ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Effects of Topical Coenzyme Q10 in Conjunction with Vitamin E on Tear Function Tests in Glaucoma Patients: Retrospective Study

Glokom Hastalarında E Vitamini ve Topikal Koenzim Q10 Kombinasyonunun Gözyaşı Fonksiyon Testleri Üzerindeki Etkileri: Retrospektif Çalışma

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ABSTRACT Objective: To evaluate the effect of topical coenzyme Q10 (CoQ10) and vitamin E combination on tear function tests in glaucoma patients. **Material and Methods:** A combination drop of CoQ10 and vitamin E was inserted to one eye of 28 patients with glaucoma who have been using antiglaucomatous drops. The eyes that received the CoQ10 and vitamin E constituted the study group, and other eyes were part of the control group. Baseline, sixth, and twelfth-month tear function tests of the groups were evaluated. **Results:** Baseline values of Schirmer's test, tear meniscus, tear break-up time test, and corneal fluorescein staining did not significantly differ between the groups. When all values at baseline, six, and twelve months were compared, no difference was found in the study group, while a statistically significant decrease was observed in the mean of tear meniscus areas and tear meniscus depths in the control group (p=0.038, p=0.041, respectively). **Conclusion:** Although CoQ10 and vitamin E combination may positively eaffect tear function tests in patients with glaucoma, this effect was not statistically significant. Further studies with larger patient groups may help reveal the effects of these agents on glaucoma patients.

Keywords: Coenzyme Q10; dry eye; glaucoma; tear function test; vitamin E

ÖZET Amaç: Glokom olgularında topikal koenzim Q10 [coenzyme Q10 (CoQ10)] ve E vitamini kombinasyonunun gözyaşı fonksiyon testleri üzerindeki etkisini değerlendirmek. **Gereç ve Yöntemler:** Antiglokomatöz damla kullanan 28 glokom olgusunun bir gözüne bir CoQ10 ve E vitamini kombinasyonu eklendi. CoQ10 ve E vitamini eklenen gözler çalışma grubunu diğer gözler kontrol grubunu oluşturdu. Grupların başlangıç, 6. ve 12. ayda yapılan gözyaşı fonksiyon testleri değerlendirildi. **Bulgular:** Schirmer testi, gözyaşı menisküs, gözyaşı kırılma zamanı testi ve kornea floresein boyamasının başlangıç değerleri gruplar arasında anlamlı farklılık göstermedi. Başlangıç, 6. ve 12. aydaki tüm değerler karşılaştırıldığında çalışma grubunda fark bulunmazken, kontrol grubunda gözyaşı menisküs alanları ve gözyaşı menisküs derinlikleri ortalamasında istatistiksel olarak anlamlı bir düşüş gözlendi (sırasıyla p=0,038, p=0,041). **Sonuç:** CoQ10 ve E vitamini kombinasyonu glokomlu olgularda gözyaşı fonksiyon testleri üzerinde olumlu bir etkiye sahip olmasına rağmen bu etki istatistiksel olarak anlamlı değildi. Daha büyük olgu gruplarıyla yapılacak ileri çalışmalar, bu ajanların glokom olguları üzerindeki etkilerini ortaya çıkarmaya yardımcı olabilir.

Anahtar Kelimeler: Koenzim Q10; kuru göz; glokom; gözyaşı fonksiyon testi; vitamin E

Glaucoma is one of the leading causes of progressive and irreversible blindness.[1] Topical medications are preferred as the first step in treatment plans. However, with chronic use, the antiglaucomatous substance itself or the preservative substances can cause dry eye disease with allergic, toxic, or immune-inflammatory effects.[2-5] Many studies have shown that topical medication users develop dry eye disease.[6,7]

Dry eye worsens quality of life and reduces compliance with ongoing glaucoma treatments.[8] Extensive research has been directed to reduce ocular surface disorders in glaucoma patients.[9]

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Coenzyme Q10 (CoQ10), also known as ubiquinone, has recently been used topically as an antioxidant therapy for dry eye disease.[10] Studies have shown that CoQ10 prevents apoptosis by controlling the increase in mitochondrial permeability and normalizing glutamate levels.[11,12] In addition, CoQ10 is involved in energy metabolism as part of the mitochondrial electron transport chain.[13]

