Comparison of Optical Coherence Angiography Measurements in Patients with Neovascular and Non-Neovascular Age-Related Macular Degeneration

Mehmet Demir, Cetin Akpolat, Turgay Ucak, Zeynep Yilmaz, Emine Betul Akbas Ozyurek

Department of Ophthalmology, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: The purpose of the study was to determine the differences of optical coherence tomography angiography (OCTA) measurements between the patients with neovascular age-related macular degeneration (AMD) and non-neovascular early AMD.

Methods: This retrospectively designed study included patients with neovascular AMD (N-AMD group) and non-neovascular early AMD (NN-AMD group). The patients had a completed ocular examination including best-corrected visual acuity (BCVA, in decimal), intraocular pressure (IOP, mmHg), and OCTA measurements such as choroidal blood flow (au) and retinal vessel density (VD, %).

Results: The N-AMD group (1.46±0.28 au) showed a lower mean choroidal flow measurement than the NN-AMD group (1.73±0.32 au), (p<0.001). The patients in the N-AMD group had reduced VD measurements in all superficial and deep retinal layers compared with the NN-AMD group. However, significant differences in VD measurements were observed only in total superficial parafovea and in the superior and inferior quadrants of superficial parafovea while comparing the N-AMD and NN-AMD groups (p<0.05 for all). Almost all deep retinal VD measurements (p<0.05 for them) were significantly different in the N-AMD group except the overall and foveal zones (p=0.144 and p=0.433, respectively).

Conclusion: Retinal VD is reduced in patients with N-AMD when compared to NN-AMD. This outcome offered a retinal vessel contribution to AMD pathogenesis.

Keywords: Neovascular age-related macular degeneration, Non-neovascular age-related macular degeneration, Optical coherence tomography angiography, Retinal vessel density

Address for correspondence: Cetin Akpolat, MD. Sisli Hamidiye Etfal Egitim ve Arastirma Hastanesi, Goz Hastaliklari Bolumu, Istanbul, Turkey
Phone: +90 530 324 49 36 E-mail: akpolatcetin@yahoo.com
Submitted Date: August 04, 2021 Accepted Date: October 11, 2021 Available Online Date: March 28, 2022

Copyright 2022 by The Medical Bulletin of Sisli Etfal Hospital - Available online at www.sislietfaltip.org

OPEN ACCESS This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).
fluid exudation, and fibrosis.\textsuperscript{[2,3]} In contrast to N-AMD, non-neovascular type AMD (NN-AMD) defines macular degeneration without choroidal neovascularization.

Optical coherence tomography angiography (OCTA) is a relatively new imaging device that combines the structural information of a standard optical coherence tomography (OCT) section through visualization of blood flow, providing high-resolution and three-dimensional data of different vascular layers. Thus, it enables high-quality imaging of the retinal and choroidal circulation without the need for dye injection.\textsuperscript{[3,4]} When evaluated together with structural OCT sections, OCTA is an effective tool for both diagnosis and classification of N-AMD and has higher sensitivity and specificity than conventional methods such as fluorescein angiography or indocyanine green angiography.\textsuperscript{[4-6]} Therefore, OCTA can help to make the right treatment decision and prevent unnecessary anti-VEGF injections by providing identification and classification of the choroidal neovascularization lesions.\textsuperscript{[4]} In this study, we aimed to evaluate quantitative results of retinal and choroidal OCTA measurements in patients with N-AMD and early NN-AMD.

Methods

The study was conducted retrospectively and cross-sectionally at a tertiary eye clinic. Fully informed and written consent was obtained from all patients before the image acquisition. The study was adhered to the requirements of the Declaration of Helsinki and approved by the local ethics committee (Date: December 01, 2020, Number: 3022).

