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RESEARCH

THE CORRELATION OF CHOROIDAL THICKNESS AND OCULAR PULSE AMPLITUDE IN NON-EXUDATIVE AGE-RELATED MACULAR DEGENERATION

ABSTRACT

Introduction: The choroid is involved in the pathogenesis of various retinal diseases, including age-related macular degeneration (AMD). The ocular pulse amplitude (OPA) gives useful information about intraocular blood flow and is an indirect indicator of choroidal perfusion. In this study, we aimed to assess the correlation between the OPA and choroidal thickness (CT) in the eyes of healthy individuals and of individuals with non-exudative early stage AMD.

Materials and Method: Forty-four eyes of 44 non-exudative AMD patients and 41 age-matched eyes of 41 healthy individuals were included in the study. All eyes underwent a detailed ophthalmic evaluation, including axial length (AL) and ocular pulse amplitude (OPA) measurements. The CT was measured using optical coherence tomography. Parameters were compared between the two groups and correlation between OPA and CT was assessed.

Results: The mean subfoveal, foveal, and parafoveal CT were $245.82 \pm 24.29 \mu\text{m}$, $230.66 \pm 23.44 \mu\text{m}$, $219.55 \pm 25.39 \mu\text{m}$ in AMD group, respectively. The corresponding values were $278.44 \pm 34.18 \mu\text{m}$, $263.76 \pm 32.45 \mu\text{m}$, and $253.79 \pm 34.81 \mu\text{m}$ in control group, respectively. The mean ages of groups were 69.6 ± 8.97 years, and 65.0 ± 5.89 years, respectively. The mean OPA was $3.43 \pm 1.14 \text{ mmHg}$ and $3.49 \pm 1.12 \text{ mmHg}$, respectively. The average CT in AMD patients were significantly lower than the control group in all three regions (subfoveal-foveal-parafoveal) (all $p < 0.001$). In controls, there was a moderate positive correlation between the OPA and CT in the three segments ($p = 0.002$, 0.009 , and 0.003 ; respectively). However only the foveal CT showed significant positive correlation with the OPA in AMD group ($p = 0.047$).

Conclusion: Our results showed a considerable correlation between ocular pulse amplitude and choroidal thickness in healthy subject. In non-exudative AMD group, there was a weak correlation between them. It can be hypothesized that; in patients with AMD, degeneration and/or thinning of choroidal pattern is a reason for this result.

Key Words: Choroidal Thickness; Ocular Pulse Amplitude; Dynamic Contour Tonometry; EDI Mode Optical Coherence Tomography.



ARAŞTIRMA

NON-EKSUDATİF YAŞA BAĞLI MAKULA DEJENERASYONUNDA OKÜLER NABİZ AMPLİTÜDÜ VE KOROID KALINLIĞININ KORELASYONU

Öz

Giriş: Koroid tabakası yaşa bağlı makula dejenerasyonunu (YBMD) da içeren birçok retinal hastalığın patogeneğinde yer alır. Oküler nabiz amplitüdü (ONA) ise intraoküler kan akımı hakkında bilgi verir ve koroidal perfüzyonun indirekt göstergesidir. Bu çalışmada sağlıklı gözler ve YBMD olan gözlerde ONA ve koroid kalınlığını (KK) değerlendirmeyi ve kıyaslamayı amaçladık.

Gereç ve Yöntem: Kırkdört YBMD hastasının 44 gözü ile, yaş uyumlu 41 sağlıklı katılımcının 41 gözü çalışmaya dahil edildi. Aksiyel uzunluk (AU) ve ONA ölçümünü içeren kapsamlı oftalmik muayene yapıldı. Optik koherens tomografi cihazı ile KK ölçüldü. Parametreler iki grup arasında kıyaslandı ve KK ile ONA arasındaki korelasyon değerlendirildi.

