Adult-Onset Foveomacular Vitelliform Dystrophy and Early Stage Macula: An OCTA Study

Neşe Çetin Doğan[1], Emine Çiloğlu[2]

ABSTRACT

Purpose: To investigate alterations of superficial and deep retinal vascular densities, macular thickness and the area of the foveal avascular zone (FAZ) in patients with adult-onset foveomacular vitelliform dystrophy (AOFVD) and dry age-related macular degeneration (AMD).

Methods: In this retrospective study fifteen eyes of 13 patients affected by AOFVD, 42 eyes of 42 patients affected by AMD and 27 eyes of 20 healthy individuals were enrolled. AMD eyes was divided into two groups as patients with early and intermediate stage lesions. Fourteen eyes were affected by early AMD, 28 eyes were affected by intermediate AMD. Ophthalmologic examination including color fundus photography, fundus floresein angiography, fundus autofloresence, optic coherence tomography angiography (OCTA) were performed all patients. Outcome measures were superficial (SVD) and deep vessel density (DVD), foveal (FMT)and parafoveal macular thickness (PMT) and foveal avascular zone (FAZ). Statistical analyses were performed using SPSS 16.0 Software (SSPS Inc, Chicago, Illinois, USA). The descriptive statistics were presented as as frequency (percentage) and mean±SD. The normality was checked by Kolmogorov-Smirnov test, but none of the continuous variables were distributed normally ($p<0.05$). Therefore, Kruskal-Wallis test was used for comparing the variables between the study groups. The relations between the categorical variables was determined by Chi-square test. $p<0.05$ values were considered as statistically significant result for 5% type-I error.

Results: Foveal and parafoveal SVD were similar in all groups and statistically were not meaningful. When foveal DVD were compared between the groups, there was no difference in the subgroups of AMD with AOFVD separately, while parafoveal DVD was found statistically significant difference only between early- AMD (52.30±3.75 %) and AOFVD (51.77±6.14 %) ($p = 0.016$). When the groups were compared with AOFVD, there was no statistically significant difference between the groups in terms of FAZ. ($p=0.332$) FMT was found as significantly higher in the AOFVD group than all other groups ($p=0.001$). PMT did not differ significantly when compared with AOFVD separately ($p=0.175$). There were no statistically difference between the AMD stages and healty eyes in regard to DVD.

Conclusion: We demonstrated that parafoveal DVD were significantly increased in patients with AOFVD, after the comparison with intermediate patients with AMD. On the other hand, it was decreased, compared to early AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in AMD that OCTA could be useful in differentiate early stages of these two diseases. In addition, considering the vascular pathologies likely to play a role in the progression of early AMD to intermediate AMD, OCTA can be considered as a useful non-invasive method in early AMD intermediate AMD staging and progression follow-up.

Keywords: Adult-onset foveomacular vitelliform dystrophy, age-related macular degeneration, optic coherence tomography angiography, capillary density.

INTRODUCTION

Adult Onset Foveomacular vitelliform dystrophy (AOFVD) is a clinically heterogeneous maculopathy and one of the most prevalent forms of macular degeneration. In 1974 Gass first described in a case report called peculiar foveomacular dystrophy[1]. Later in 1997 it was renamed AOFVD and has since been classified as one of the several forms of pattern dystrophy[2]. It mainly occurs between 4th and 6th decades of life[3]. AOFVD is inherited and usually presents as unilateral or bilateral subfoveal or perifoveal yellowish lesions above the retina pigment epithelium and under the neurosensorial retina[4,5]. Multimodal imaging is useful in diagnosis of AOFVD. On fundus autofloresence (FOF), AOFVD is characterized by hyperautofloresence due to abnormal accumulation of lipofuscin[6]. An early central hypofloresence surrounded

1- MD, Adana Training and Research Hospital Adana, Turkey
2- Assist. Prof., Adana Training and Research Hospital Adana, Turkey

