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ORIGINAL ARTICLE

Effects of Topical Coenzyme Q10 on Retinal Nerve Fiber Layer and Ganglion Cell Complex in Patients with Open-Angle Glaucoma

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Abstract

Introduction: Recent studies have shown that retinal ganglion cell apoptosis is of great importance in the pathophysiology of glaucoma. Coenzyme Q10 (CQ10) is a molecule used for its neuroprotective effect in the treatment of glaucoma. Our aim was to evaluate the effect of CQ10 and Vitamin E (Vit E) combination on retinal nerve fiber layer (RNFL) and ganglion cell complex in open-angle glaucoma (OAG) patients by optical coherence tomography (OCT).

Methods: In this retrospective study, thirty-one OAG patients with glaucoma in both eyes (intraocular pressure [IOP] <21 mmHg with medical treatment) were enrolled. Data of 28 patients were included in the study. At baseline and after 6 months, OCT parameters were obtained from patients treated with a combination of CQ10 and Vit E (CoQun ophthalmic drop twice daily) in addition to antiglaucomatous therapy in one eye (GC group); fellow eyes received antiglaucomatous therapy only (GT group).

Results: IOP and OCT parameters were similar in both groups (p>0.05) at baseline. There was a significant increase in the average RNFL value at baseline and after 6 months of treatment in the GC group (p=0.045). In the GC group, the differences in the superior RNFL and the average RNFL values after 6 months were significantly greater than those recorded in the GT group (p=0.019, p=0.034, respectively).

Discussion and Conclusion: In our study, we found a statistically significant effect of CQ10 on the RNFL. The combination of CQ10 and Vit E treatment can have beneficial effects on the RNFL in primary OAG patients.

Keywords: Coenzyme Q10; ganglion cell complex; glaucoma; retinal nerve fiber layer.

Glaucoma is a progressive optic neuropathy that causes degeneration of retinal ganglion cells and axons. Nerve fiber damage which results from glaucoma is irreversible, so early diagnosis and treatment are crucial[1,2].

Pathophysiology of glaucoma is better understood with recent studies, and the most important underlying mechanism has been shown to be retinal ganglion cell apoptosis[3,4]. As the retinal ganglion cell death mechanism resulting from glaucoma is better understood, studies aimed at stopping this process through inhibiting apoptosis have gained speed. One of the neuroprotective molecules examined in various studies is coenzyme Q10 (CQ10)[5-7]. Many studies suggest that pores which control mitochondrial permeability, an important step of apoptosis, can be regulated with CQ10[8]. In addition to its antiapoptotic effect, CQ10 also acts as a free oxygen radical scavenger

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and displays antioxidant properties by normalizing toxic glutamate levels in the environment, especially in case of ischemia and re-perfusion[9].

It has also been shown that the quantitative data of peripapillary retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) obtained by optical coherence tomography (OCT) are reliable in glaucoma diagnosis and progression[10-13].

In our study, we aimed to evaluate the effect of topical CQ10 and Vitamin E (Vit E) combination (100 ml of physiological solution, CQ10 100 mg, Vit E 500 mg; Coqun, Visufarma, Rome, Italy) on RNFL and GCC in patients with open-angle glaucoma (OAG) by OCT.

Materials and Methods

The following study was carried out in accordance with the tenets of the Helsinki declaration and was approved by the Research Protocol and Ethics Committee of Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK 2016/KK/49). All participants gave informed consent. The design of the study was retrospective and based on the analysis of cases and controls.

OAG patients were selected on the basis of the following inclusion criteria: Refractive errors not >±3 diopters as spherical equivalent; best-corrected visual acuity between 0.7 and 1.0; intraocular pressure (IOP) <21 mmHg with medical treatment; Humphrey Field Analysis 24/2 MD >-8 dB; corrected pattern SD (CPSD) <+6 Db; fixation losses, false-positive rate, and false-negative rate of each <20%. Exclusion criteria were as follows: narrow or closed-angle on gonioscopic examination; previous history of eye surgery (except for uncomplicated cataract surgery); posterior segment pathologies (disc anomaly, macular pathology, retinal vascular diseases, etc.); pathologies that may impair the transparency of the environment (cataract, corneal pathology, etc.); secondary glaucoma (inflammation, trauma, and conditions that cause IOP elevation due to lens).

