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# Optical Coherence Tomography Angiography Based Assessment of Macular Vessel Density in Eyes with Keratoconus: Case Control Study

## Keratokonuslu Gözlerde Optik Koherens Tomografi Anjiyografi Tabanlı Makula Damar Yoğunluğunun Değerlendirilmesi: Vaka Kontrol Çalışması

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**ABSTRACT Objective:** To evaluate the retinal and choroidal microvascular flow measurements in the eyes with keratoconus by using optical coherence tomography angiography (OCTA) and compared with a healthy age-gender matched control group. **Material and Methods:** This is a prospective case-control study in which OCTA data of 30 keratoconus patients and 30 healthy, volunteers were analyzed. The foveal avascular zone (FAZ) area, the superficial capillary plexus (SCP) deep capillary plexus (DCP) and central macular thickness (CMT) were evaluated and compared with healthy volunteers. **Results:** A statistically significant decrease was found in all parts of the SCP of patients with keratoconus compared to the control group. In the DCP layer, whole image (p=0.017), superior-hemi (p=0.46), inferior-hemi (p=0.021), perifoveal (p=0.013), perifoveal superior-hemi (p=0.024), perifoveal inferior (0.01), perifoveal temporal (0.03), perifoveal superior (p=0.013), perifoveal inferior (p=0.005) segments in the keratoconus group were found to be significantly lower than the healthy control group. There were no significant differences in FAZ area and CMT between the groups. **Conclusion:** This study demonstrates that subclinical anterior segment inflammation in keratoconus can affect the retinal vascular structure. OCTA may be a new clinical marker for evaluating disease activity in keratoconus.

**Keywords:** Keratoconus; optical coherence tomography angiography; vessel density; inflammation

**ÖZET Amaç:** Keratokonuslu gözlerde retinal ve koroidal mikrovasküler akım ölçümlerini optik koherens tomografi anjiyografi (OKTA) ile değerlendirmek ve sağlıklı yaş-cinsiyet eşleştirilmiş kontrol grubu ile karşılaştırmak. **Gereç ve Yöntemler:** Bu, 30 keratokonus hastası ve 30 sağlıklı gönüllünün OKTA verilerinin analiz edildiği prospektif bir vaka-kontrol çalışmasıdır. Foveal avasküler bölge [foveal avascular zone (FAZ)] alanı, yüzeysel kapiller pleksus (YKP), derin kapiller pleksus (DKP) ve santral makula kalınlığı (SMK) değerlendirildi ve sağlıklı gönüllülerle karşılaştırıldı. **Bulgular:** Keratokonuslu hastaların YKP'sinin tüm bölümlerinde kontrol grubuna göre istatistiksel olarak anlamlı bir azalma bulundu. DKP katmanında tüm görüntü (p=0,017), superior-hemi (p=0,46), inferior-hemi (p=0,021), perifoveal (p=0,013), perifoveal superior-hemi (p=0,024), perifoveal inferior (0,01), perifoveal temporal (0,03), perifoveal superior (p=0,013), perifoveal inferior (p=0,005) segmentlerinde keratokonus grubunda sağlıklı kontrol grubuna göre anlamlı olarak düşük bulundu. Gruplar arasında FAZ alanı ve SMK'de anlamlı fark yoktu. **Sonuç:** Bu çalışma, keratokonusta subklinik ön segment inflamasyonunun retina damar yapısını etkileyebileceğini göstermektedir. OKTA, keratokonusta hastalık aktivitesini değerlendirmek için yeni bir klinik belirteç olabilir.

**Anahtar Kelimeler:** Keratokonus; optik koherens tomografi anjiyografi; damar dansitesi; inflamasyon

Keratoconus is a corneal ectasia characterized by progressive, bilateral, asymmetric steep corneal thinning that leads to irregular astigmatism and decreased vision.[1-3] Although the exact etiology remains unknown, the contribution of genetic predisposition, allergy and environmental factors has been suggested in the pathogenesis of the disease. It has been known for a long time that atopy and high serum immunoglobulin (IgE) levels are associated with keratoconus.[4-8] Recently, the role of several pro-

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inflammatory mediators via induction of inflammation has been noted in the etiology of keratoconus.[9] It has been strongly suggested that allergy and related eye itching may play a role in the progression of keratoconus by stimulating the release of inflammatory substances in the tissues.[8] However, given that the inflammation is chronic and subclinical, inflammatory findings may not be detectable clinically.