Received: 07.04.2021
Accepted: 07.04.2021
Ret-Vit 2021; 30:285-290
DOİ: 10.37845/ret.vit.2021.30.49

Correspondence Adress:
Neşe Çetin Doğan
Adana Training and Research Hospital Adana, Turkey
Phone: +90 542 621 2210
E-mail: drnesecetindgn78@gmail.com

by a ring of hyperflouresence is demostrated by fundus floresein angiography (FFA)[7]. Spectral-domain optic coherence tomography (SD-OCT) shows hyperreflective materials between the retina pigment epithelium and the photoreceptors[8]. OCT angiography (OCTA) is a new dyless imaging modality that visualizes and enables the quantification of the blood flow in retinal and choroidal vessels[9]. OCTA let us to study both the superficial and the deep retinal vascular plexuses[10].

In this study, we aimed to research superficial and deep retinal vascular densities and macular thickness of fovea and parafoveal areas in AOFVD patients and to compare these with AMD and control groups. Although early AMD and AOFVD appear to be clinically similar entities, progression and treatment modalities of diseases are differ. It may be possible to reveal the early differences of these diseases with OCTA.

MATERIALS AND METHODS

In this retrospective study patients 13 eyes of 15 patients with AOFVD and 42 eyes of 42 patients with early and intermediate AMD were included consecutively. In AMD group 14 eyes had early stage AMD and 28 eyes had intermediate stage AMD. As a control group, 27 eyes of 20 age and sex matched healthy subjects were also analysed.

All patients underwent to a complete ophthalmologic examinations, FOF, FFA and OCTA. The study was approved by the local ethical committee (913/2020) and adhered to the tenets of the Declaration of Helsinki.

The diagnosis of AOFVD was based on age >40, well circumscribed area of macular yellowish deposits on fundus examination, hyper autoflourescent spots on FOF and late staining without leakage in FFA. We included only the patients affected by either the vitelliform or the pseudohypopyon or the vitelliruptive stage. Patients in atrophic and fibrotic stage or progress in to neovascular stage were excluded.

42 eyes of 42 patients affected by AMD investigated and staging was based on the clinical AMD classification proposed by Ferris FL et al in 2013[11]. 63-125 µ drusen without pigmentary abnormalities considered as early AMD subjects with large drusen> 125µ or with pigmentary abnormalities considered as intermediate AMD. Staging was determined by two independent investigators in a blind manner. No patients affected by late AMD with neovascularization or geograghic atrophy included to analysis.

Exclusion criteria for both AOFVD and AMD were similar. Evidence or history of neovascularization, presence of geographic atrophy, previous ocular surgery or intravitreal therapy, any maculopathy secondery to other diseases including vitreomacular traction syndrome, epiretinal membrane.

Foveal and Parafoveal SVD, DVD, FAZ, FMT and PMT were measured with OCTA device. XR Avanti AngioVue OCTA (Optovue Inc, Fremont, CA) is a device with a high-speed of 70,000 axial scans per second, using a high-speed of 70,000 axial scans per second, using al ighth source of 840 nm, an axial resolution of 5µm. The ANgiouVue OCTA system based on split spectrum amplitude decorrelation angiography algorithm (Software version is 2017.1.0.151) uses blood flow as intrinsic contrast. When using this software, it makes it possible to noninvasively visualize the retinal and choroidal vasculature via motion contrast. Each OCTA volume was acquired in 3 seconds, and two orthogonal OCTA volumes were acquired to perform motion correction to minimize motion artifacts due to microsaccades and fixation changes. Before imaging, each subject's pupil was dilated with a combination of 0.5% tropicamide and 10% phenylephrine. Study participants underwent SD-OCT imaging following a protocol that included AngioVue OCT 3D volume set of 3 mmx3 mm, consisting of 304 pixelsx304 pixels in the transverse dimension. Objective quantification of vessel density was evaluated for each eye using the split-spectrum amplitude decorrelation angiography software. Quantitative analysis was performed on the OCTA en face image using the AngioVue software. The vessel density was defined as the percentage area occupied by vessels in a circle region of interest centered on the center of the FAZ and with a diameter of 2.5 mm. The AngioVue software automatically split the region of interest into two fields: 1. the foveal area, a central circle with a diameter of 1 mm; and 2. the parafoveal area that constitutes the remaining part inside the region of interest. The AngioVue software automatically outputs the vessel density percentage inside the foveal area (foveal vessel density) and the parafoveal area (parafoveal vessel density). (Figure 1, 2, 3)