Study Protocol and Patient Selection

A total of 71 right eyes of 71 patients with N-AMD and NN-AMD were recircuited in the study. Thirty-three eyes of 33 patients with the clinical diagnosis of NN-AMD had type 2 choroidal neovascularization and served as the N-AMD group. The remaining 38 eyes of 38 patients with the clinical diagnosis of early NN-AMD comprised the NN-AMD group. The demographic (age and gender) and clinical data (lens status, previous intravitreal injections, follow-up time, ophthalmic examination findings, and ocular measurements including visual acuity, intraocular pressure, choroidal flow, and OCTA scans) were obtained from medical chart records. Patients with a definitive number of intravitreal injections were included in the N-AMD group. All patients underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA, in decimal), intraocular pressure (IOP, mmHg, non-contact pneumatic tonometry), anterior segment assessment with slit-lamp biomicroscope, dilated fundus examination, choroidal blood flow (au), and OCTA measurements. Clinical fundus characteristics of early NN-AMD patients included drusen and RPE abnormalities. Clinical fundus characteristics of N-AMD patients included neovascular derangement (choroidal neovascularization formation), subretinal fibrosis, and subretinal fluid or hemorrhage/hard exudate. Patients with high ametropia (spherical equivalent >−6 D, >+4 D), media opacity, concomitant macular diseases other than AMD, previous vitreoretinal surgeries, geographic atrophy, non-AMD-related choroidal neovascularization, and poor-quality images were excluded from the study.

Measurement Protocol

An enhanced depth imaging and spectral-domain OCTA (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA, USA) was used for image acquisition. This commercially available, standard deviation (SD)-OCTA can perform 70,000 A-scans per second using fixation tracking software and a motion correction algorithm. Scans with significant artifacts (such as large floaters, segmentation errors, and blinking or motion artifacts) and signal strength lower than 7/10 were excluded and repeated till the appropriate scans were captured. The measurements were performed by the same experienced and masked technician. The scans were captured over a 3 × 3 mm area centered on the fovea. Superficial retinal vessel density (VD, %) measurement was automated segmented from the ILM to the inner plexiform layer (IPL) and deep retinal VD measurement was automated segmented from the IPL to the outer plexiform layer (Fig. 1). VD was quantified as the total number of pixels contributing to the blood flow signal detectable by OCTA. There are no vascular structures above the RPE level in healthy eyes. Therefore, OCTA is not expected to detect blood flow at
the level of the outer retinal layers. VD measurements were analyzed in overall, foveal, and parafoveal areas. Parafoveal measurements were assessed in the temporal, superior, nasal, and inferior quadrants.

**Statistical Analysis**

Statistical analyses of the data were performed using SPSS software (IBM Corp., NY, USA; version 22.0). Constant variables were expressed as the mean±SD. The Kolmogorov–Smirnov test was performed to assess the normal distribution. Parametric or non-parametric tests were used whether the data distribution is normal or not. Categorical variables were evaluated by the Chi-square test. The comparison of scale variables was performed using independent samples t-test or Mann–Whitney U-tests. The Pearson or Spearman tests were used for correlation analysis. P<0.05 was accepted as statistically significant.

**Results**

The NN-AMD group was slightly younger than the N-AMD group (p=0.045). There was not any statistical difference in the gender numbers of the patients between the N-AMD and NN-AMD groups (p=0.845). The NN-AMD group was less likely to be pseudo-phakic than the N-AMD group (42.1% vs. 57.6%, p=0.044). The numbers of the patients with controlled systemic hypertension and type 2 diabetes mellitus were similar in the N-AMD and NN-AMD groups (p>0.05 for both). The N-AMD and NN-AMD groups had similar mean follow-up duration (p=0.237). The N-AMD group presented with a poorer mean BCVA than the NN-AMD group (p<0.001). The N-AMD and NN-AMD groups had similar mean IOP measurements (p=0.304). The N-AMD group had a lower mean choroidal flow value than the NN-AMD group (p<0.001). All these data are represented in Table 1.