The files of thirty-one patients who were followed up at the glaucoma clinic, whose IOPs were under control with antiglaucomatous medications, but who used Coqun due to glaucoma progression in one eye were examined retrospectively. Progression of glaucoma was determined as a decrease of >5 µm/year in average RNFL thickness and/or >-1.5dB/year in the mean defect in the visual field. Three of the patients were excluded from the study due to incomplete follow-up. Data of 28 patients were included in the study. Patients used Coqun drops in one eye twice daily. Eyes that received Coqun as an addition to the antiglaucomatous drugs constituted the study group (GC) whereas the other eyes that received only antiglaucomatous drugs constituted the control group (GT). Ophthalmologic examinations and OCT parameters of the patients at the beginning of the study and at 6th month were evaluated.

All ophthalmological examinations including visual acuity, slit-lamb anterior and posterior segment examination, measurement of IOP with Goldmann applanation tonometry, and fundus examination were performed on all patients who were included in the study. RNFL and GCC thickness were measured in all cases with RTVue-100 (Optovue, Inc., Fremont, CA) OCT device.

RNFL thickness was measured using 13 concentric ring scans 1.3–4.9 mm in diameter (587–965 different axial scans per ring) centered on the optic disc (Fig. 1a). The GCC was measured using the scan protocol "GCC." The Average (Avg), superior (Sup), inferior (Inf) RNFL, and GCC measurements were evaluated (Fig. 1b).

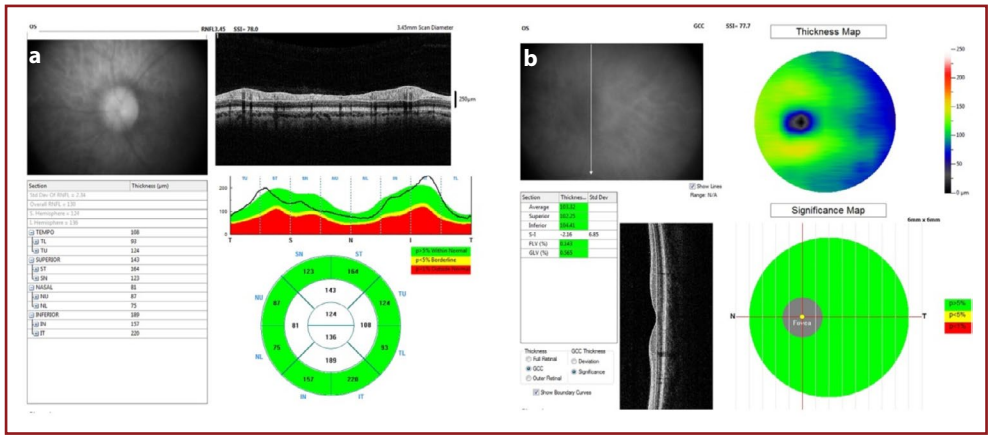

Figure 2. (a) Measuring RNFL thickness using 13 concentric ring scans 1.3 to 4.9 mm in diameter centered on the optic disc **(b)** Measuring GCC thickness using the scan protocol GCC.

Statistical Analysis

The results are expressed as mean±standard deviation. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois, USA). The data were tested initially whether the distribution of variables was normal with the Kolmogorov–Smirnov test. As a result of this test, it was observed that the data did not have a normal distribution therefore Mann-Whitney *U* test was used to compare the groups in the first statistical study. The second study was performed for baseline and 6 months' binary comparisons of GC and GT groups. Since the distribution of the data was not normal, Wilcoxon test was used. The third study compared the difference between the 6th month and baseline values between the two groups with the Mann–Whitney U test. Statistical significance level was determined as $p<0.05$ in all three studies.

Results

Of the twenty-eight patients, 16 (57.14%) were female and 12 (42.85%) male. The mean age of the patients was 59.44±11.18 years. Twelve patients (42.85%) were using a single antiglaucomatous medication and all of these antiglaucomatous medications were prostaglandin analogs. Eight patients were using two (28.57%), six patients were using three (21.42%), and two (7.14%) patients were using four antiglaucomatous medications. Only eight (28.57%) patients were using brimonidine. All patients instilled the same antiglaucomatous drops to both eyes.