Statistical analyses were performed using SPSS 16.0 Software (SSPS Inc, Chicago, Illinois, USA). Power analysis was performed to determine the sample size as 15 patients for each study groups. The sample size was calculated using 5% type-I error, 0.85 power and 0.73 effect size obtained by measurements in the pilot study. The descriptive statistics were presented as as frequency (percentage) and mean±SD. The normality was checked by Kolmogorov-Smirnov test, but none of the continuous variables were distributed normally ($p<0.05$). Therefore, Kruskal-Wallis test was used for comparing the variables

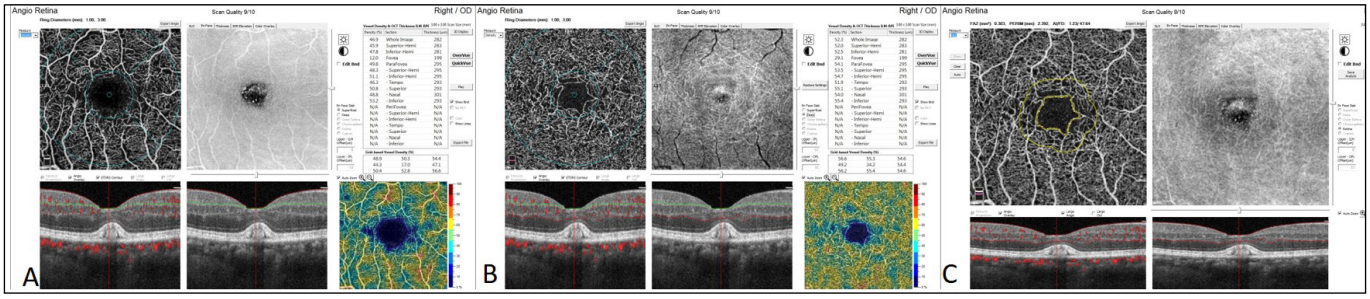

Figure 1: *OCTA figures with segmentation of the retina of adult ocult foveal vitelliform dystrophy. **A**: Superficial vessel density, Foveal macular thickness, Parafoveal macular thickness, **B:** Deep vessel density, **C:** Foveal avascular zone.*

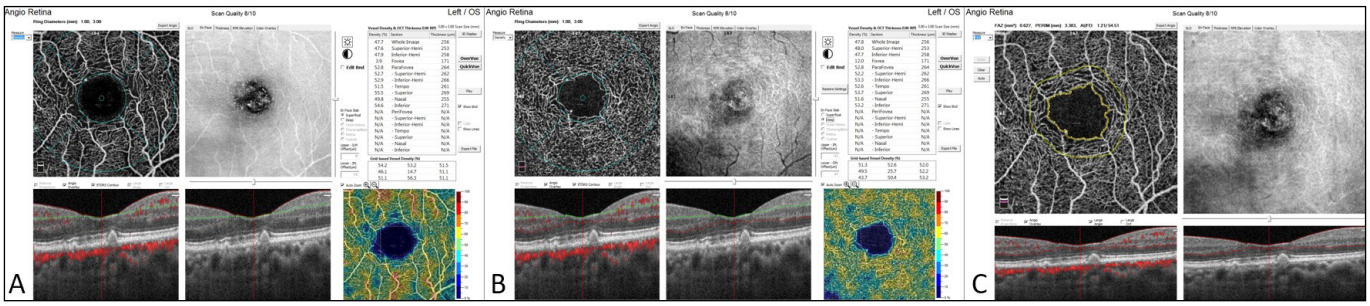

Figure 2: *OCTA figures with segmentation of the retina of early- age related macular degeneration. **A:** Superficial vessel density, Foveal macular thickness, Parafoveal macular thickness, **B:** Deep vessel density, **C:** Foveal avascular zone.*

