

Relation between Fundus Autofluorescence and Optical Coherence Tomography in Age Related Macular Degeneration

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ABSTRACT

Background: age-related macular degeneration (AMD) is a macular neurodegenerative disease that nowadays constitutes one of the main socioeconomic health issues worldwide, affecting the elderly population. The exponentially increasing prevalence of AMD is linked to progressive aging of the population, and it is the leading cause of legal blindness in the developed world.

Objective: the study was designed to assess the relation between fundus autofluorescence (FAF) and Optical Coherence Tomography (OCT) in cases of age related macular degeneration.

Patients and Methods: this study is prospective randomized, non-interventional uncontrolled cross-sectional study was conducted on thirty patients. These patients already diagnosed to have age related macular degeneration either dry or wet form by fundus examination.

Results: it was found from this study fifty eyes of thirty patients having AMD, Sex distribution in female more than male, age distribution revealed that the age ranged from 50 to 75 years, FAF and OCT cannot replace FFA in cases of CNV.

Conclusion: FAF provides the opportunity to evaluate the retinal functional status. OCT obtains a detailed picture of the retinal anatomy.

Keywords: Age related macular degeneration, FAF, OCT.

INTRODUCTION

Age-related macular degeneration (AMD) is a multifactorial disease that represents the most common cause of irreversible visual impairment among people over the age of 50 in Europe, the United States, and Australia, accounting for up to 50% of all cases of central blindness⁽¹⁾.

Risk factors of AMD are heterogeneous, mainly including increasing age and different genetic predispositions, together with several environmental/epigenetic factors, that is, cigarette smoking, dietary habits, and phototoxic exposure. In the aging retina, free radicals and oxidized lipoproteins are considered to be major causes of tissue stress resulting in local triggers for parainflammation, a chronic status which contributes to initiation and/or progression of many human neurodegenerative diseases such as AMD⁽¹⁾.

AMD is primary characterized by the development of drusen, Retinal pigmented epithelium (RPE) dystrophy, macular pigmentary changes, and/or thickening of Bruch's membrane⁽²⁾. Advanced AMD can manifest as either dry form or wet one. In dry AMD, geographic atrophy with RPE and photoreceptors degenerative changes occurs. Conversely, wet AMD is characterized by the presence of choroidal neovascularization (CNV) with exudative and hemorrhagic phenomena leading to fibrotic scar formation⁽²⁾.

Due to its heterogeneous presentation, it can be challenging to distinguish AMD from several macular diseases that can mimic the features of AMD. This clinical overlap may potentially lead to misdiagnosis⁽²⁾.

Fundus autofluorescence (FAF) imaging is a noninvasive technique that can acquire a topographic map of the lipofuscin distribution in the retinal pigment epithelium (RPE) cells. Earlier studies have shown that excessive accumulation of lipofuscin in the RPE cells can occur in various retinal diseases, *e.g.* retinitis pigmentosa and age-related macular degeneration⁽³⁾.

Autofluorescence pattern observed in the FAF images depends on accumulation of lipofuscin, and a normal FAF pattern indicates the presence of intact photoreceptors and normal RPE function. On the other hand, an abnormal hyperautofluorescence level indicates increased metabolic load on the RPE due to degenerated photoreceptor outer segments. A hypoautofluorescent pattern indicates an absence or death of photoreceptor cells following RPE atrophy or the presence of materials that block the FAF signals⁽⁴⁾.

Optical coherence tomography (OCT) is now a standard of care in ophthalmology and is considered essential for the diagnosis and monitoring of many retinal diseases⁽⁵⁾.

It is a noninvasive imaging technique that provides high-resolution, cross-sectional images of the retina, retinal nerve fiber layer and the optic nerve head⁽⁶⁾.

Spectral-domain optical coherence tomography (SD-OCT) provides new insights into the understanding of age-related macular degeneration (AMD) but limited information on the nature of hyperreflective tissue at the level of the retinal pigment epithelium⁽⁷⁾.

FAF imaging is an imaging method that provides additional information compared to conventional techniques. It permits to topographically

map lipofuscin distribution of the retinal pigment epithelial while, SD-OCT allows for high-speed, high-resolution imaging of retinal structures and provides non-invasive three-dimensional information on retinal pathology in situ and in real time. It thus leads to a more profound understanding of RPE status ⁽⁸⁾.