There was no difference between the two groups in terms of IOP baseline GC (mean 15.92±2.87 mmHg) and GT (mean 15.83±3.14 mmHg) (p=0.993). There was no significant difference in GC (p=0.372) and GT (p=0.70) between the baseline and 6th month comparisons of IOP. In Table 1, all parameters were similar in both GC and GT groups at baseline (p>0.05). In Table 2, there were no significant differences between mean values of the absolute values of Sup RNFL, Inf RNFL, Sup GCC, Inf GCC, Avg GCC at baseline and after 6 months of treatment in the GC and GT eyes (p>0.05). There was a significant increase in the Avg RNFL value at baseline and after 6 months of treatment in the GC group (p=0.045).

Table 3 shows the differences between the 6th month and baseline values of all OCT parameters. Accordingly, there was a significant increase in the differences between the 6th month and baseline values of Sup RNFL and in the differences between the 6th month and baseline values of Avg RNFL in the GC group (p=0.019, p=0.034, respectively). Non-significant differences between mean GCC values were found at baseline and 6th months of treatment in GC and GT eyes (p>0.05).

Table 1. Mean values of IOP, VFI, MD, RNFL, GCC at baseline in eyes treated with coenzyme Q10 Plus Vitamin E (GC eyes) and in non-treated eyes (GT eyes)

	GC eyes (Mean±SD)	GT eyes (Mean±SD)	p
IOP (mmHg)	15.79±2.76	15.68±2.95	0.993
VFI (%)	95.96±4.01	95.62±4.45	0.675
MD (dB)	−3.59±1.88	−3.07±1.68	0.448
RNLF(µm)			
Sup	94.50±16.29	99.00±12.22	0.276
Inf	94.14±14.26	99.11±14.05	0.272
Avg	94.28±13.92	99.00±11.56	0.184
GCC (µm)			
Sup	89.56±9.51	91.78±8.11	0.589
Inf	90.60±9.84	92.97±7.18	0.394
Avg	90.08±9.12	92.61±7.15	0.451

IOP: Intraocular pressure; VFI: Visual field index; MD: Mean defect; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; Sup: Superior; Inf: Inferior; Avg: Average; Mann–Whitney U test; p<0.05 is statistically significant.

Table 2. Mean values of RNFL and GCC at baseline and 6th months in eyes treated with Coenzyme Q10 Plus Vitamin E (GC eyes) and in non-treated eyes (GT eyes)

	Baseline (Mean± SD)	6 months (Mean± SD)	p
RNFL (µm)			
Sup			
GC (n=28)	94.50±16.29	99.42±16.15	0.077
GT (n=27)	99.00±12.22	97.40±12.82	0.063
Inf			
GC (n=28)	94.14±14.26	94.92±14.12	0.566
GT (n=27)	99.11±14.05	99.96±12.99	0.76
Avg			
GC (n=28)	94.28±13.92	95.71±14.01	0.045*
GT (n=27)	99.00±11.56	98.74±12.07	0.266
GCC (µm)			
Sup			
GC (n=28)	89.56±9.51	89.47±8.85	0.946
GT (n=28)	91.78±8.11	91.15±7.35	0.21
Inf			
GC (n=28)	90.60±9.84	90.81±9.73	0.873
GT (n=28)	92.97±7.18	92.77±6.53	0.539
Avg			
GC (n=28)	90.08±9.12	90.16±8.80	0.82
GT (n=28)	92.61±7.15	91.95±6.61	0.133

RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; Sup: Superior; Inf: İnferior; Avg: Average; SD: Standard deviation; Wilcoxon test; *p<0.05.