Recently, CoQ10 has been used topically for the treatment of glaucoma as well as dry eye disease.[14] Unlike CoQ10 preparations used in dry eyes, CoQ10 preparations for glaucoma aim to reduce the residence time on the ocular surface and increase penetration into the eye for optic nerve neuroprotection. Coqun (Visufarma, Italy), a topical preparation of CoQ10 for the treatment of glaucoma, is available in combination with vitamin E (CoQ10 in 100 mL physiological solution 100 mg, vitamin E 500 mg). The bottle design was carried out using the Ophthalmic Squeeze Dispenser technique, which eliminates the use of preservatives.

In this study, we evaluated the effects of topical CoQ10 use on tear function tests in glaucoma patients receiving topical antiglaucomatous drugs. To our knowledge, this is the first study to demonstrate the effects of topical CoQ10 on tear function test of glaucoma patients.

MATERIAL AND METHODS

This retrospective study was carried out by the tenets of the Helsinki Declaration and was approved by the Research Protocol and Ethics Committee of Haydarpaşa Numune Training and Research Hospital (date: February 21, 2022, no: HNEAH-KAEK 2022/42). Informed written consent for data collection was obtained from all participants after an explanation of the nature of the study.

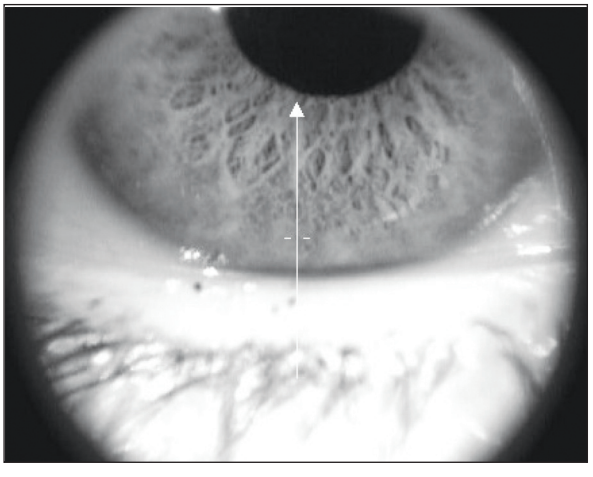
The files of 34 patients who were followed up with at the glaucoma clinic and whose intraocular pressure (IOP) was under control with antiglaucomatous medications but used Coqun due to decreased retinal nerve fiber layer (RNFL) or worsening in the visual field in one eye were examined retrospectively. Data from 28 patients were included in the study. The patients used Coqun drops in one eye twice daily. The eyes to which CoQ10 was applied constituted the study group, and the other eyes of the patients were used as the control group.

Patients who had previously undergone surgery, had corneal pathologies, had been followed up with for secondary glaucoma (due to inflammation or trauma), and failed to use the drug properly were excluded from the study.

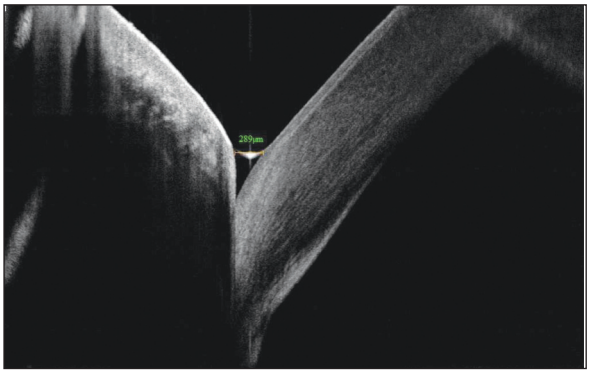
Tear function tests performed included tear meniscus (TM) measurement, tear breakup time (TBUT), corneal fluorescein staining (CFS), and Schirmer's test (SIT) at the basal, 6th and 12th months.