AIM OF THE WORK

To study the relation between fundus autofluorescence (FAF) and optical coherence tomography (OCT) in cases of age related macular degeneration (AMD).

PATIENTS AND METHODS

This prospective is randomized, non-interventional uncontrolled cross-sectional study inducted on thirty patients. These patients already diagnosed to have age related macular degeneration either dry or wet form by fundus examination. These patients are collected from the outpatient clinic of ophthalmology department Al-Azhar University Hospitals.

Ethical consideration and Written informed consent:

An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Inclusion Criteria:

- Patients aged 50 years or more.
- Clear media.
- Patients have drusen or any form of AMD (either dry or wet) as diagnosed by fundus examination and FFA

Exclusion Criteria:

- Any other retinal disorders as (Diabetic retinopathy, Hypertensive retinopathy, Retinal vein occlusion and Retinal artery occlusion).
- Any media opacity (Corneal Opacity, Dense Cataract, Vitreous hemorrhage).
- Other causes of CNV (e.g. myopic retinopathy)
- Other degenerative retinal disease.
- Previous retinal surgery.

All subjects were subjected to the following:

1. **Full history:** Age, Sex, Other vitreoretinal diseases or Systemic diseases, with particular emphasis on the symptoms onset, duration, treatment of AMD and its complications, if present.
2. **Comprehensive ophthalmic examination:**
 - a. Visual acuity (BCVA using Snellen's chart, then VA will be converted to log MAR for statistical analysis).
 - b. Anterior segment examination by slit lamp-biomicroscopy.
 - c. Intraocular pressure by applanation tonometry.
 - d. Amsler grid chart.
3. **Fundus examination** by slit lamp-biomicroscopy using VOLK90D lens, indirect ophthalmoscope

after pupillary dilatation with tropicamide 1% and cyclopentolate HCL 1%, were apply two or three drops of 1% solution into each eye, which may be repeated in five to ten minutes if necessary.

4. Ophthalmic investigations:

i. Fluorescein angiography:

- Pupillary dilatation with tropicamide 1% and cyclopentolate HCL 1%.
- Five ml 10% fluorescein sodium were injected rapidly to median antecubital vein or dorsal hand veins. After injection, serial retinal photographs were taken for 5 minutes.
- FAF imaging was done with Topcon triton fundus camera.
- The eye was stimulated by light in the range of 465-490 nm and then it enters into a higher energy state. The molecule emits longer wavelength fluorescence, between 520 and 530 nm.

ii. Optical Coherence Tomography and Fundus Autofluorescence:

- They were done using the Spectral Topcon Triton OCT (DRI OCT Triton swept source OCT, Japan) after pupillary dilatation with tropicamide 1% and cyclopentolate HCL 1% before photography.
- FAF was done with excitation laser beam with wavelength 488 nm and emission filter (barrier filter) 500 nm.

Statistical analysis

Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 20 (SPSS Inc. Released 2011. IBM SPSS statistics for windows, version 20.0, Armonk, NY: IBM Corp.).

Two types of statistical analysis were done:

- a) **Descriptive statistics:** was expressed in: Number (No), percentage (%) mean (X) and standard deviation (SD).
- b) **Analytic statistics:**
 - Student's t-test is a test of significance was used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data.
 - ANOVA test was used for comparison of quantitative variables between more than two groups of normally distributed data with LSD test as post Hoc test, while Kruskal Wallis test was used for comparison of quantitative variables between more than two groups of not normal distributed data with Tamhane's test as post hoc test.
 - Chi-square test (χ^2) or Fischer's Exact test was used as appropriate to study association between qualitative variables.
 - P - Value of < 0.05 was considered statistically

significant.

RESULTS

Fifty eyes of thirty patients having AMD were included in this study after analyzing the data results can be presented as follow:

- **Sex distribution:** The sex distribution revealed that the number of males was 12 patients (40%) and the number of females was 18 patients (60%), Table 1.
- **Age distribution:** The age distribution revealed that the age ranged from 50 to 75 years (table 1). Male patients mean age was 65.16±6.08 years and female patients mean age was 63.11±6.13 years (table 2).

After clinical examination and the FFA, the 50 eyes were classified to 5 groups as regarding drusen (24eyes); GA (5 eyes), CNV (16 eyes), PED (3 eyes), disciform scar (2 eyes).

