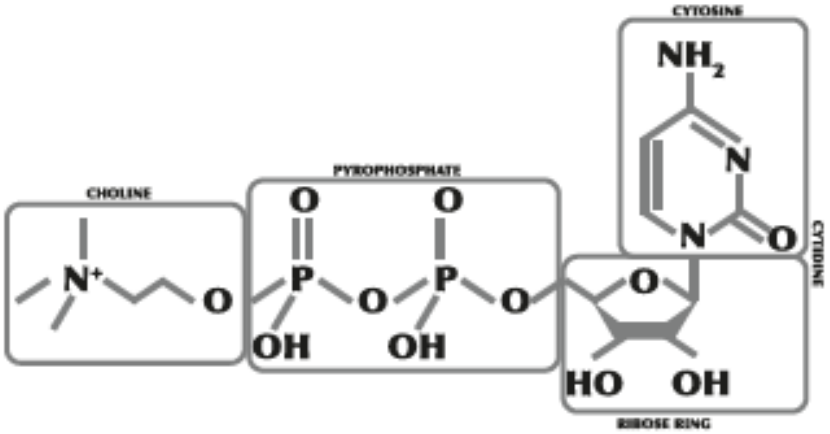
Bedeutung von Citicolin bei der Glaukomerkrankung

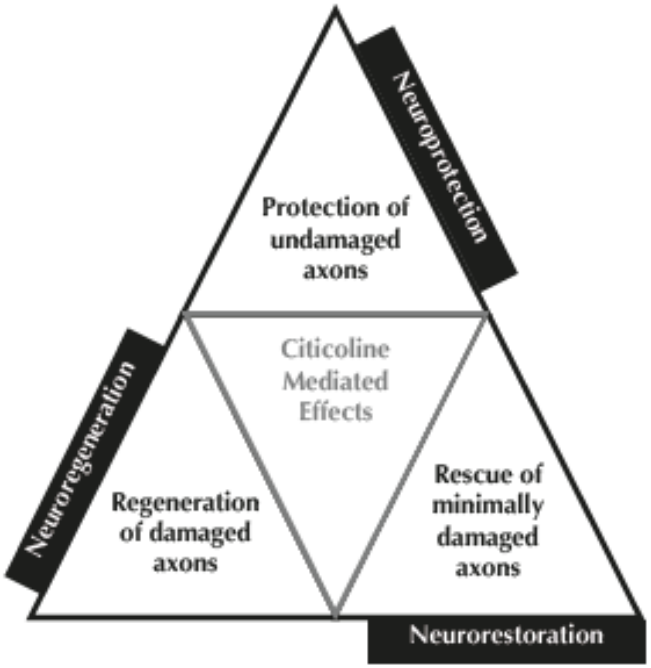
Phospholipide und Citicolin

Figure 1. Chemical structure of CDP-choline (citicoline). Adapted from Faiq et al[1].



Phospholipide und Citicolin

Figure 4. Biochemical and biological activities of citicoline into the triad of pharmacodynamics for treating neurodegeneration. *Adapted from Faiq et al*[1].



Phospholipide und Citicolin

Wirkweise von Neuroprotektiva

Da auch nach IOD-Senkung die Glaukomerkrankung fortschreiten kann, scheinen neuroprotektive Substanzen hilfreich zu sein, und es liegt nahe, die IOD-senkende Therapie durch eine neuroprotektive Therapie zu ergänzen. Neuroprotektive Substanzen zum Erhalt der visuellen Funktion korrigieren das Ungleichgewicht zwischen pro- und antiapoptotischen Signalen und reduzieren bzw. verhindern so den RGZ-Untergang und Sehbahnschaden.

» Neuroprotektiva korrigieren das Ungleichgewicht zwischen pro- und antiapoptotischen Signalen

Phospholipide und Citicolin

Citicolin

Indikationen

Citicolin oder CDP-Cholin, ein nootroper und neurotroper Wirkstoff, welcher in oraler Form seit fast 5 Jahrzehnten in klinischer Anwendung ist und seit einigen Jahren auch als Nahrungsergänzungsmittel in den USA und der EU zur Verfügung steht, erfüllt diese genannte Anforderung zur Prävention und Therapie der glaukomatösen Neurodegeneration. Citicolin eignet sich nach Ansicht der Autoren als ein Neuroprotektivum für alle an der Glaukomerkrankung beteiligten zerebralen Neurone.