The recent developments in optical coherence tomography technologies have enabled better visualization of the choroid, and changes in choroidal thickness and vascularity have been reported in several ocular and systemic inflammatory diseases. Gutierrez-Bonet et al. reported that the choroidal thickness in eyes with keratoconus was thicker than in the healthy normal population, similar to findings in other inflammatory diseases.[10]

The co-existence of inflammation and ischemia has been consistently reported in retinal vascular diseases and uveitis. It has been reported that inflammatory mediators may have a role in the damage of retina-choroid microvascular structures.[11,12] A new non-invasive device optical coherence tomography angiography (OCTA) allows the reflection of a light source from the surface of static and motile blood cells and the visualization of retinal and choroidal blood flow by comparing the amount of reflected light without the need for intravenous dye application. Currently, OCTA has become a widely-used imaging method in the diagnosis and treatment of many retinal and choroidal diseases, while providing important information on retinal and systemic diseases.[12,13] Based on the above information, we thought that subclinical inflammation in eyes with keratoconus may also have an effect on retinal and choroidal tissues in the eye and to the best of our knowledge, there are no studies on this subject.

Therefore, in this study, retinal and choroidal microvascular flow measurements were evaluated in the eyes with keratoconus by using OCTA and compared with normal and age-matched individuals.

## MATERIAL AND METHODS

Our study which was case-controlled, prospective study, was conducted in Ulucanlar Eye Training and Research Hospital. The study was conducted in line with the Helsinki Declaration principles and was approved by the Clinical Research Ethics Committee of Ankara Training and Research Hospital (date: August 27, 2020, no: 233). Informed consent forms regarding the file data were signed by the patients.

A total of 30 eligible patients with newly-diagnosed or former keratoconus who consented to participate in the study were included in this study. The diagnosis of keratoconus was based on the presence of at least one of the biomicroscopic examination (the Vogt striae, Fleischer ring, Munson sign, apical thinning and Rizutti's sign), and Rabinowitz corneal topography criteria including central corneal keratometry >47D, inferior/superior dioptric asymmetry (I-S value) >1.2, Sim-K (Simulated Keratometry Readings) astigmatism >1.4 D and skewed radial aces (SRAX)> 21°. However, keratoconus patients with corneal scar and hydrops sequelae were not included in the study due to the likely effects of these conditions on OCTA image quality.

The study included patients with Stage 2 and higher keratoconus according to the Amsler-Krumeich classification, who had not previously undergone cross-linking treatment. Those with non-keratoconus corneal disease (corneal dystrophies, etc.), retinal and/or optic nerve disease (e.g., glaucoma, optic disc anomalies, macular degeneration) were removed from the study. There was no active atopic/vernal keratoconjunctivitis in the keratoconus patients included in the study group. Age- and gender- matched 30 healthy volunteers who admitted to our outpatient clinic for standard examination and consented to participate in the study were included as the control group. The participants did not have any ocular and/or systemic disease or use of any systemic or topical drugs.

Visual acuity, intraocular pressure measurement on Snellen chart, fundus examination with 90D lens after dilatation was performed in each participant. All patients were examined with Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany) and corneal and XR Avanti AngioVue OCTA (Optovue, Fremont, With California, USA) (Version 2017.1.0.151), while retinal and choroidal capillary measurements