From table (3): It was found that the visual acuity in the eyes that having Disciform scar was markedly decreased than in eyes with other lesions, and the visual acuity in the eyes that having Drusen was affected less than in eyes with other lesions. From the p value these findings were had significant differences as P less than 0.01.

From table (4): FAF increased in 14 eyes (11 eyes having drusen 78.6% and 3 eyes having PED 21.4%), decreased in 21 eyes (14 eyes having CNV 66.7%, 5 eyes having GA 23.8%, and 2 eyes having DS 9.5%), normal in 6 eyes (4 eyes having drusen 66.7% and 2 eyes having CNV 33.3%) and mixed in 9 eyes (100% having drusen). From the p value these findings were had a significant differences as P less than 0.01.

Table (5) showed that there were significant differences between the studied groups in amsler grid among regarding the lesions (P less than 0.01).

Table (6) showed that there were significant differences between FAF signal intensity regarding RPE changes among the studied groups (P < 0.01).

Table (1): Number and percentage distribution of gender and age categories among the studied group

Gender	No.	%
Male:	12	40.0
Female:	18	60.0
Age (year):		
50-60: 6f, 3m	9	30.0
60-70: 10f, 4m	14	46.7
70 or more: 2f, 5m	7	23.3

Table (2): Mean age for group study regarding sex distribution.

	Male (n=12) Mean ±SD	Female (n=18) Mean ±SD	t- test	P value
Age	65.16 ± 6.08	63.11 ± 6.13	0.90	0.37

Table (3): Mean VA (LogMar) regarding different lesions among study group.

Lesions	VA (LogMar) Mean ±SD	Kruskal Wallis	P value
Drusen (N=24):	0.83 ±0.16	36.86	0.001
CNV (N = 16):	1.28 ±0.17		
PED (N = 3):	1.25 ±0.21		
GA (N = 5):	1.28 ±0.10		
Scar (N = 2):	1.50 ±0.00		

Table (4): The FAF signal intensity regarding the lesion among the studied group

Lesion:	FAF								χ ²	P value
	Decreased (n=21)		Normal (n=6)		Increased (n=14)		Mixed (n=9)			
	No.	%	No.	%	No.	%	No.	%		
Drusen:	0.0	0.0	4.0	66.7	11.0	78.6	9.0	100.0	36.09	0.002
CNV:	14.0	66.7	2.0	33.3	0.0	0.0	0.0	0.0		
PED:	0.0	0.0	0.0	0.0	3.0	21.4	0.0	0.0		
GA:	5.0	23.8	0.0	0.0	0.0	0.0	0.0	0.0		
Scar:	2.0	9.5	0.0	0.0	0.0	0.0	0.0	0.0		

Table (5): Amsler grid among the studied group regarding the lesions

Lesions	Amsler grid				χ ²	P value
	Negative (n=34)		Positive (n=16)			
	No.	%	No.	%		
Drusen:	24	70.6	0	0.0	28.59	0.001
CNV:	3	8.8	13	81.3		
PED:	2	5.9	1	6.3		
GA:	3	8.8	2	12.5		
Scar:	1	2.9	1	6.3		

Table (6): Relationship of different FAF signal intensity regarding RPE changes as seen by OCT

RPE changes:-	FAF								χ^2	P value
	Decreased (n=21)		Normal (n=6)		Increased (n=14)		Mixed (n=9)			
	No.	%	No.	%	No.	%	No.	%		
Undulation:	0.0	0.0	4.0	66.7	11.0	78.6	9.0	100.0	50.32	0.001
Unspecific changes:	16.0	76.2	2.0	33.3	0.0	0.0	0.0	0.0		
Atrophy:	5.0	23.8	0.0	0.0	0.0	0.0	0.0	0.0		
Detached:	0.0	0.0	0.0	0.0	3.0	21.4	0.0	0.0		

CASE (1)