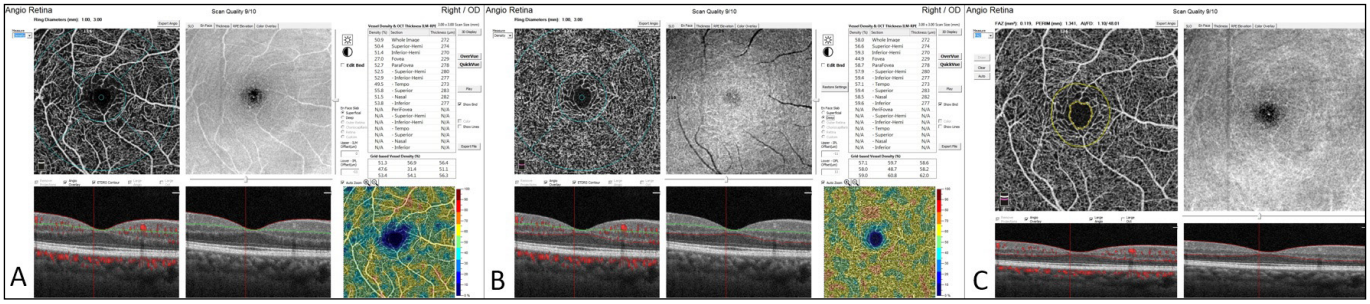

Figure 3: *OCTA figures with segmentation of the retina of healthy subject. **A:** Superficial vessel density, Foveal macular thickness, Parafoveal macular thickness, **B:** Deep vessel density, **C:** Foveal avascular zone.*

between the study groups. The relations between the categorical variables was determined by Chi-square test. $p<0.05$ values were considered as statistically significant result for 5% type-I error.

RESULTS

Mean age of patients with AOFVD was 63.33±7.29 years (54-79 years), patients with early AMD was 64.42±7.91 years (47-73 years), patients with intermediate AMD was 68.35±7.52 (53-78 years) and healty subjects was 66.81±10.18 years (53-76 years) (p=0.245). There was no statistical difference in age and gender between the groups. Demographic data of patients and the healty subjects are reported in the Table 1.

Foveal and parafoveal SVD were not significantly different between the groups (Foveal SVD; AOFVD;

Table 1: *Demographic data of patients and the healty subjects.*

	Patients with AOFVD (n=15)	**Patients with early AMD (n=14)**	**Patients with Intermediate AMD (n=28)**	**Healty Subjects (n=27)**	***p***
Age, years	63.33±7.29	64.42±7.91	68.35±7.52	66.81±10.18	*0.245*
Gender, Male n (%) Female n (%)	10 (66.7) 5 (33.3)	7 (50.0) 7 (50.0)	14 (50.0) 14 (50.0)	15 (55.6) 12 (44.4)	*0.751*

AOFVD: Adult ocult foveal vitelliform dystrophy, **AMD:** Age related macular degeneration

16.21±5.75 %, Early AMD: 15.41±5.97%, intermediate AMD:12.58±4.41% Healty subjects: 15.41±5.97%) Parafoveal SVD; AOFVD; 46.39±7.30%, Early AMD: 42.14±7.03%, intermediate AMD:44.18±6.01% Healty subjects: 46.5±4.91%) (Table 2).

When foveal DVD were compared between the groups, there was no difference in the subgroups of AMD with AOFVD separately (Foveal DVD; AOFVD; 34.44±6.95 %, Early AMD: 28.65±6.77%, intermediate AMD: 27.96±6.57% Healty subjects: 31.82±6.13%). Parafoveal DVD was found statistically significant only between early AMD and AOFVD (P = 0.016) (Table 2).