were made between 2-4 pm as standard by the same retina specialist. The data of the keratoconus patients and controls with a signal strength index >70 on scans were subjected to the quantitative analysis. Data on retinal vascularity and choriocapillary density and retinal thickness were obtained after the analysis of 6x6 mm OCTA images of the macula.[14,15] Vessel densities and choriocapillary flow area in angio-retinal scans; in the horizontal plane, 3 circles with radii of 1, 3 and 6 mm, considered central fovea and vertically superficial (SCP) and deep capillary plexus (DCP) were examined. In the macular vessel density measurements, inner circle with a diameter of 1 mm was established as the foveal region, the surrounding 1-3 mm area was the parafoveal region, and the outermost 3-6 mm area was established as the perifoveal region. With the software analysis of the results, the non-foveal areas were divided into 4 quadrants as superior, inferior, temporal and nasal, and superior and inferior hemispheric regions. Perifoveal and parafoveal mean values were obtained from the obtained data. The foveal avascular zone (FAZ) was evaluated from the SCP with the nonflow evaluation parameters of OCTA, and the flow area, FAZ area, FAZ perimetry, acircularity index of FAZ (AI) and foveal density (FD) data were achieved.

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Student's t-test was used for the groups with normal distribution variables including the superficial and complete retinal vasculature FAZ area measurements in the foveal, parafoveal and perifoveal regions, the measurements of DCP and SCP vessel density. Only AI of FAZ and FD data showed nonparametric distribution and was evaluated by Mann-Whitney U test. In the expression of the data, "mean (standard deviation)", minimum-maximum, and percentage (%) were used where appropriate. Statistically, p value <0.05 was considered significant.

## RESULTS

This cross-sectional study included 30 keratoconus patients and 30 age- and sex-matched healthy controls. The age range was 14-40 (mean 23.2) in the keratoconus group and 15-39 (mean 22.7) in the control group (p=0.75).

The mean Kmax values of the keratoconus patients included in the study were 51.30 D (61-46). Considering the keratoconus stages, 21 (70%) patients were at Stage 2 and the rest were at Stage 3 according to the Amsler-Krumeich classification.

Comparative outflow and FAZ evaluation parameters of keratoconus and control group are shown in Table 1. There were no statistically significant differences were shown among the groups in values of FAZ (p=0.524), FAZ perimeter (p=0.282), AI of FAZ (p=0.076) and FD (p=0.739). Choriocapillaris flow area data were similar between study groups (p=0.86).

OCTA findings on the retina thickness between the Internal limiting membrane and retinal pigment epithelium thickness; full thickness, superior-hemi, inferior-hemi, fovea, parafoveal area, temporal, superior, nasal, temp superior-hemi, inferior-hemi, parts of parafovea and perifovea, the entire area of perifovea are presented in Table 2 and and no significant difference was found between the groups (p>0.05).

The vessel density evaluation parameters in SCP in OCTA of the study groups were shown in Table 3. When compared with the control group, a statistically significant decrease was found in all sections of the SCP of patients with keratoconus (p>0.5).

In Table 4, comparative DCP data of the healthy and keratoconus groups are shown. In this layer, in the keratoconus group; the whole image (p=0.017), superior-hemi (p=0.46), inferior-hemi (p=0.021), perifoveal (p=0.013), perifoveal superior-hemi (p=0.024), perifoveal inferior (0.01), perifoveal temporal (0.03), perifoveal superior (p=0.013),

**TABLE 1:** Macula flow evaluation, the difference between each 2 groups for 3 parameters.

| | Keratoconus Mean (±SD) | Control Mean (±SD) | p value |
|---|---|---|---|
| Flow area | 1.10 (0.56) | 0.85 (0.5) | 0.086[a] |
| FAZ ($mm^2$) | 0.32 (0.18) | 0.29 (0.06) | 0.524[a] |
| PERIMETRI mm | 2.03 (0.37) | 2.13 (0.33) | 0.282[a] |
| AI | 1.09 (0.03) | 1.07 (0.04). | 0.076[b] |
| FD | 52.2 (5.4) | 51.8 (5.5) | 0.739[b] |

p>0.05; [a]t-test, AI and FD; [b]Mann-Whitney U test; SD: Standard deviation; FAZ: Foveal avascular zone; AI: Acircularity index; FD: Foveal density.