Overall, foveal, parafoveal (temporal, superior, nasal, and inferior quadrants) VD measurements obtained from superficial and deep retinal layers are represented in Tables 2 and 3, respectively. The N-AMD group presented with lower VD measurements in all superficial and deep retinal layers than the NN-AMD group. Significant differences in retinal VD measurements were noted only in the total superficial parafovea and in the superior and inferior quadrants of superficial parafovea between the N-AMD and NN-AMD groups (p<0.05 for all). Almost all deep retinal VD measurements (p<0.05 for them) showed significant differences between the groups except the overall and foveal assessments (p=0.144 and p=0.433, respectively).

**Discussion**

It is essential to assess the choroidal neovascularization lesions in detail for the diagnosis, treatment decision, and follow-up of N-AMD. Furthermore, in N- or NN-AMD, OCTA scans play an important role and provide benefits to elimi-

| Table 1. Demographic and clinical features of the patients in the N-AMD and NN-AMD groups |
|-----------------|------------------|-----------------|---|
| **Characteristics** | **N-AMD group (n=33)** | **NN-AMD group (n=38)** | **P*** |
| Age (years) | 73.69±10.17 (58–79) | 65.03±7.79 (55–74) | 0.045 |
| Gender (n) | 0.845 | | |
| Female | 19 (57.6%) | 21 (55.3%) | 0.044 |
| Male | 14 (42.4%) | 17 (44.7%) | |
| Lens Status (n) | | | |
| Phakic | 14 | 22 | |
| Pseudo-phakic | 19 | 16 | |
| BCVA (in decimal) | 0.18±0.09 | 0.64±0.25 | <0.001 |
| IOP (mmHg) | 14.38±3.53 | 13.84±4.06 | 0.304 |
| Choroidal flow (au) | 1.46±0.28 | 1.73±0.32 | <0.001 |
| Systemic disease (n) | | | |
| Hypertension | 8 | 6 | 0.372 |
| Diabetes | 6 | 5 | 0.222 |
| Follow-up duration (years) | 3.58±2.03 (1–7) | 3.05±1.65 (1–4) | 0.237 |
| Intravitreal injection (n) | | | |
| Bevacizumab | 3.02±1.14 (0–7) | - | |
| Afibercept | 3.46±1.02 (0–7) | - | |

AMD: Age-related macular degeneration, *the Chi-square and independent samples Student’s t-tests were used; n: Number; BCVA: Best-corrected visual acuity, IOP: Intraocular pressure.
nate choroidal neovascularization lesions associated with non-vascularized macular drusen and drusenoid pigment epithelial detachment accompanied by subretinal fluid.\textsuperscript{4,7,8} The development of OCTA has enabled segmental analysis of the retinal and choroidal vascular structures without dye injection.\textsuperscript{9} Compared to fluorescein angiography, OCTA provides excellent quality images with high resolutions and more accurate three-dimensional visualization of the retinal and choroidal vasculature, especially in the deep layers.\textsuperscript{10} Retinal VD may be affected in any type of AMD, but choroidal neovascularization is mainly located in the deep retinal vascular plexus, outer nuclear layer, ellipsoid zone, and choroid.\textsuperscript{10} This study investigated the potential alterations in vascular plexuses for further understanding of the possible impact of vascular hemodynamic factors in the pathogenesis of AMD. In the present study, OCTA was used to examine and compare the superficial and deep retinal VD measurements in the N-AMD and NN-AMD groups. The results of the study demonstrated significantly lower VD measurements in almost all areas of the deep retinal layer, whereas VD measurements were significantly lower in certain areas of the superficial retinal layer in the N-AMD group compared with the NN-AMD group. Meanwhile, the N-AMD group represented mean poorer BCVA and lower choroidal flow values than the dry-AMD group.