There was no statistically significant difference according to FAZ between the groups (p=0.332) (Table 2).

FMT was found as significantly higher in the AOFVD group than all other groups (p=0.001). PMT did not differ significantly when compared with AOFVD separately (p=0.175) (Table 2).

DISCUSSION

In this study, we performed a quantitative analysis of vessel density values measured with OCTA in patients with AOFVD and early-intermediate AMD. As a result of the study, we found a significant difference in parafoveal DVD only between the early AMD group and the AOFVD group. Also we detected increased FMT in AOVFD patients compared to all other groups.

Vitelliform lesions are known to be similar to subretinal deposits, which are also associated with AMD. In the long-term follow-up, it has been shown that patients who were diagnosed with AMD and were followed-up turned into vitelliform degeneration in the following years[12]. Perhaps patients who were diagnosed with vitelliform at the time of diagnosis were considered as early stage AMD in earlier years.

Many factors have been implicated in AMD pathogenesis and progression, such as inflammation, oxidative damage, ageing, genetic predisposition and environmental elements[13,14]. In recent years, several studies have reported vascular factors playing an important role in AMD pathogenesis[15-18].

It is known that retinal vasculature and choroidal vasculature are damaged in AMD eyes and that this impairment might contribute to AMD progression[15,16]. Systemic hypertension[19], dietary fat intake[20,21] and a history of coronary, carotid and peripheral vascular disease[22] are risk factors for AMD and for vascular disease. AOFVD is seen at earlier ages than AMD, genetic factors are more prominent and has a better visual prognosis than AMD.

It was showed in histopatologically that the subretinal vitelliform deposists were composed primarily of extraselular fotoreseptor debris and RPE derived material. It was hypothesised that RPE hypertrophy, RPE attenuetion and finally loss of apical RPE microvilli and the release of pigment as subretinal deposits are the stages in AOVFD. Unlike typically AMD, in which bazal laminar deposits are an early finding, photoreseptors seem to be first cells affected in AOFVD.[23]

Few OCTA studies are available with AOFVD patients[24-28]. The application of OCTA to AOFVD was first described by Luipidi et al. They compared OCTA to conventional FFA in its ability to detect coroidal neovascularisation in AOFVD. In their study with 25 eyes with AOFVD from each stage, they reported 80% sensitivity and 100% specificity for OCTA when compared with FFA[24].

Table 2: *The optical coherence tomography angiography findings of the groups.*

	AOFVD	Healthy subjects	Early AMD	Intermediate AMD	*p*
Foveal SVD (%)	16.21±5.75	15.41±5.97	14.26±5.37	12.58±4.41	*0.115*
Parafoveal SVD (%)	46.39±7.30	46.50±4.91	42.14±7.03	44.18±6.01	*0.130*
Foveal DVD (%)	34.44±6.95	31.82±6.13	28.65±6.77	27.96±6.57	*0.531*
Parafoveal DVD (%)	51.77±6.14*	51.86±4.68	52.30±3.75*	49.99±5.48	***0.016***
FAZ (µm)	0.28±0.08	0.27±0.09	0.35±0.09	0.34±0.10	*0.332*
FMT (µm)	246.40±47.12+,*,†	220.07±17.03+	214.07±17.84*	206.00±26.86†	***0.001***
PMT (µm)	282.40±23.42	275.70±18.10	270.21±20.18	267.10±20.41	*0.175*

SVD: Superficial vessel density, **DVD:** Deep vessel density, **FAZ:** Foveal avascular zone, **FMT:** Foveal macular thickness, **PMT:** Parafoveal macular thickness, **AOFVD:** Adult ocult foveal vitelliform dystrophy, **AMD:** Age related macular degeneration

*: significant at 0.05 level accroding to Kruskal-Wallis post-hoc test (AOFVD and Early AMD groups)

+,*,†: significant at 0.05 level accroding to Kruskal-Wallis post-hoc test (AOFVD and Early AMD, AOFVD and healthy, AOFVD and Intermediate AMD groups)

Querques et al performed a morphological OCTA study in 2016 with AOFVD in various stages, vitelliform, pseudohipopion and vitelliruptive[25]. They noted displacement of blood vessels in the superficial and deep retinal vascular layers because of subretinal and subfoveal deposits. Furthermore they noted rarefaction of blood vessels in choriocapillaris. They stated that it is controversial whether foveal flow decreases are due to blood rarefaction secondary to subfoveal accumulation or to the pathogenesis of the disease.