**TABLE 2:** Retinal thickness, t-test, difference between each 2 group for all parameters.

| | Keratoconus Mean (±SD) | Control Mean (±SD) | p value |
|---|---|---|---|
| Whole image | 289.7 (20.9) | 284.1 (9.1) | 0.194 |
| Superior-hemi | 288.0 (11.1) | 286.1 (9.6) | 0.480 |
| Inferior-hemi | 284.6 (10.8) | 282.0 (9.1) | 0.322 |
| Fovea | 243.1 (21.9) | 239.8 (14.2) | 0.505 |
| Parafovea | 322.9 8(14.9) | 321.1 (12.1) | 0.613 |
| -Superior-hemi | 323.6 (14.9) | 321.9 (12.2) | 0.628 |
| -Inferior-hemi | 322.0 (14.7) | 320.4 (12.1) | 0.647 |
| -Temporal | 313.1 (14.7) | 310.3 (11.2) | 0.429 |
| -Superior | 328.4 (15.2) | 326.8 (12.5) | 0.667 |
| -Nasal | 325.6 (15.7) | 324.6 (13.6) | 0.793 |
| -Inferior | 324.4 (15.2) | 322.7 (12.5) | 0.648 |
| Perifovea | 285.0 (11.0) | 282.5 (9.6) | 0.351 |
| -Superior-hemi | 287.2 (11.3) | 285.0 (9.8) | 0.422 |
| -Inferior-hemi | 282.6 (11.4) | 280.1 (10.1) | 0.372 |
| -Temporal | 271.3 (11.5) | 266.9 (10.7) | 0.130 |
| -Superior | 286.9 (11.2) | 285.0 (9.9) | 0.487 |
| -Nasal | 303.9 (12.8) | 303.8 (11.7) | 0.982 |
| -Inferior | 277.4 (11.6) | 274.7 (9.7) | 0.330 |

p>0.05, t-test; SD: Standard deviation.

**TABLE 3:** Macular superficial capillary plexus vessel density parameters of optical coherence tomography angiography.

| | Keratoconus Mean (±SD) | Control Mean (±SD) | p value |
|---|---|---|---|
| Whole image | 47.4 (4.1) | 50.9 (2.7) | 0.000* |
| Superior-hemi | 47.5 (4.1) | 51.1 (3.1) | 0.000* |
| Inferior-hemi | 47.4 (4.5) | 50.9 (2.6) | 0.001* |
| Fovea | 17.6 (8.6) | 19.8 (4.7) | 0.030* |
| Parafovea | 48.4 (6.5) | 53.7 (4.3) | 0.001* |
| -Superior-hemi | 48.9 (6.3) | 53.8 (4.7) | 0.002* |
| -Inferior-hemi | 47.5 (7.8) | 53.6 (4.2) | 0.001* |
| -Temporal | 47.8 (6.2) | 53.4 (4.3) | 0.000* |
| -Superior | 50.3 (6.9) | 54.7 (5.3) | 0.009 |
| -Nasal | 46.1 (7.0) | 52.5 (4.2) | 0.000* |
| -Inferior | 49.4 (7.9) | 54.1 (4.7) | 0.008* |
| Perifovea | 48.3 (4.7) | 51.7 (2.7) | 0.001* |
| -Superior-hemi | 48.1 (4.5) | 51.7 (3.0) | 0.001* |
| -Inferior-hemi | 48.4 (5.2) | 51.6 (2.5) | 0.004* |
| -Temporal | 43.5 (5.5) | 48.3 (3.2) | 0.000* |
| -Superior | 48.1 (4.8) | 51.4 (3.2) | 0.003* |
| -Nasal | 52.2 (5.2) | 55.4 (2.7) | 0.043 |
| -Inferior | 48.2 (5.1) | 51.6 (3.0) | 0.003* |

SD: Standard deviation. *: value was p<0.05

perifoveal inferior (p=0.005) segments were detected to be significantly different from than the healthy control group.