It is known that the pathophysiology of AMD is complex and multifactorial, which is associated with genetics, age, and environmental conditions.\textsuperscript{11} Choroidal vasculature alterations in AMD might be secondary to dietary aging, oxidative stress, fat intake, smoking, systemic hypertension, carotid, coronary, and peripheral vascular disorders causing atherosclerosis, loss of vascular compliance, and increased vascular stiffness, which are also known risk factors for the development and progression of AMD.\textsuperscript{11,12,13} Choroidal vascular damage has been demonstrated in NN-AMD as well as the N-AMD.\textsuperscript{12,13} Similar to our results, early laser Doppler flowmetry investigation showed decreased choroidal blood flow in the eyes of AMD patients.\textsuperscript{16} Supporting our study, the histological investigations represented that vascular impairment of the choriocapillaris could precede the structural damage of RPE in choroidal neovascularization.\textsuperscript{15} It has been documented that VEGF is essential to increase vascular permeability since it changes the blood-retina barrier, thereby affecting the exudation of the retina and choroid.

### Table 2. The comparison of the superficial retinal vessel density measurements between the N-AMD and NN-AMD groups

| VD measurements (%)          | N-AMD group (n=33) | NN-AMD group (n=38) | P*   |
|------------------------------|-------------------|---------------------|------|
| Superficial overall          | 40.59±7.07        | 43.05±4.20          | 0.085|
| Superficial fovea            | 20.82±9.92        | 21.61±6.45          | 0.354|
| Superficial parafovea        | 40.82±6.29        | 46.38±4.74          | 0.039|
| • Temporal quadrant          | 44.45±6.85        | 44.61±4.93          | 0.903|
| • Superior quadrant          | 42.06±7.74        | 47.32±5.16          | 0.045|
| • Nasal quadrant             | 42.09±8.76        | 44.10±4.98          | 0.231|
| • Inferior quadrant          | 41.07±7.42        | 47.91±5.33          | 0.034|

AMD: Age-related macular degeneration, VD: Vessel density, *the independent samples Student's t-test was used.

### Table 3. The comparison of the deep retinal vessel density measurements between the N-AMD and NN-AMD groups

| VD measurements (%)          | N-AMD group (n=33) | NN-AMD group (n=38) | P*   |
|------------------------------|-------------------|---------------------|------|
| Deep overall                 | 42.83±7.23        | 45.59±8.44          | 0.144|
| Deep fovea                   | 31.45±12.69       | 33.48±8.24          | 0.433|
| Deep parafovea               | 45.30±7.23        | 50.18±3.96          | 0.001|
| • Temporal quadrant          | 44.70±8.52        | 51.18±4.11          | <0.001|
| • Superior quadrant          | 45.03±9.54        | 49.67±4.64          | 0.014|
| • Nasal quadrant             | 44.43±11.30       | 50.73±4.18          | 0.002|
| • Inferior quadrant          | 42.33±10.59       | 49.77±4.85          | 0.001|

CNV: Choroidal neovascular membrane, AMD: Age-related macular degeneration, VD: Vessel density, *the independent samples Student's t-test was used.
The anti-VEGF injection can act on the retinal and choroidal vascularization, decrease their vascular permeability, exudation, and modify VD distribution.\textsuperscript{[11]}

The influence of choroidal hemodynamics on the AMD pathogenesis has been well documented, but the impact of retinal vasculature on the AMD pathogenesis has remained unclear. Similar to our findings, a study showed that both superficial and deep retinal vascular layers changed in the late stages of AMD.\textsuperscript{[13]} Moreover, the authors also observed a significant reduction in the mean superficial VD measurements of eyes with intermediate AMD, but not early AMD.\textsuperscript{[19]}

A study concluded that retinal VD measurements showed a reduction in intermediate AMD when compared to age-matched normal controls, but longitudinal alterations in retinal capillary plexus did not represent a correlation with drusen volume increase during 12 months.\textsuperscript{[20]} A retrospective study reported that superficial retinal VD reduced in N-AMD when compared to NN-AMD, but anti-VEGF therapy did not have an impact on the VD measurements.\textsuperscript{[21]}