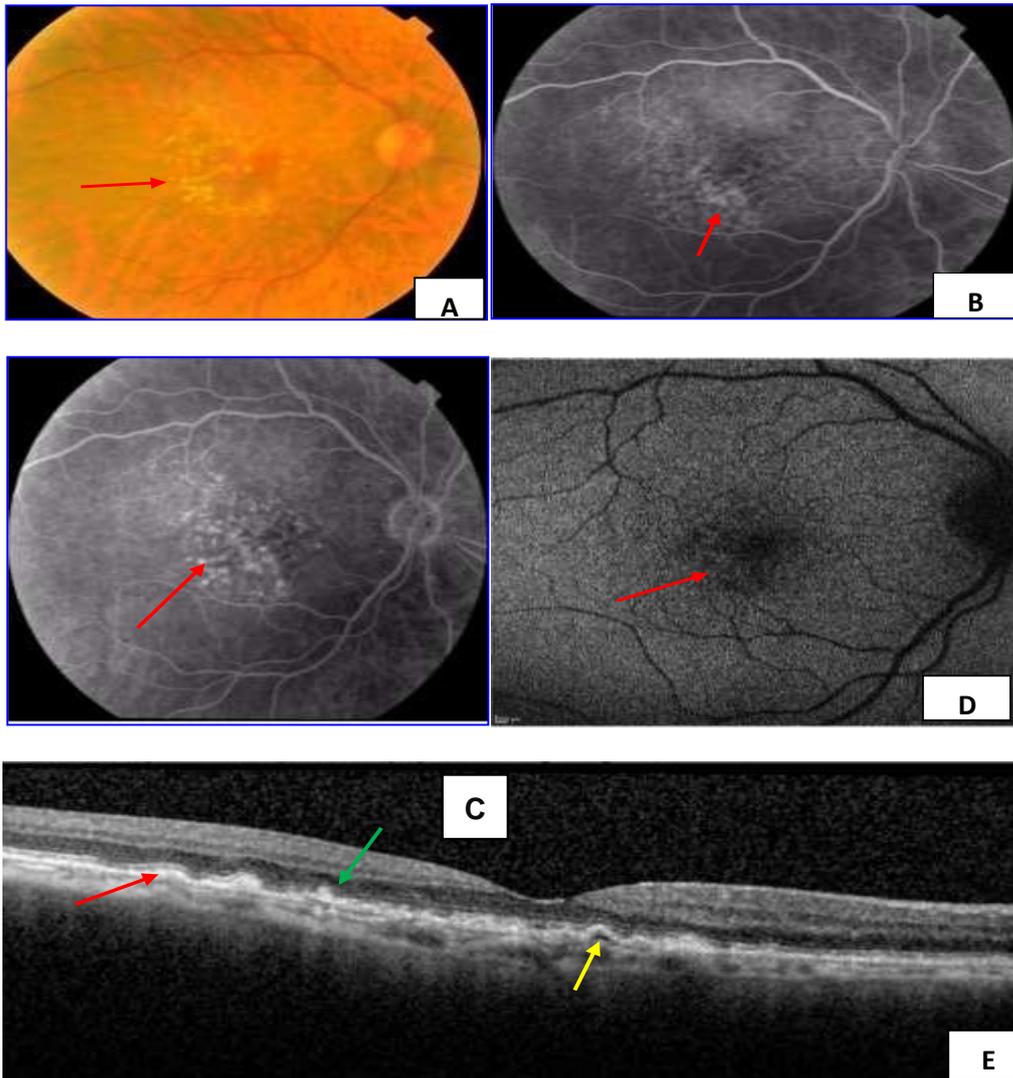


Figure (1): Fundus colored photo (A), early and late FA (B, C), FAF (D) and OCT (E) Of Rt eye in female patient 66 years old with multiple hard drusen.

- **In the Colored photo (A):** there are scattered yellow deposits clustered at the posterior pole.
- **In early and late FA (B, C):** there is early hyperfluorescence with late variable staining with no evidence of dye leakage.
- **In the FAF (D):** there are small hyper autofluorescent spots.
- **In the OCT (E):** there is focal undulation and irregularity in the hyper reflective RPE layer with areas of disrupted RPE, IS-OS junction and ELM (green arrow) and other areas of intact overlying RPE, IS-OS junction and ELM (red arrow), drusenoid RPE detachment (yellow arrow).