Parodi et al.in their study in 2017, they found increased flow density in the parafoveal and perifoveal deep retina vascular layers when compared with the healthy control group in 20 patients with AOFVD. They suggested that this may be caused by the AOFVD subfoveal deposit accumulation forcing retinal vessels to migrate. However, although this contradicted the argument, FAZ did not differ between the groups in the study of Parodi and in our study. The Parodi also suggested that the increased flow density may be related to increased metabolic dysfunction due to accumulation in AOFVD patients[26].

Treder et al in their study in 2017 compared the patients with AOFVD to the control group and reported reduced flow density in both superficial and deep vascular layers. They found no change in FAZ and parafoveal macular thickness[27].

Totto et al. in their study comparing AOFVD and intermediate AMD patients, demostrated that both superficial and deep vessel densities are significantly increased in patients with AOFVD. They noted that pathogenic mechanisms are different in AOFVD from those in intermediate AMD and OCTA could be useful to diffirentiate early stages of these two diseases[28]. In our study, as in this study, it was found higher parafoveal DVD in the AOFVD group than in the intermediate AMD group, although it was not statistically significant. However, a significantly lower parafoveal DVD was detected in AOFVD compared to the early AMD group. In the light of these findings, we can think that, unlike AOFVD, in the progression of early AMD to intermediate AMD, first increased and then decreased parafoveal DVD resulted in a decrease in vascularity with the addition of vascularity due to increased metabolic activity in the early period and atrophy and RPE damage in the later period. To clarify the vascular theory further evaluation including FFA and OCTA corelation is advised. In the pathogenesis of both AOFVD and AMD, there are differences in the results reported in the literature due to the possibility of many different factors. More comprehensive studies are needed on this subject.

Among the limitations of our study; we can say small sample size, the unequal patient distribution between groups. The number of patients included in the study was different between the groups due to the lower incidence of AOFVD. Another limitation is that AOFVD is not divided into staging and the groups are not compared with each other. To support this study further comparative studies with larger series are needed.

As a result; it is important to differentiate the two pathologies in the early period because the course, prognosis and treatment approach of AMD and AOFVD are different. In this context, OCTA, which is a new technology for the early separation of AMD and AOFVD, two entities that may appear with similar morphological images, is an effective imaging method.

Declarations of interest: none.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Gass JD. A clinicopathologic of a peculiar foveomacular dystrophy. Trans Am Ophthalmol Soc 1974; 72: 139-56
2. Gass JD. Stereoscopic Atlas of Macular Diseases. Mosby, St Louis. 1997.
3. Greaves AH, Sarks JP, Sarks SH. Adult vitelliform macular degeneration: A clinical spectrum. Aust N Z J Ophthalmol. 1990 May;18: 171-8.
4. Jaffe GJ, Schatz H. Histopathologic features of adult-onset foveomacular pigment epithelial dystrophy. Arch Ophthalmol 1988; 106: 958-60.
5. Patrinely JR, Lewis RA, Font RL. Foveomacular vitelliform dystrophy, adult type. A clinicopathologic study including electron microscopic observations. Ophthalmology 1985; 92: 1712-8.
6. Parodi MB, Iacona P, Pedio M, et al. Autofluorescence in adult-onset foveomacular vitelliform dystrophy. Retina 2008; 28, 801-7.
7. Renner AB, Tillac H, Kraus H, et al. Morphology and functional charecteristics in adult vitelliform macular dystrophy. Retina 2004; 24, 929-39.
8. Puche N, Querques G, Benhamou N, et al. High-resolution spectral domain optical coherence yomography featuresin adult onset foveomacular vitelliform dystrophy. Br. J. Ohthalmol. 2010; 94:1190-6.
9. Spaide RF, Klancnik JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol 2015; 133:45-50.
10. Makita S, Hong Y, Yamanari M, et al. Optical coherence angiography. Opt Express 2006; 14:7821-7840.