The results of a study showed that the existence of the cilio-retinal artery can prevent the development of N-AMD, but whether the artery traverses the center of the fovea did not affect this condition.\textsuperscript{[22]} This suggests that macular retinal perfusion might have an important effect on the pathogenesis of AMD or CNV, but foveal center perfusion might not have such an important role. The findings of the present study representing similar superficial and deep foveal VD measurements in the N-AMD and NN-AMD groups support this situation.\textsuperscript{[21, 22]}

The current study focused on the superficial retinal VD besides the deep retinal VD, because the VD measurements in the superficial retinal layer have been well established using the OCTA system and are less likely to be affected by the N-AMD pathologies located in the outer layers of the retina.\textsuperscript{[21, 22]} The benefit of examining the superficial layers of the retina is abstinence of artifacts and poor signal quality related to drusen and other pathologies of AMD as well as the avoidance of shadowing actions that may affect the deeper layers of the retina while measuring VD using OCTA.\textsuperscript{[24]} It has been also demonstrated that anti-VEGF injections impaired the deep retinal VD and the choriocapillaris, but not superficial VD in exudative AMD, indicating the requirement for more robust investigations of different layers of the retina.\textsuperscript{[25]}

However, various OCTA algorithms measure different borders for the segmentation of retinal layers, which might give different results in the VD measurements.\textsuperscript{[26]}

Nonetheless, this study has some limitations, including a relatively small sample size, retrospective nature, and lack of choriocapillaris measurements. Due to the retrospective nature of our study, we could not hypothesize whether decreased retinal VD might increase the risk of NN-AMD progression to N-AMD development. Considering these limitations, new studies with larger sample sizes and the inclusion of choriocapillaris measurement should be conducted in future investigations.

**Conclusion**

Our results support the interesting opinion that the vasculature of the superficial retina might have an impact on the pathogenesis of the N-AMD and may enable prognostic data regarding the risk for the development and progression of the N-AMD.\textsuperscript{[17, 19-21, 25, 26]} Regardless of the number of intravitreal injections, N-AMD lesions may cause a significant decrease additionally in certain areas of the superficial retinal layer besides the prominent reductions in all areas of the deep retinal layer. As expected, decreased blood flow and visual impairment were noted in the N-AMD group. To the best of our knowledge, this study might be among the limited reports demonstrating reduced superficial and deep retinal VD measurements in N-AMD patients when compared to NN-AMD patients.

**Disclosures**

**Ethics Committee Approval:** The study was adhered to the requirements of the Declaration of Helsinki and approved by the local ethics committee (Date: December 01, 2020, Number: 3022)

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.D.; Design – M.D., C.A.; Supervision – M.D.; Materials – E.B.A.O., Z.Y.; Data collection &/or processing – Z.Y., E.B.A.O.; Analysis and/or interpretation – T.U., C.A.; Literature search – C.A., T.U.; Writing – C.A.; Critical review – M.D.

**References**

1. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health 2021;9:e144–60.
2. Demir M, Akarsu P, Güven D, Sendül Y, Çınar S. Intravitreal injections and complications. Sisli Etfal Hastan Tip Bul 2015;49:35–9.
3. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmo 2003;48:257–93.
4. Spaidge RF, Fujimoto JG, Waheed NK, Sadda SR, Stuurghen G. Optical coherence tomography angiography. Prog Retin Eye Res 2018;64:1–55.
5. Scharf J, Corradetti G, Corvi F, Sadda S, Sarraf D. Optical coherence tomography angiography of the choriocapillaris in age-related macular degeneration. J Clin Med 2021;10:751.
6. Corvi F, Cozzi M, Invernizzi A, Pace L, Sadda SR, Staurenghi G. Optical coherence tomography angiography for detection of macular neovascularization associated with atrophy in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2021;259:291–9.

7. Inoue M, Jung JJ, Balaratnasingam C, Dansingani KK, Dhrami-Gavazi E, Suzuki M, et al; COFT-1 Study Group. A comparison between optical coherence tomography angiography and fluorescein angiography for the imaging of type 1 neovascularization. Invest Ophthalmol Vis Sci 2016;57:OCT314–23.