CASE (2)

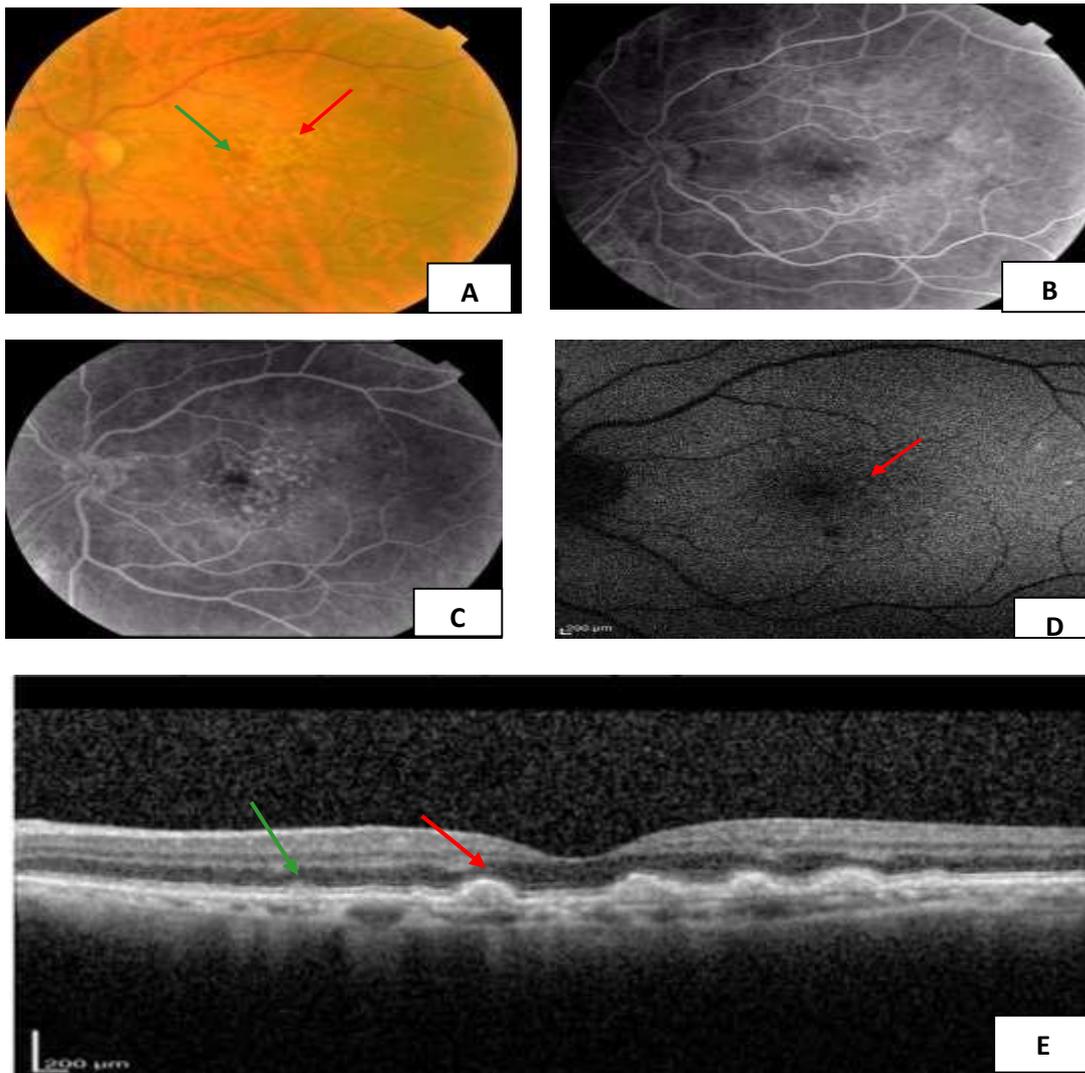


Figure (2): Fundus colored photo (A), early and late FA (B, C), FAF (D) and OCT (E) Of Lt Eye in female patient 65 years old with drusen.

- **In the colored photo (A):** there are scattered yellow deposits (red arrow) with area of RBE hyperpigmentation (green arrow).
- **In the FA (B, C):** there is early hyperfluorescence with late variable staining with no evidence of dye leakage.
- **In the FAF (D):** there are small hyper autofluorescent spots.
- **In the OCT (E):** there is focal undulation and irregularity in the hyper reflective RPE layer with areas of disrupted RPE, IS-OS junction and ELM(green arrow) and other areas of intact overlying RPE, IS-OS junction and ELM (red arrow).