Table 3. p-values of the individual differences (6th month minus baseline) in RNFL and GCC thickness observed in eyes treated with Coenzyme Q10 Plus Vitamin E (GC eyes) and in non-treated eyes (GT eyes)

Thickness (µm)	6th month-Baseline GC eyes Mean±SD	6th month-Baseline GC eyes Mean±SD	p
Sup RNFL	1.92±5.36	−1.7±4.83	0.019*
Inf RNFL	0.78±5.19	0.03±5.78	0.839
Avg RNFL	1.42±3.6	−0.74±3.3	0.034*
Sup GCC	−0.09±2.73	−0.64±2.84	0.342
Inf GCC	0.21±2.75	−0.21±2.42	0.617
Avg GCC	0.07±2.37	−0.67±2.09	0.176

RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; Sup: Superior; Inf: Inferior; Avg: Average; SD: Standard deviation; Mann–Whitney U test; *p<0.05.

Discussion

In the present study, we aimed at evaluating the effects of CQ10 on RNFL and GCC thicknesses. There was a significant increase in the Avg RNFL value after 6 months of treatment in the GC group in our study. In recent years, studies on glaucoma treatment have focused on neuroprotection. Oxidative stress and mitochondrial dysfunction are important steps in apoptosis in retinal ganglion cell death as a result of glaucoma[3,4]. CQ10 has come to the fore in the treatment of glaucoma as a neuroprotective agent with its antioxidant properties and supporting effect of mitochondrial electron transport[8]. In an animal study which created an experimental glaucoma model, topical CQ10 use has been shown to protect against apoptosis in all retinal layers[14]. Furthermore, in another recent study, it has been reported that the neuronprotective effect of topical CoQ10 and Vit E molecules may be effective in experimental glaucoma model[15].

In our study, there was not a statistically significant difference between GC and GT in RNFL and GCC values at baseline. However, baseline median values of the GC group are less than those of the GT group. In addition, a statistically significant increase in Sup and Avg RNFL values after 6 months in the GC group suggests a possible anatomical improvement. There was no statistically significant increase in GCC values between baseline and 6 month values in GC and GT groups.

There are few human studies in the literature investigating the effectiveness of CQ10 in patients with glaucoma. In a study conducted by Parisi et al.,[16] in OAG patients, CQ10 and Vit E treatment were added to the patient group using topical beta-blockers; an increase in electroretinogram (ERG) and visual evoked potential (VEP) amplitudes has been observed. Electrophysiological improvement in glaucoma patients after topical CQ10 and Vit E treatment has been demonstrated with ERG and VEP responses, but no structural evaluation has been made after treatment.

CQ10 is available in combination with Vit E and it is applied topically. Vit E improves bioavailability of CoQ. It has been shown in a study by Romana et al.[17] that topical application of CQ10 can reach sufficient vitreous levels in humans. In addition, Davis et al.[8] in an in vivo study on rats compared a group that received CQ10 and Vit E with a group that received only Vit E. They found that the number of apoptotic retinal ganglion cells were significantly lower in the group receiving CQ10 and Vit E.

In our study, patients with IOP under control with medical treatment, without any corneal pathology or maculopathy or cataract were included. Patients with vascular diseases that may disrupt optic disc blood supply and neurological diseases affecting optic nerve fiber thickness were not included in the study. The average age of the patients included in the study was 59.44±11.18 years. CoQ10 levels in the retina can decline with age.[18] Therefore, it is yet to be determined whether CQ10 would have the same effects in the older age group with OAG. Another limiting factor of our study is the difference in medical treatments for glaucoma in our patient group. In one study, Parisi et al.[16] investigated the effect of CQ10 in OAG patients where the entire patient group was using solely beta-blockers and found that CQ10 positive effects on VEP results. It is possible to contemplate that the number of medications used, the difference in the mechanism of action of these medications, and the severity of glaucoma damage can affect the neuroprotective effect of CQ10.

Contrary to other studies, we believe that the fellow eyes used as the control group eyes who receive the same antiglaucomatous treatment with the study group eyes and have the same glaucomatous damage will provide a more accurate assessment of the effect of CQ10. A comprehensive study showed that the use of topical CQ10 does not affect plasma levels and remains solely in the vitreous body and that the treatment applied to one eye of the same patient does not cause neuroprotective effects in the other eye[17].

Conclusion

In conclusion, CQ10 can be an important therapeutic agent in the treatment of glaucoma to stop apoptosis and ganglion damage. In our study, we found a statistically significant effect of CQ10 on the RNFL. This evidence should be supported by larger follow-up studies and a larger patient population receiving uniform antiglaucomatous medication.