To evaluate the patients' tear function, TM measurements were performed by attaching an anterior segment adapter to the optic coherence tomography device (Optovue, USA) (Appendix 1). The TM height (TMH) was calculated as the distance (μm) between the corneal meniscus junction and the lower eyelid meniscus junction (Appendix 2). Tear meniscus depth (TMD) was calculated as the distance (μm) between the midpoint of the air-meniscus interface and the lower eyelid of the corneal junction (Appendix 3). The TM area (TMA) was measured in mm^2 by determining the limits of the meniscus (Appendix 4).

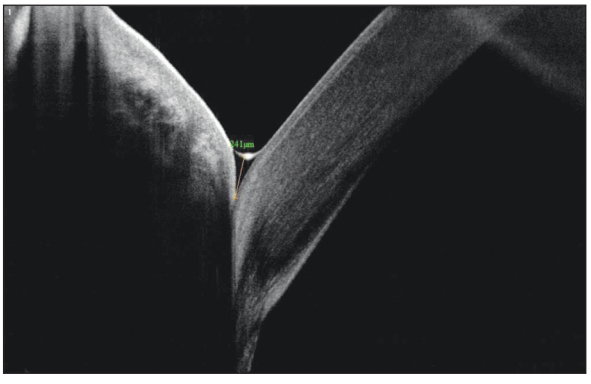
After the administration of fluorescein for the TBUT, the patient was asked to blink three times. Then, while the patient remained without blinking his/her eye, the formation time of the first dry area in the cornea under cobalt blue was recorded. Fluores-



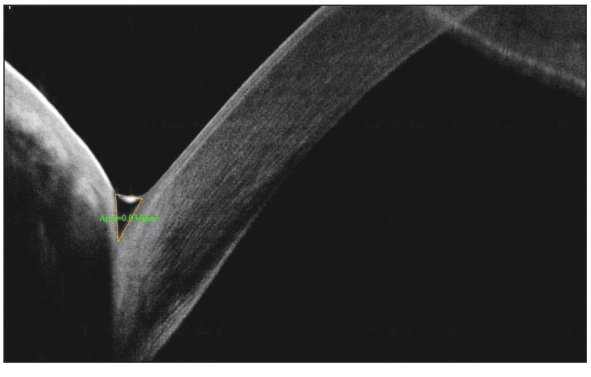
APPENDIX 1: Evaluation of tear meniscus by optical coherence tomography.



APPENDIX 2: Evaluation of tear meniscus heigh.



APPENDIX 3: Evaluation of tear meniscus depth.



APPENDIX 4: Evaluation of tear meniscus area.

cein staining of the cornea was divided into four categories: 0=No staining, 1=Several points in one-third of the cornea, 2=Moderate staining, and 3=Intensive staining of the entire corneal area.

For the SIT, a topical anesthetic (proparacaine hydrochloride, Alcaine 0.5%, Alcon, Texas, USA) was administered. After drying the lower fornix, SIT papers were placed on the lateral one-third of the lid margin. After five minutes, the amount of wetness of the test paper was noted in mm.

Statistical analysis was performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The variables were investigated using the Shapiro-Wilk test to determine whether they were normally distributed. Data were not normally distributed; therefore, the Mann-Whitney U test was used to compare examinations between the two groups. The difference between the baseline, 6th-, and 12th-month examinations was analyzed using the Friedman test. In case of differences between groups, binary comparisons were made using the Wilcoxon test. The chi-squared test or McNemar test, where appropriate, was used to compare the categorical variables in the different groups. The values were given as mean±standard deviation and/or median with range, and a p value <0.05 was considered statistically significant.

RESULTS

A total of 28 patients, 16 females and 12 males with primary open-angle glaucoma were evaluated. The mean age of the patients was 59.54 (±11.27) years. All patients used similar antiglaucoma medications in both eyes. The number of preservatives in patients' eyes was one in 36 eyes (64.28%), two in 16 eyes (28.57%), and three in 4 eyes (7.14%).