**TABLE 4:** Macular deep capillary plexus vessel density parameters of optical coherence tomography angiography.

| | Keratoconus Mean (±SD) | Control Mean (±SD) | p value |
|---|---|---|---|
| Whole image | 46.5 (7.7) | 50.8 (5.7) | 0.017 * |
| Superior-hemi | 46.5 (7.7) | 50.5 (7.2) | 0.046* |
| Inferior-hemi | 46.4 (8.2) | 50.7 (5.5) | 0.021* |
| Fovea | 36.4 (5.3) | 36.2 (5.2) | 0.957 |
| Parafovea | 54.8 (5.3) | 54.9 (5.0) | 0.933 |
| -Superior-hemi | 55.3 (5.3) | 54.8 (5.4) | 0.741 |
| -Inferior-hemi | 54.3 (5.9) | 55.0 (4.7) | 0.620 |
| -Temporal | 55.9 (5.1) | 55.7 (4.8) | 0.845 |
| -Superior | 54.2 (5.5) | 54.2 (5.9) | 0.961 |
| -Nasal | 55.9 (6.0) | 55.8 (4.9) | 0.948 |
| -Inferior | 53.1 (7.5) | 54.0 (5.3) | 0.590 |
| Perifovea | 47.2 (8.5) | 52.3 (6.1) | 0.013* |
| -Superior-hemi | 47.6 (8.6) | 52.2 (6.5) | 0.024* |
| -Inferior-hemi | 46.9 (9.1) | 52.3 (6.2) | 0.010* |
| -Temporal | 51.1 (7.6) | 54.9 (5.5) | 0.030* |
| -Superior | 45.2 (10.2) | 51.1 (6.8) | 0.013* |
| -Nasal | 47.5 (8.5) | 51.4 (7.1) | 0.063 |
| -Inferior | 45.2 (10.2) | 51.7 (6.4) | 0.005* |

SD: Standard deviation. *: value was p<0.05

## DISCUSSION

Although it has been suggested that keratoconus has a multifactorial etiopathogenesis such as environmental factors, atopy, genetic susceptibility, eye rubbing, the exact pathogenesis remains unknown. The role of atopy and eye rubbing, together with genetic factors, in the pathogenesis of keratoconus has been known for a long time.[16]

In addition, although classical inflammation findings have not been observed in keratoconus, there are different studies supporting a subclinical, chronic inflammation in its etiology. In a study by Lema et al., significantly higher levels of interleukin-6 (IL-6), Matrix Metalloproteinase-9 and tumor necrosis factor-α (TNF-α) were reported in both eyes of unilateral keratoconus patients and in tears of subclinical keratoconus patients compared to the healthy control group.[17] Other studies with findings on increased in tear levels of IL-1 ß, IL-4, IL-6, IL-10, interferon gamma (IFN-γ), and TNF-α among keratoconus patients indicate an intense inflammation in the microenvironment.[18,19] In addition, Jun et al. found high levels of IL-6 in the tear fluid of keratoconus patients,

but low levels of IL-12, TNF-$\alpha$, IFN-$\gamma$, IL-4, IL-13 and CCL5.[20] In another study, an interesting finding was reported that keratoconus severity was higher in keratoconus patients with bronchial asthma, accompanying the high tear mediators.[21] This indicates the likelihood of inflammation not to be limited to tear but to have systemic effects. In addition, it has been shown that atopy, IgE and eye scratching which are well-known factors, also trigger mast cell degradation and inflammation besides their mechanical effects.[22-24]

In a review in which many publications were reviewed, it is shown that the posterior segment is affected by showing changes in structures such as retina and choroid in individuals with keratoconus.[25] Even Pierro et al. showed a decrease in lamina cribrosa curvature and retinal nerve fiber thickness and vascularity even in patients with early stage keratoconus.[26]

In current study, we purposed to estimate the efficacy of subclinical inflammation accompanying the eyes with keratoconus on the retina and choroidal layers by using OCTA. OCTA is a new device that shows retinal vascularity and choriocapillary circulation by measuring the contrast formed by blood moving in the vascular structure without any dye injection.[27-29] We did not experience poor image quality or imaging problems in any of the keratoconus patients, possibly related to the inclusion of Grade 2 and 3 keratoconus patients.