Bulgular: Yaşa bağlı makula dejenerasyonunu grubunda ortalama koroid kalınlıkları subfoveal, foveal ve parafoveal alanlarda sırasıyla $245.82 \pm 24.29 \mu\text{m}$, $230.66 \pm 23.44 \mu\text{m}$, $219.55 \pm 25.39 \mu\text{m}$ iken, kontrol grubunda sırasıyla $278.44 \pm 34.18 \mu\text{m}$, $263.76 \pm 32.45 \mu\text{m}$ ve $253.79 \pm 34.81 \mu\text{m}$ idi. Ortalama yaş YBMD grubunda 69.6 ± 8.97 ; kontrol grubunda 65.0 ± 5.89 yıl idi. Ortalama ONA iki grup için sırasıyla $3.43 \pm 1.14 \text{ mmHg}$ ve $3.49 \pm 1.12 \text{ mmHg}$ olarak ölçüldü. Ortalama KK tüm bölgelerde (subfoveal-foveal-parafoveal) YBMD grubunda kontrol grubuna kıyasla anlamlı düzeyde düşüktü ($p < 0.001$). Kontrol grubunda ONA ile KK arasında her üç bölgede de anlamlı pozitif korelasyon varken ($p = 0.002$, 0.009 , 0.003), YBMD grubunda sadece foveal KK ile ONA arasında ilişki saptandı ($p = 0.047$).

Sonuç: Sonuçlarımız sağlıklı grupta KK ile ONA arasında dikkate değer bir korelasyon olduğunu gösterdi. Non-eksudatif YBMD grubunda ise zayıf bir korelasyon mevcuttu. YBMD hastalarında koroidal paterndeki dejenerasyon ve/veya inceltme bu korelasyonun bozulmasının sebebi olabilir.

Anahtar Sözcükler: Koroid Kalınlığı; Oküler Nabiz Amplitüdü; Dinamik Kontür Tonometre; EDI Mod Optik Koherens Tomografi.



INTRODUCTION

The choroid is known to have an important role in ocular nutrition, volume regulation, and temperature control (1). Furthermore, it is involved in the pathogenesis of various retinal diseases, including age-related macular degeneration (AMD) (2,3). Age-related macular degeneration is characterized by changes in retinal pigment epithelium (RPE) and Bruch's membrane, which are both fed by choroidal blood flow. Therefore, choroidal vascular insufficiency may lead to AMD (4).

Adequate visualization and assessment of the choroid was not possible until the development of techniques such as partial coherence interferometry and spectral domain optical coherence tomography (SD-OCT) that permit measurements of the living choroid (5). The recent development of enhanced depth imaging (EDI) has now made choroidal examination using SD-OCT even more precise (6).

The ocular pulse amplitude (OPA) gives useful information about intraocular blood flow and is an indirect indicator of choroidal perfusion (7,8). Dynamic contour tonometry (DCT) is a contact tonometer that measures intraocular pressure (IOP) independently of central corneal thickness and corneal curvature. Interestingly, Mori et al. found that ocular blood flow and OPA were lower in patients with exudative AMD than in those with non-exudative AMD and controls. Therefore, it was suggested that reduced choroidal blood flow contributes to the development of choroidal neovascularization in AMD (9).

In this study, we aimed to assess the correlation between the OPA and choroidal thickness in the eyes of healthy individuals and of individuals with non-exudative early stage AMD.

MATERIALS AND METHOD

This prospective, comparative study was approved by the Ethical Review Committee of Ufuk University and adhered to the provisions of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all participants. In total, we included 44 eyes of patients with non-exudative AMD and 41 eyes of age- and sex matched individuals in the study. The following criteria were used for inclusion in the AMD group: extensive (>15) small drusen; a few (<20) medium-size drusen with soft borders; numerous (≥20 with soft borders, but ≥65 with distinct boundaries) medium-size drusen; or pigment abnormal-

ities (e.g. increased pigmentation or depigmentation, but not geographic atrophy). The following eligibility criterion was used for inclusion in the control group: aged 55 years or older with eyes considered normal by funduscopy and OCT. For both groups, we excluded the following: eyes with known ocular diseases, including glaucoma, uveitis, diabetic retinopathy, and a history of previous intraocular surgery or injection; eyes with refractive errors of 6 D or more as spherical equivalent; and eyes in which the ocular fundus could not be observed because of media opacities.

All eyes underwent a thorough ophthalmic evaluation, including slit-lamp biomicroscopy, fundus examination, and axial length measurement (Sonomed, A/B Scan 500, Lake Success, NY, USA). OCT (Cirrus, Carl Zeiss Meditec, Inc., Dublin, CA, USA) measurements were performed at the same time (in the morning between 9 am and 11 am) to avoid the diurnal variation of the choroidal thickness measurement. We used the HD 5 line raster scan with the EDI mode to evaluate the choroid. The protocol consisted of 6-mm parallel lines with 1024 A-scans/B-scans, averaging 4 B-scans per image. Choroidal thickness was measured by two independent observers who were blind to each other's results. The correlation of the choroidal thickness values obtained from the two observers was evaluated.