11. Ferris FL, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. Ophthalmology 2013; 120:844-851.
12. Chowers I, Tiasano L, Audo I, et al. Adult-onset foveomacular vitelliform dystrophy: A fresh perspective. Prog Retin Eye Res 2015; 47:64-85.
13. Zarbin MA, Rosenfeld PJ. Pathway-based therapies for age-related macular degeneration: an integrated survey of emerging treatment alternatives. Retina 2010; 30:1350-67.
14. Leveziel N, Tilleul J, Puche N, et al. Genetic factors associated with age-related macular degeneration. Ophthalmologica 2011; 226:87-102.
15. Wang JJ, Mitchell P, Rochtchina E, et al. Retinal vessel wall signs and the 5 year ncidence of age related maculopathy: the Blue Mountains Eye Study. Br J Ophthalmol 2004; 88:104-9.
16. Remsch H, Spraul CW, Lang GK et al. Changes of retinal capillary blood flow in age-related maculopathy. Graefes Arch Clin Exp Ophthalmol 2000; 238:960-4.
17. Boltz A, Luksch A, Wimpissinger B, et al. Choroidal blood flow and progression of age-related macular degeneration in the fellow eye in patients with unilateral choroidal neovascularization. Invest Ophthalmol Vis Sci 2010; 51:4220-5.
18. Feigl B. Age-related maculopathy linking aetiology and pathophysiological changes to the ischaemia hypothesis. Prog Retin Eye Res 2009; 28:63-86.
19. Hyman L, Schachat AP, He Q, et al. Hypertension, cardiovascular disease, and age-related macular degeneration. Age-Related Macular Degeneration Risk Factors Study Group. Arch Ophthalmol 2000; 118:351-8.
20. Mares-Perlman JA, Brady WE, Klein R, et al. Dietary fat and age-related maculopathy. Arch Ophthalmol 1995; 113:743-8.
21. Zerbib J, Delcourt C, Puche N, 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.
22. Vingerling JR, Dielemans I, Bots ML, et al. Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. Am J Epidemiol 1995; 142:404-9.
23. Arnold JJ, Sarks JP, Killingsworth MC, et al. Adult vitelliform macular degeneration: A clinicopathological study. Eye (Lond) 2003; 17:717-26.
24. Lupidi M, Coscas G, Cagini C, et al: Optical coherence tomography angiography of a choroidal neovascularization in adult onset foveomacular vitelliform dystrophy: pearls and pitfalls. Invest Ophtahalmol Vic Sci 2015; 56:7638-45
25. Querques G, Zambrowski O, Corvi F, et al: Optical coherence tomography angiography in adult onset foveomacular vitelliform dystrophy. Br J Ophthalmol 2016; 100: 1724-30.
26. Parodi M, Rabiolo A, Cicinelli M, et al: Quantitive analysis of optical coherence tomography anggiography in adult onset foveomacular vitelliform dystrophy. Retina 2018 38:237-44.
27. Maximillian T, Louermann J L, Alnawaisseh M, et al: Quantitative changes in flow density in patients with adult onset foveomacular vitelliform dystrophy: an OCT angiography study. Graefes Arch Clin Exp Opthalmol 2018;256:23-8 .
28. Toto L. Borrelli E, Mastropasqua R, et al: Adult-Onset Foveomacular Vitelliform Dystrophy Evaluated by Means Of Optical Coherence Tomography Angiography. A comparison with Dry Age-related macular degeneration and healty eyes. Retina 2018;38: 731-8.