Although studies using enhanced depth imaging-optical coherence tomography for choroidal assessment revealed different findings in keratoconus eyes, the studies reporting increased choroidal thickness are more common in the literature. In these studies, increased choroidal thickness has been explained by the inflammation evident in the keratoconus.[10,30-32]

Recently, OCTA-based analysis of the inflammation-related changes in retinal-choroidal blood flow has been reported in uveitic patients. Wintergerst et al. compared 29 intermediate uveitis eyes without macular edema and 30 control eyes by OCTA; and in SCP and DCP, a significant decrease was detected in uveitis eyes compared to the control group in all OCTA parameters.[31,33] In a controlled OCTA study in Behcet's patients without ocular involvement, a significant decrease in vessel density in SCP and DCP and an influence on FAZ were shown in Behcet's patients. They argued that retinal and choroidal microvascular structures are affected before ocular manifestations appear clinically.[34] This shows that the intense intraocular inflammation affects the vascular structures and causes a significant reduce in vascular density in the capillary plexuses and enlargement in the FAZ.

In our study, a significant decrease in SCP was found in all sections, while deep capillary vascular density was less affected, FAZ and choriocapillaris were not affected. Based on these results, we can conclude that the subclinical inflammation present in keratoconus eyes is more likely to affect the superficial layers of the retina rather than the entire retina-choroid layers. The lack of involvement of all layers may be explained by the absence of significant inflammation.

In addition, the patients participating in our study aged between 15-40 years, which is the age range considered to be associated with the progression of keratoconus and the presence of active inflammation. This seems to indirectly confirm the findings in the current study. Although it is thought to be only a local inflammation when inflammatory substances are detected higher in keratoconic corneal tissue cultures and in tears of keratoconus patients, the accompanying systemic conditions such as atopy and asthma make us think of a more widespread inflammation.[20,21] This suggests that not only the cornea but also the posterior segment may be affected.

## CONCLUSION

This is the first OCTA-based clinical study of retinal-choroidal microvascular changes in eyes with keratoconus.

Our results confirm that the posterior segment is affected by the subclinical anterior segment inflammation. Further studies are needed to investigate the chorioretinal vascular structures in keratoconus patients in relation to the stage of the disease and the age-dependent progression period.

The evaluation of retinal-choroidal vascular structures in keratoconus eyes will contribute to the understanding of the pathogenesis of the disease. We

belive that more detailed results will be obtained in future studies with larger series and comparing all stages of keratoconus.


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*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:*** *Berrak Şekeryapan Gediz, Burcu Kazancı;* ***Design:*** *Berrak Şekeryapan Gediz, Burcu Kazancı;* ***Control/Supervision:*** *Yasemin Özdamar Erol, Berrak Şekeryapan Gediz, Burcu Kazancı, Fatma Çorak Eroğlu;* ***Data Collection and/or Processing:*** *Yasemin Özdamar Erol, Berrak Şekeryapan Gediz, Burcu Kazancı, Fatma Çorak Eroğlu;* ***Analysis and/or Interpretation:*** *Berrak Şekeryapan Gediz, Yasemin Özdamar Erol;* ***Literature Review:*** *Berrak Şekeryapan Gediz, Yasemin Özdamar Erol, Fatma Çorak Eroğlu, Burcu Kazancı;* ***Writing the Article:*** *Burcu Kazancı, Berrak Şekeryapan Gediz, Yasemin Özdamar Erol, Fatma Çorak Eroğlu;* ***Critical Review:*** *Yasemin Özdamar Erol, Berrak Şekeryapan Gediz;* ***References and Fundings:*** *Burcu Kazancı, Berrak Şekeryapan Gediz;* ***Materials:*** *Berrak Şekeryapan Gediz, Burcu Kazancı, Yasemin Özdamar Erol, Fatma Çorak Eroğlu.*

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