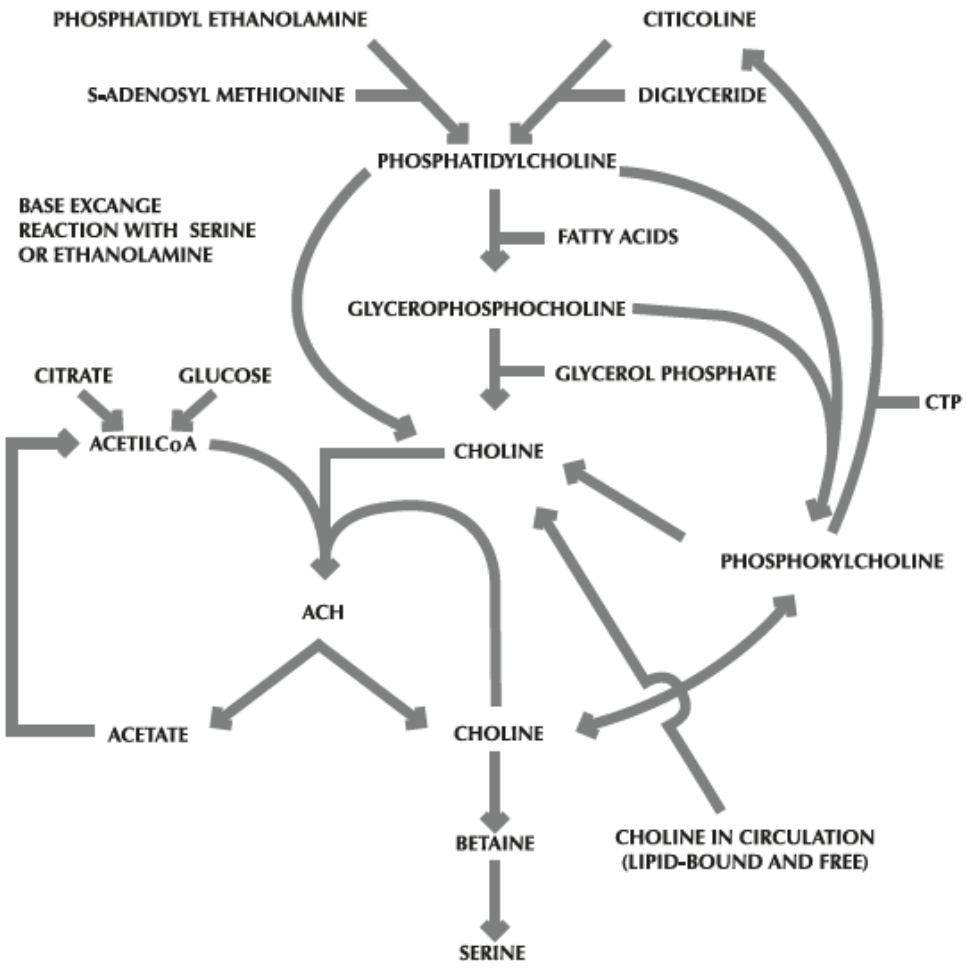
Citicolin zeigt auch bei anderen Erkrankungen neuroprotektive Wirkungen. So sind positive Effekt bei der Amblyopie [15] und bei der nichtarteriitischen ischämischen Optikusneuropathie [35] beschrieben. Topisches Citicolin verbessert auch die Funktion und Morphologie der Hornhautnerven bei Diabetes mellitus [14].

Phospholipide und Citicolin

Wirkmechanismen

Citicolin ist eine Vorstufe des Neurotransmitters Acteylcholin sowie anderer neuronaler Membrankomponenten wie Phosphatidylcholin und Sphingomyelin. In verschiedensten experimentellen Ansätzen sind neuroprotektive Eigenschaften von Citicolin nachgewiesen worden. Dabei spielt eine beschleunigte Synthese von Phosphatidylcholin und Phospholipiden eine zentrale Rolle.

Figure 2. Relationship between citicoline and choline metabolism, cerebral phospholipids and acetylcholine. Adapted from Secades et al[6].