The subfoveal choroidal thickness was determined manually from the outer edge of the hyperreflective RPE to the inner sclera centered on the fovea by the observer (Figure 1A). The choroidal thickness was measured at 500 µm intervals, up to 1000 µm temporal and nasal to the foveola, from a total of 5 points so measurements were taken from a total of 5 points. The central measurement was considered subfoveal, consecutive measurements were used for the foveal and parafoveal choroidal thicknesses (Figure 1B). Corresponding nasal and temporal measurements were averaged for each eye. The eye with the best visualization of the border between the choroid and sclera (i.e., the choroidal-scleral interface was used in patients with AMD patients and in controls.

The IOP and OPA readings were acquired using Pascal DCT (Swiss Microtechnology AG, Port, Switzerland), which is a slit-lamp-mounted contact tonometer that can monitor IOP and OPA simultaneously. After instillation of proparacaine eye drops, the probe was left on the cornea for 8 to 10 s. Measurement with quality scores less than 3 were preferred (scale 1 to 5); therefore, measurements were repeated until scores of 1an IOP reading with a quality score between 1-3 were obtained.

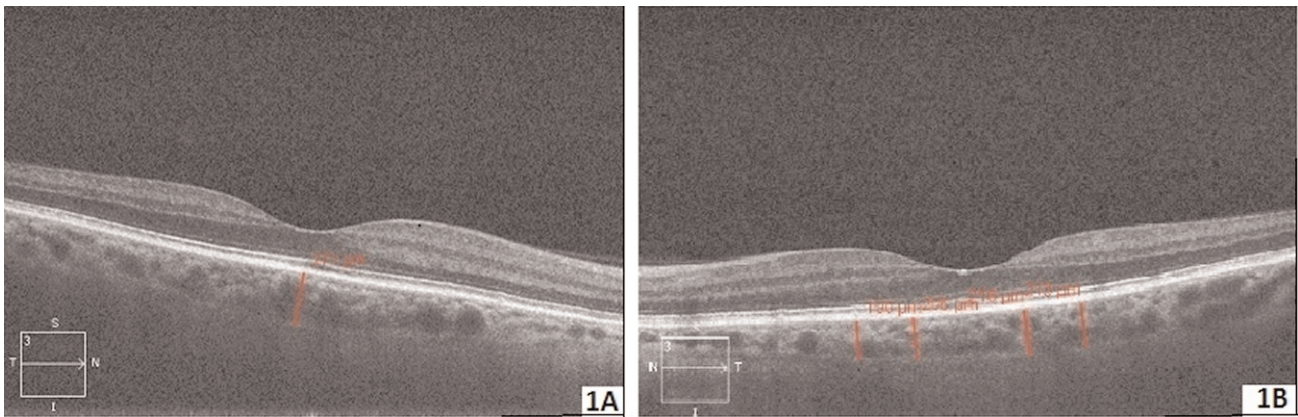


Figure 1— Choroidal images were obtained by spectral-domain optical coherence tomography using enhanced depth imaging mode. **1A.** Subfoveal choroidal thickness; **1B.** Foveal and parafoveal choroidal thicknesses.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (version 17.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distributions for all variable groups. Parametric Student-*t* tests were used to compare variables with normal distributions. Pearson's correlation analyses were used coefficient test was applied to determine the relationship between the findings. For all tests, a *p*-value of <0.05 was considered significant.

RESULTS

Forty-four cases of non-exudative AMD were included in this study from 44 patients who fulfilled the inclusion criteria. These were compared against a normal control group of 41 eyes from 41 control subjects. Table 1 reports all descrip-

tive and statistical information for the AMD and control groups. There were no statistically significant differences in age, sex distribution, IOP, OPA, and axial length values between the groups.

The mean choroidal thicknesses for the subfoveal, foveal, and parafoveal locations in the AMD group were 245.82 ± 24.29 , 230.66 ± 23.44 , and 219.55 ± 25.39 μm , respectively. The corresponding values in control group were 278.44 ± 34.18 , 263.76 ± 32.45 , and 253.79 ± 34.81 μm , respectively. The average choroidal thickness was significantly lower in patients with AMD than that in control subjects for all the three regions ($p < 0.001$) (Table 2). In addition, there was a strong correlation for the choroidal thickness measurements between observers at each locations ($p < 0.001$).