There was no statistically significant difference in the basal, 6th-, and 12th- month values between the study and control groups in terms of SIT, TMH, TMD, TMA, TBUT, and CFS (p>0.05) (Table 1). There were no significant differences between the basal, 6th-, and 12th- month values in terms of SIT, TBUT, TMA, TMH, and TMD in the CoQ10 group (p>0.05). There were no significant differences between the basal, 6th-, and 12th- month values in terms of SIT, TBUT, and TMH in the control group (p>0.05). There were statistically significant differences between basal, 6th-, and 12th-month values in terms of TMA and TMD in the control group (p=0.038 and p=0.041, respectively) (Table 2).

TABLE 1: Baseline of tear meniscus variables and clinical parameters of all subjects in each groups.

Parameter	Study Group $\bar{X}$±SD	Control Group $\bar{X}$±SD	p value
SIT (mm)	7.39±5.49	7.71±5.66	0.85
TBUT (s)	8.93±5.89	9.2±5.1	0.50
TMA (mm^2)	0.032±0.032	0.045±0.076	0.53
TMH (µm)	319.4±144.2	358.5±239.1	0.52
TMD (µm)	239.2±106.6	250.8±122.7	0.87

SD: Standard deviation; SIT: Schirmer's test; TBUT: Tear breakup time; TMA: Tear meniscus area; TMH: Tear meniscus height; TMD: Tear meniscus depth.

TABLE 2: Mean changes of tear function test parameters from baseline to 12 months for all subjects in each group.

Parameter		Baseline $\bar{X}$±SD	6th month $\bar{X}$±SD	12th month $\bar{X}$±SD	p value
SIT (mm)	CoQ10	7.39±5.49	7.82±6.98	8.57±8.66	[1]p=0.805
	Control	7.71±5.66	8.5±7.39	8.14±8.57	[1]p=0.805
TBUT (s)	CoQ10	8.93±5.89	9.46±4.8	8.64±5.13	[1]p=0.322
	Control	9.25±5.10	9.89±5.37	7.41±3.52	[1]p=0.091
TMA (mm^2)	CoQ10	0.038±0.04	0.044±0.07	0.040±0.07	[1]p=0.987
	Control	0.044±0.07	0.039±0.06	0.025±0.03	**[1]p=0.038***
					6-0 month
					[2]p=0.23
					12-0 month
					[2]p=0.029*
					12-6 month
					[2]p=0.184
TMH (µm)	CoQ10	335±173.66	358.48±218.23	306.65±164.01	[1]p=0.923
	Control	315±104.75	301.19±151.65	259.23±75.793	[1]p=0.186
TMD (µm)	CoQ10	239.2±106.6	238.3±134.1	212.7±117.54	[1]p=0.264
	Control	250.75±122.7	202.68±122.01	203.89±110.51	**[1]p=0.041***
					6-0 month
					[2]p=0.012*
					12-0 month
					[2]p=0.003*
					12-6 month
					[2]p=0.838

[1]Friedman test; [2]Wilcoxon test; *p<0.05; SD: Standard deviation; SIT: Schirmer's test; CoQ10: Coenzyme Q10; TBUT: Tear breakup time; TMA: Tear meniscus area; TMH: Tear meniscus height; TMD: Tear meniscus depth.

The mean SIT values showed an increase in the CoQ10 group at the 6th and 12th months compared to the baseline values. In the control group, there was an increase in the mean SIT values in the 6th month, but there was a decrease in month 12 (Figure 1).

Figure 2 shows that the TBUT values decreased in both groups after the 6th month, but this decrease was more significant in the control group. Figure 3 shows that while the CoQ10 group did not change at the 6th and 12th months in terms of the mean TMA, the control group continued to decrease. Figure 4 shows the changes in the TMH and TMD values in the study and control groups at the basal, 6th, and 12th months.

CFS was evaluated using the McNemar test. There was no difference in terms of baseline, 6th, and 12th month values in both groups (p>0.05).