Phospholipide und Citicolin

Klinische Evidenz

Inzwischen sind 11 klinische Studien publiziert, die alle einen neuroprotektiven Effekt von Citicolin auf die Glaukomerkrankung nachweisen konnten (Tab. 1). Der erste Bericht über eine Behandlung mit Citicolin bei der Glaukomerkrankung (primäres Offenwinkelglaukom, POWG) mittels i.m.-Citicolin-Injektionen stammt von Pecori-Giraldi et al. aus dem Jahr 1989 [37].

Tab. 1 Klinische Studien mit Nachweis eines neuroprotektiven Effekts von Citicolin auf die Glaukomerkrankung

Autoren	Studien-design	Patienten	Alter (Jahre) MD (dB)	IOD[a] (mm Hg)	Appli-kation	Dosis (pro Tag)	Therapie-schema	Follow-up	Endpunkte
Pecori-Giraldi 1989 [37]	Kohortenstudie	OWG ($n=30$, A=47)	52,12 (25–75)	–	i.m.	1 g	10 Tage	3 Monate	Perimetrie
Parisi 1999 [36]	Doppelmaskiert, placebokontrol-liert	OWG ($n=40$) 25 C, 15 K	45,6 ± 4,3 –3 bis –6 dB	25,10 ± 1,55 (23–27)	i.m.	1 g	60 Tage 120 Tage w/o 2 Zyklen	360 Tage	VEP, MERG
Virno 2000 [48]	Fall-Kontroll-Studie	OWG ($n=23$) 11 C, 12 K	–	–	i.m.	1 g	15 Tage alle 6 Monate 20 Zyklen	10 Jahre	Perimetrie
Rejdak 2003 [40]	Kohortenstudie	OWG ($n=21$)	–	–	p.o.	1 g	14 Tage 2 Tage w/o 2 Zyklen	56 Tage	VEP
Parisi 2005 [32]	Doppelmaskiert, placebokontrol-liert	OWG ($n=30$) 15 C, 15 K	–3 bis –6 dB	25,10 ± 1,55 (23–27) 17,5 ± 1,3[b]	i.m.	1 g	60 Tage 120 Tage w/o 14 Zyklen	8 Jahre	VEP, MERG
Parisi 2008 [34]	Fall-Kontroll-Studie	OWG ($n=60$, A=70)	52,77 ± 5,28 (38–62) –2 bis –14 dB	–	i.m. oral	1 g 1,6 g	60 Tage 120 Tage w/o 2 Zyklen	360 Tage	VEP, MERG
Ottobelli 2013 [31]	Kohortenstudie	POWG ($n=41$)	72,5 ± 11,6 –1,1 ± 0,7 dB/Jahr[c]	15,5 ± 2,6	p.o.	0,5 g	4 × 120 Tage 60 Tage w/o 4 Zyklen	2 Jahre	Perimetrie
Roberti 2014 [41]	Doppelmaskiert, placebokontrol-liert	OWG ($n=34$) 16 C, 18 K	–3 bis –12 dB	–	AT	3 ×	60 Tage	90 Tage	VEP, MERG
Parisi 2015 [33]	Fall-Kontroll-Studie	OWG ($n=56$) 28 C, 18 K	52,4 ± 4,72 (40–60) > –10 dB	23–28	AT	3 ×	120 Tage 60 Tage w/o	180 Tage	VEP, MERG
Lanza 2009 [25]	Fall-Kontroll-Studie	OWG ($n=60$) 30 C, 30 K	C 64,1 ± 5,8 K 62,9 ± 7,2 1,0–1,5 dB/Jahr[c] C –6,51 ± 2,65 K –6,39 ± 2,03	< 18	p.o.	0,5 g	120 Tage 60 Tage w/o 4 Zyklen	2 Jahre	Perimetrie, OCT
Marino 2020 [27]	Cross-over-Studie	OWG ($n=109$)	C 66,5, K 68,0 –1,72 dB (–19,0 bis +3,18 dB)	16 (10–25)	p.o.	0,5 g	120 Tage 120 Tage w/o	4 Monate	SPARCS, GQL-15
Rossetti 2020 [42]	Doppelmaskiert, placebokontrol-liert	OWG ($n=80$) 40 C, 40 K	C 74,0, K 71,4 –9,0 dB 0,8 dB/Jahr[c]	C 14,3 K 13,8 < 18[b]	AT	3 ×	3 Jahre	3 Jahre	Perimetrie, OCT