8. Hilely A, Au A, Freund KB, Loewenstein A, Souied EH, Zur D, et al. Non-neovascular age-related macular degeneration with subretinal fluid. Br J Ophthalmol 2021;105:1415–20.

9. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol 2015;133:45–50.

10. Meyer JH, Larsen PP, Strack C, Harmening WM, Krohne TU, Holz FG, et al. Optical coherence tomography angiography (OCT-A) in an animal model of laser-induced choroidal neovascularization. Exp Eye Res 2019;184:162–71.

11. Zerbib J, Delcourt C, Puche N, Querques G, Cohen SY, Sahel J, et al. Risk factors for exudative age-related macular degeneration in a large French case-control study. Graefes Arch Clin Exp Ophthalmol 2014;252:899–907.

12. Snyder K, Yazdanyar A, Mahajan A, Yiu G. Association between the cilioretinal artery and choroidal neovascularization in age-related macular degeneration: a secondary analysis from the age-related eye disease study. JAMA Ophthalmol 2018;136:1008–14.

13. Sugiura T, Dohi Y, Takase H, Yamashita S, Fuji S, Ohte N. Oxidative stress is closely associated with increased arterial stiffness, especially in aged male smokers without previous cardiovascular events: a cross-sectional study. J Atheroscler Thromb 2017;24:1186–98.

14. Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. JAMA Ophthalmol 2014;132:338–45.

15. Remsch H, Spraul CW, Lang GK, Lang GE. Changes of retinal capillary blood flow in age-related maculopathy. Graefes Arch Clin Exp Ophthalmol 2000;238:960–4.

16. Zarbin MA, Rosenfeld PJ. Pathway-based therapies for age-related macular degeneration: an integrated survey of emerging treatment alternatives. Retina 2010;30:1350–67.

17. Klaassen I, Van Noorden CJ, Schlingemann RO. Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. Prog Retin Eye Res 2013;34:19–48.

18. Terasaki H, Sakamoto T, Shirasawa M, Yoshiihara N, Otsuka H, Sonoda S, et al. Penetration of bevacizumab and ranibizumab through retinal pigment epithelial layer in vitro. Retina 2015;35:1007–15.

19. Toto L, Borrelli E, Di Antonio L, Carpineto P, Mastropasqua R. Retinal vascular plexuses' changes in dry age-related macular degeneration, evaluated by means of optical coherence tomography angiography. Retina 2016;36:1566–72.

20. Reiter GS, Told R, Schlantz FG, Baumann L, Schmidt-Erfurth U, Sacu S. Longitudinal association between drusen volume and retinal capillary perfusion in intermediate age-related macular degeneration. Invest Ophthalmol Vis Sci 2019;60:2503–8.

21. Lee SC, Tran S, Amin A, Morse LS, Moshiri A, Park SS, et al. Retinal vessel density in exudative and nonexudative age-related macular degeneration on optical coherence tomography angiography. Am J Ophthalmol 2020;212:7–16.

22. Snyder K, Yiu GC. Statistical Issues on evaluating association between the cilioretinal artery and age-related macular degeneration-reply. JAMA Ophthalmol 2019;137:856.

23. Durbin MK, An L, Shemonski ND, Soares M, Santos T, Lopes M, et al. Quantification of retinal microvascular density in optical coherence tomographic angiography images in diabetic retinopathy. JAMA Ophthalmol 2017;135:370–6.

24. Alten F, Lauermann JL, Clemens CR, Heiduschka P, Eter N. Signal reduction in choriocapillaris and segmentation errors in spectral domain OCT angiography caused by soft drusen. Graefes Arch Clin Exp Ophthalmol 2017;255:2347–55.

25. Hikichi T, Agarie M. Reduced vessel density of the choriocapillaris during anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2019;60:1088–95.

26. Spaide RF, Curcio CA. Evaluation of segmentation of the superficial and deep vascular layers of the retina by optical coherence tomography angiography in normal eyes. JAMA Ophthalmol 2017;135:259–62.