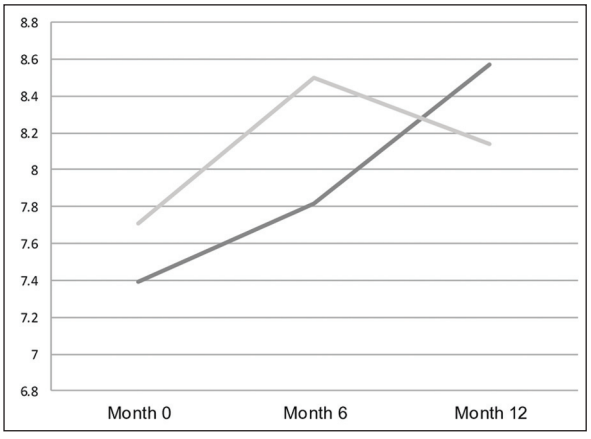


FIGURE 1: Mean change of Schirmer's test.

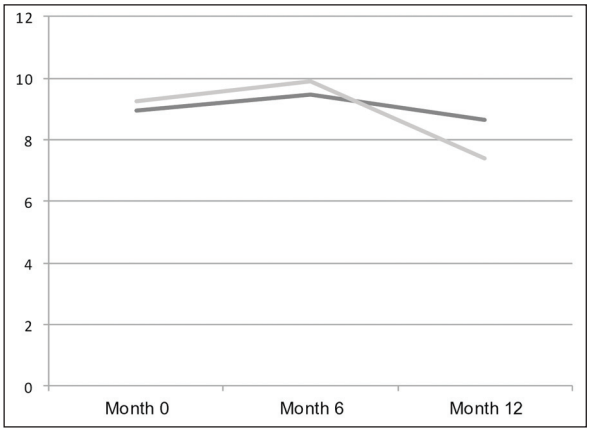


FIGURE 2: Mean change of tears break up time.

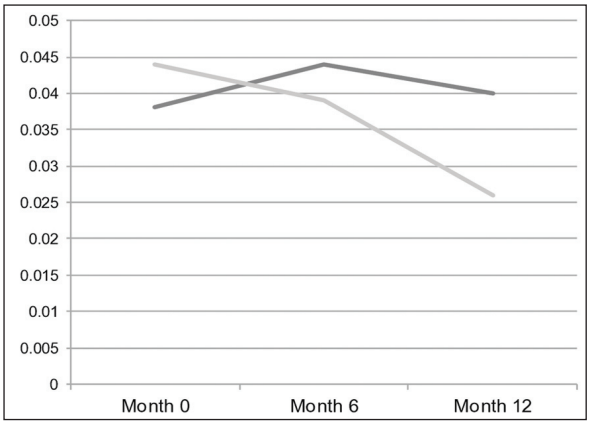


FIGURE 3: Mean change of tear meniscus area.

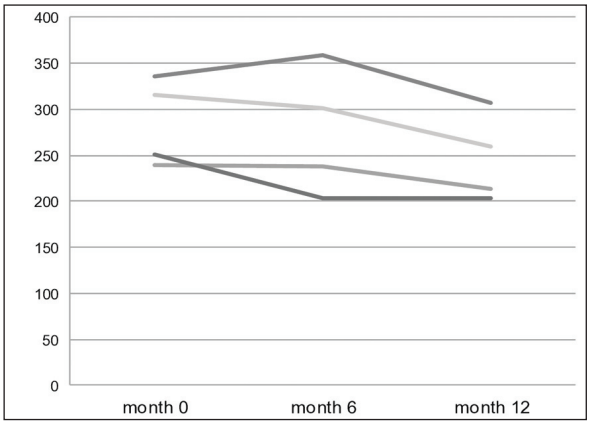


FIGURE 4: Mean change of tear meniscus height and tear meniscus depth.

DISCUSSION

This study aimed to evaluate the effects of topical CoQ10 on the tear function tests results of glaucoma patients who have been using antiglaucomatous drops. While no difference was observed in the tear function test results in eyes where the combination of CoQ10 and vitamin E was used for one year, a significant decrease was observed in the TMA and TMD values in the control group.