Ethics Committee Approval: Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK 2016/KK/49).

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Conflict of Interest: None declared.

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References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262–7.
2. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. Lancet 2017;390:2183–93. [CrossRef]
3. Osborne NN. Mitochondria: Their role in ganglion cell death and survival in primary open angle glaucoma. Exp Eye Res 2010;90:750–7. [CrossRef]
4. Zhou RR, Li HB, You QS, Rong R, You ML, Xiong K, et al. Silencing of GAS5 alleviates glaucoma in rat models by reducing retinal ganglion cell apoptosis. Hum Gene Ther 2019;30:1505–19.
5. Manzar H, Abdulhussein D, Yap TE, Cordeiro MF. Cellular consequences of coenzyme Q10 deficiency in neurodegeneration of the retina and Brain. Int J Mol Sci 2020;21:9299. [CrossRef]
6. Nakajima Y, Inokuchi Y, Nishi M, Shimazawa M, Otsubo K, Hara H. Coenzyme Q10 protects retinal cells against oxidative stress in vitro and in vivo. Brain Res 2008;1226:226–33. [CrossRef]
7. Ju WK, Shim MS, Kim KY, Bu JH, Park TL, Ahn S, et al. Ubiquinol promotes retinal ganglion cell survival and blocks the apoptotic pathway in ischemic retinal degeneration. Biochem Biophys Res Commun 2018;503:2639–45. [CrossRef]
8. Davis BM, Tian K, Pahlitzsch M, Brenton J, Ravindran N, Butt G, et al. Topical coenzyme Q10 demonstrates mitochondrial-mediated neuroprotection in a rodent model of ocular hypertension. Mitochondrion 2017;36:114–23. [CrossRef]
9. Nucci C, Tartaglione R, Cerulli A, Mancino R, Spanò A, Cavaliere F, et al. Retinal damage caused by high intraocular pressure-induced transient ischemia is prevented by coenzyme Q10 in rat. Int Rev Neurobiol 2007;82:397–406. [CrossRef]
10. Tatham AJ, Medeiros FA. Detecting structural progression in glaucoma with optical coherence tomography. Ophthalmology 2017;124:S57–S65. [CrossRef]
11. Renard JP, Fénolland JR, Giraud JM. Glaucoma progression analysis by spectral-domain optical coherence tomography (SD-OCT). J Fr Ophtalmol 2019;42:499–516. [CrossRef]
12. Diniz-Filho A, Abe RY, Zangwill LM, Gracitelli CP, Weinreb RN, Girkin CA, et al. Association between intraocular pressure and rates of retinal nerve fiber layer loss measured by optical coherence tomography. Ophthalmology 2016;123:2058–65. [CrossRef]
13. Vidas S, Popović-Suić S, Novak Lauš K, Jandroković S, Tomić M, Jukić T, et al. Analysis of ganglion cell complex and retinal nerve fiber layer thickness in glaucoma diagnosis. Acta Clin Croat 2017;56:382–90. [CrossRef]
14. Lulli M, Witort E, Papucci L, Torre E, Schipani C, Bergamini C, et al. 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 retinal damage. Invest Ophthalmol Vis Sci 2012;53:8295–302. [CrossRef]
15. Ekicier Acar S, Sarıcaoğlu MS, Çolak A, Aktaş Z, Sepici Dinçel A. Neuroprotective effects of topical coenzyme Q10 + vitamin E in mechanic optic nerve injury model. Eur J Ophthalmol 2020;30:714–22. [CrossRef]
16. Parisi V, Centofanti M, Gandolfi S, Marangoni D, Rossetti L, Tanga L, 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. [CrossRef]
17. Fato R, Bergamini C, Leoni S, Pinna A, Carta F, Cardascia N, et al. Coenzyme Q10 vitreous levels after administration of coenzyme Q10 eyedrops in patients undergoing vitrectomy. Acta Ophthalmol 2010;88:e150–1. [CrossRef]
18. Qu J, Kaufman Y, Washington I. Coenzyme Q10 in the human retina. Invest Ophthalmol Vis Sci 2009;50:1814–8. [CrossRef]