When all participants were assessed together, there was a weak correlation between OPA and IOP, but this was not statistically significant ($p = 0.066$; $r = 0.202$). However, when the

Table 1— Patient Characteristics.

| Parameters | AMD Group | Control Group | <i>p</i> |
|-------------------------|---------------------|---------------------|----------|
| Patients, n (%) | 44 (51.8%) | 41 (48.2%) | |
| Age (\pm SD) (years) | 69.6(\pm 8.97) | 65.0 (\pm 5.89) | 0.630 |
| Sex (eyes) M/F | 16/28 | 17/24 | 0.125 |
| IOP (\pm SD) (mmHg) | 17.04 (\pm 2.33) | 17.43 (\pm 2.95) | 0.497 |
| OPA (\pm SD) (mmHg) | 3.43 (\pm 1.14) | 3.49 (\pm 1.12) | 0.816 |
| AL (\pm SD) (mm) | 24.45 (\pm 2.67) | 24.62 (\pm 2.42) | 0.567 |

AL, Axial length; AMD, Age-related macular degeneration; F, female; IOP intraocular pressure; M, male; OPA, ocular pulse amplitude; SD, standard deviation.

**Table 2**— Mean Choroidal Thicknesses in the Eyes of Control Individuals and Patients with Age-related Macular Degeneration.

| Choroidal Thickness (μm) | AMD Group | Control Group | p |
|---------------------------------------|-----------------------|-----------------------|--------|
| Subfoveal (\pm SD) | 245.82 (\pm 24.29) | 278.44 (\pm 34.18) | <0.001 |
| Foveal (\pm SD) | 230.66 (\pm 23.44) | 263.76 (\pm 32.45) | <0.001 |
| Parafoveal (\pm SD) | 219.55 (\pm 25.39) | 253.79 (\pm 34.81) | <0.001 |

AMD, Age-related macular degeneration; SD, standard deviation

groups were considered separately, there was a statistically significant positive correlation in the control group ($p=0.041$; $r=0.313$).

The choroidal thickness was not correlated with age at either the subfoveal, foveal, or parafoveal locations. The respective p values were 0.358, 0.699, and 0.840 in the compared and 0.788, 0.568 in the control group. Additionally, there was no significant correlation between age and OPA, in either group (AMD group, $p=0.352$; control group, $p=0.524$). In both groups, the mean choroidal thickness was greatest in the subfoveal region, and decreased gradually increasing distance from the fovea.

There was a moderate positive correlation between choroidal thickness and OPA at all three studied regions, in controls. However, only the foveal area showed a significant positive correlation in the eyes of AMD patients (Table 3).

DISCUSSION

The choroidal vascularity has a prominent in maintaining normal retinal morphology and function. Abnormal choroidal blood volume and decreased flow can result in photoreceptor dysfunction and death (10). A possible sign of decreased choroidal blood perfusion could be thinning of the choroid. Until recently, information about the choroidal thickness

could be acquired only by histologic examination, which is unlikely to reflect the true thickness of the living choroid, because of changes in the prominence of blood vessels. The development of methods to measure choroidal thickness *in vivo* has facilitated new research into both normal and pathological processes in the choroid. Techniques such as partial coherence interferometry and SD-OCT now permit detailed measurements of the living choroid (5).

The OPA is thought to provide information about intraocular blood flow by recording the difference between the systolic and diastolic IOP, and could be used as an indirect measure of choroidal perfusion (8). Pulsatile ocular blood flow primarily measures the pulsatile component of choroidal perfusion, independently of the retinal or retrobulbar circulation. Zion et al. found that the pulsatile index of the choroid, as measured by color Doppler imaging was strongly associated with OPA (11).

In our patients with AMD, both drusens and RPE abnormalities were present, but we excluded eyes with advanced geographic atrophy to standardize the group. Because AMD is characterized by changes in both RPE and Bruch's membrane, and because these layers are nourished by the choroid blood vessels, it is possible that choroidal vascular insufficiency is associated with AMD (12). Furthermore, some individuals lose their visual acuity earlier than others that have the

Table 3— Correlation Between Ocular Pulse Amplitude and Mean Choroidal Thickness.

| | | Subfoveal Choroidal Thickness | Foveal Choroidal Thickness | Parafoveal Choroidal Thickness |
|----------------------|---|-------------------------------|----------------------------|--------------------------------|
| OPA in AMD Group | r | 0.264 | 0.305 | 0.120 |
| | p | 0.087 | 0.047 | 0.445 |
| OPA in Control Group | r | 0.462 | 0.401 | 0.459 |
| | p | 0.002 | 0.009 | 0.003 |

AMD, Age-related macular degeneration; CT, choroidal thickness; OPA, ocular pulse amplitude; p, statistically significant level p value; r, Pearson correlation coefficient.



same fundal lesions. Therefore, it is reasonable to assume that oxidative stress, genetic abnormalities, and environmental conditions and not only photoreceptor dysfunction and the presence of drusen are relevant in the development of non-exudative AMD (13).