IOD Augeninnendruck, *MD* „mean defect" in statischer Weiß-Weiß-Perimetrie, *OWG* Offenwinkelglaukom, *POWG* primäres Offenwinkelglaukom, *A* Augen, *C* Studiengruppe mit Citicolin-Therapie, *K* Kontrollgruppe, *i.m.* intramuskulär, *p.o.* per os, oral; *AT* Augentropfen, *w/o* „wash-out", *VEP* visuell evozierte Potenziale, *MERG* Muster-Elektroretinogramm, *OCT* optische Kohärenztomographie, *SPARCS* Spaeth-Richman-Contrast-Sensitivity-Test, *GQL-15* Glaucoma Quality of Life-15

[a] IOD bei Studieneinschluss

[b] Im Verlauf der Studienjahre

[c] Progressionsrate im MD in 2 Jahren vor Studienbeginn

Phospholipide und Citicolin

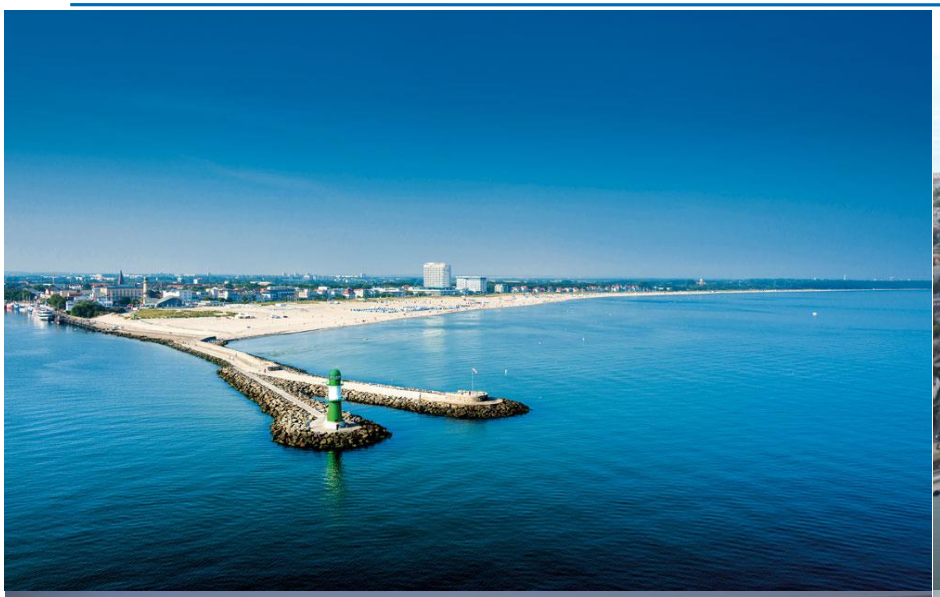
Fazit für die Praxis

- Citicolin wirkt bei Offenwinkelglaukomen neuroprotektiv.
- Die Wirkung von Citicolin ist funktionell und morphologisch nachweisbar.
- Die Neuroprotektion ist unabhängig vom Glaukomschaden und Augeninnendruck.
- Der neuroprotektive Effekt von Citicolin ist i. d. R. erst nach einem Jahr nachweisbar.
- Die Effekte von oralem Citicolin treten bei einer Tagesdosis von 500–1000 mg auf.
- Die Einnahme von Citicolin kann dauerhaft oder in Zyklen erfolgen.
- In den Studien traten bei der Einnahme von Citicolin keine Nebenwirkungen auf.
- Citicolin kann kognitive Leistungen und somit Therapieadhärenz verbessern.
- Citicolin kann die Lebensqualität bei Glaukompatienten verbessern.

4th Baltic Sea Eye Conference

-Eye Surgery Masterclass & International Rostock Beach Academy-

Fri. 22.4.2022 & Sat., 23.4.2022 – Uni-Augenklinik, Kurhaus Warnemünde & Hotel Neptun



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