Drug therapy is often the first choice for achieving the target IOP in glaucoma treatments. Chronic topical drug use may increase the inflammation of the ocular surface, resulting in dry eye.[5] The presence of free oxygen radicals in tears in dry eye patients has led to research on the use of antioxidants.[15-19] CoQ10 has recently been used as an antioxidant agent in the treatment of dry eye disease. In a comparative study on the combination of hyaluronic acid drops with hyaluronic acid and CoQ10 (VisuXL, Visufarma, Italy) in patients with mild-to-moderate dry eye, Postorino et al. reported a significant reduction in meibomian gland involvement and epithelial cell reflectivity and a significant improvement in keratocyte and corneal stroma matrix parameters in the CoQ10 group.[10]

In another study, Fogagnolo et al. assessed the combination of CoQ10 and vitamin E twice a day for 9 months in 40 randomized cataract patients.[20] Preoperatively, on day 14, and at months 3, 6, and 9, they underwent non-invasive breakup time (NIBUT) testing, SIT, TBUT, aesthesiometry, and in vivo confocal microscopy of the subbasal nerve plexus of the cornea. The results showed that nerve regeneration was faster and ocular surface stability (TBUT and NIBUT) was much better in the group that used CoQ10.

Recently, in addition to the target IOP, neuroprotection has also become a vital target of glaucoma treatments. Topical CoQ10 used in glaucoma treatments and to prevent retinal damage has been shown to protect against apoptosis in all retinal layers in animal studies.[12,21] Topical CoQ10 has been combined with vitamin E to increase its penetration into the eye and thereby act on the retina and optic nerve. Indeed, topical CoQ10 has been shown to remain in the vitreous without affecting plasma levels.[22]

Although statistically non-significant, an increase in SIT values and a preservation in TBUT values were observed in the study group compared to the control group. However, the increase in SIT values also observed in the control group may be related to the variability of the test due to eye positions.[23] However, in the 6th and 12th months, TMD and TMA values significantly lower in the control group, while basal values were preserved in the CoQ10 group. These findings may indicate the positive effects of CoQ10 on tear test results. However, since the active ingredient was combined with a substance that increased eye penetration, it may not have sufficiently demonstrated its positive effects on the ocular surface. In a study by Gumus the role of the combination of CoQ10 and vitamin E with hypromellose (Visudrop, Visufarma, Italy) was mentioned in corneal epithelial healing.[24] Hypromellose and hyaluronic acid had a lubricating effect and increased the antioxidant effects of CoQ10 by increasing the residence time of CoQ10 on the ocular surface.

In our study, CoQ10 drops were administered to the side of the eye which had a worse visual field or less RNFL thickness. The other eyes were chosen as the control group. Thus, possible differences between the two groups due to age, systemic characteristics, and environment were minimized. However, this study has some limitations. Not all patients used the same glaucoma medication. In addition, it was predicted that chronic drug use would complicate the ocular surface index scoring. As such, this scoring was not conducted. This study focused on the effects of CoQ10 used in addition to glaucoma drugs on tear function tests; however, considering the effects of glaucoma drugs on the ocular surface, positive effects may be observed better in dry eye patients who do not use glaucoma drugs.

CONCLUSION

The combination of topical CoQ10 and vitamin E in this study did not show a statistically significant effect on the tear function test results of glaucoma patients. However, a decrease in some test values within the control group was not observed in the CoQ10 group, which may indicate the protective effect of CoQ10 on tear function. In addition, the combination of CoQ10 with molecules that increase its persistence on the ocular surface and its ocular penetration may affect the tear function test results of glaucoma patients more positively. This should be confirmed by long-term and prospective studies on glaucoma patients with dry eye disease.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Okşan Alpoğan;* ***Design:*** *Okşan Alpoğan;* ***Control/Supervision:*** *Okşan Alpoğan, Hatice Tekcan;* ***Data Collection and/or Processing:*** *Okşan Alpoğan, Hatice Tekcan;* ***Analysis and/or Interpretation:*** *Okşan Alpoğan;* ***Literature Review:*** *Okşan Alpoğan, Hatice Tekcan;* ***Writing the Article:*** *Okşan Alpoğan;* ***Critical Review:*** *Hatice Tekcan;* ***References and Fundings:*** *Okşan Alpoğan, Hatice Tekcan;* ***Materials:*** *Okşan Alpoğan, Hatice Tekcan.*

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