In our control group, the choroidal thickness was 278.44 ± 34.18 μm in the subfoveal area. The variation in choroidal thickness values reported in previous studies may be result of different subject ages, OCT instruments, and different measurement methods.

In contrast, the choroidal thickness was 245.82 ± 24.29 μm in the subfoveal area in the AMD group, and the choroidal thicknesses in the subfoveal, foveal, and parafoveal areas were significantly lower in the AMD group than those in the control group. Similarly, Kim et al. examined 37 eyes with from non-exudative AMD patients, 24 eyes with neovascular AMD, and 29 control eyes and reported mean subfoveal choroidal thicknesses of 186.62 ± 64.02 , 226.46 ± 102.87 , and 241.97 ± 66.37 μm , respectively (14). Although they used a different OCT instrument (3-dimensional [3D] OCT-1000; Topcon Corp., Tokyo, Japan); therefore, produced different values to ours, the similar pattern suggests that the mean choroidal thickness is significantly reduced in non-exudative AMD.

In both groups, the mean choroidal thickness was greatest in the subfoveal region, and gradually decreased with increasing distance from the fovea. This pattern is consistent with previous studies of the choroidal thickness in normal eyes (15,16). Manjunath et al. found that the choroid was thinnest nasally, and thickest in the subfoveal region, but it thinned again temporally; however none was as thin as the choroid proximal to the disc (17). Our results were broadly similar for the healthy subjects. In addition, we observed that this pattern of the thickness was preserved in patients with AMD, even though the choroidal thickness was significantly thinner in the AMD than that in the control group. Parafoveal choroidal regions were also affected by AMD in our study.

Although, Maul et al. found that increasing age is associated with a thinner choroid, and that reduced choroidal thickness is probably associated with particular phenotypes in the aging eye (18), we found no statistically significant correlation between age and the choroidal thickness in either group. Since our study groups included patients, with presbyopia and AMD, the narrow age range, made it unlikely that we would find a difference between age and the choroidal thickness. However, because our study groups were age matched, our comparisons were probably not influenced by age-related

changes in the choroidal thickness. Therefore, reduced choroidal thickness may play an indirect role as a modulator of natural progression in AMD, or could even be cause of AMD.

It has been hypothesized that blood hypoperfusion could result from abnormal choroidal thickness, with OPA being useful as an indirect indicator of the choroidal blood supply. In our study, we found a significant positive relationship between the OPA and the choroidal thickness in subfoveal, foveal, and parafoveal locations, in the control group, but only a weak positive relationship in the fovea of patients with AMD. The lack of a significant positive relationship when comparing the AMD and control groups may be attributed to the impaired choroidal pattern in AMD group. Dervisogullari et al. found significantly decreased choroidal thicknesses with normal OPA measurements when patients with unilateral migraines had acute attacks (19), but failed to assess the correlation between these findings. Since the vascular components have a major role in migraine, one can hypothesize that the choroidal thickness is more sensitive to vascular changes.

In our study, while there was a significant difference for the choroidal thickness between the two groups, there was no difference between the groups in terms of the OPA. So, it may be hypothesized that the choroidal thickness is affected earlier than the OPA in patients with AMD, which might therefore contribute to the pathophysiology of the disease. Given that the OPA is a gross value that reflects the entire whole choroidal circulation, while AMD is a relatively localized disease, this result may indicate that the OPA does not affect the pathophysiology of AMD.

A limitation of the current study was that the Cirrus OCT did not automatically measure the choroid, even though there was a strong correlation between the two blinded observers. Other shortcomings are the relatively limited number of patients, and the absence of a longitudinal follow-up to assess possible long-term changes in the choroidal thickness and OPA.

In conclusion, we found a considerable correlation between the OPA and choroidal thickness in healthy and relatively elderly individuals, but this correlation was not preserved in patients with AMD. Although, the relationship between the OPA and choroidal thickness is not proven exactly in this study, these are the earliest results on this topic due to the lack of similar studies in the literature. Larger studies with younger patients could further clarify this relationship.

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The authors declare no conflicts of interest.



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