CASE (3)

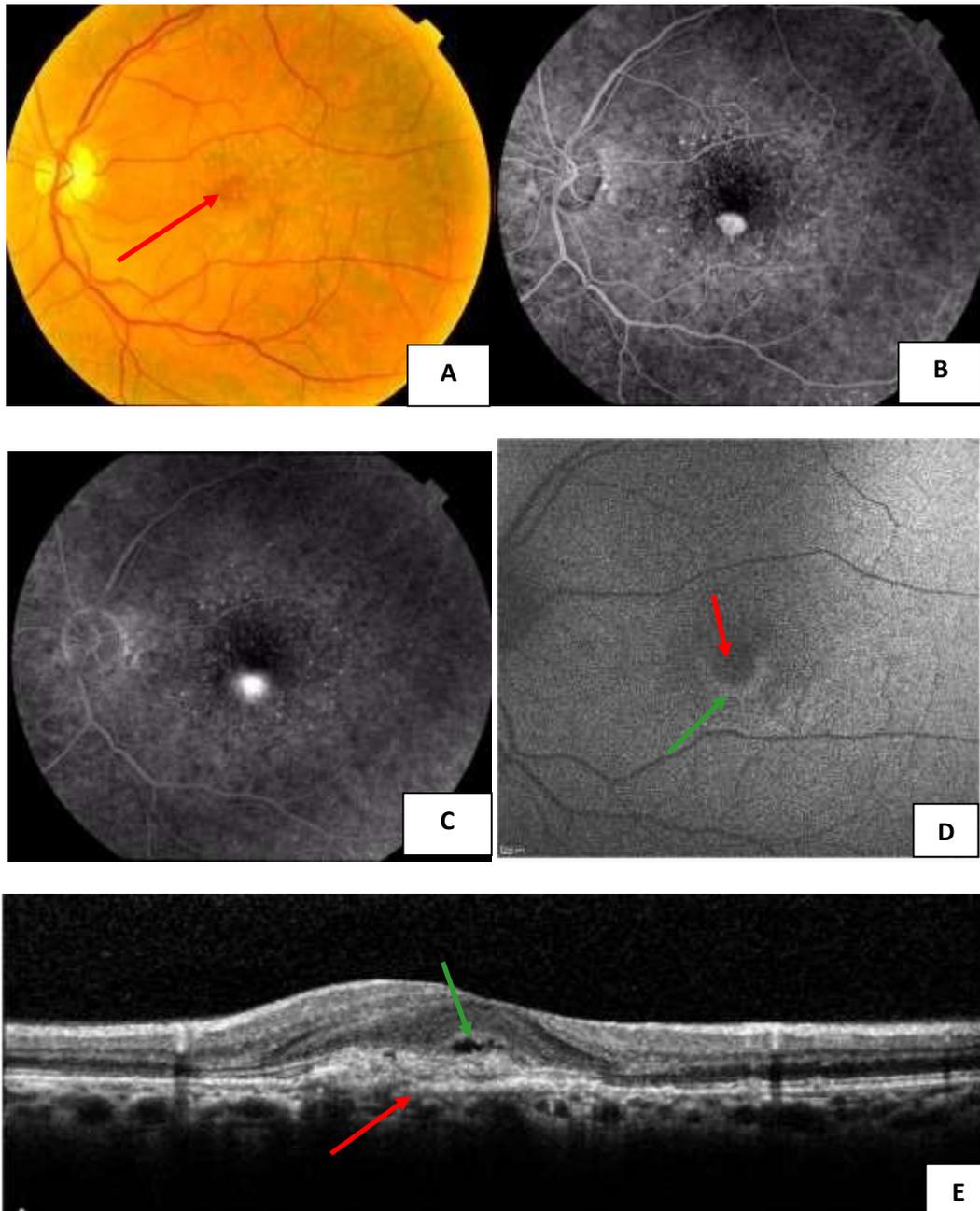


Figure (3): Fundus colored photo (A), early and late FA (B, C), FAF (D) and OCT (E) Of Lt eye in male patient 60 years old with CNV.

- **In the colored photo (A):** there is a round pinkish yellow central macular lesion.
- **In the FA (B, C):** has a lacy filling on FA with early focal hyperfluorescence that increased gradually as angiography proceeds till giving late intense fluorescence (dye leakage).
- **In the FAF (D):** has a corresponding area of decreased FAF (red arrow) with area of increased FAF (green arrow) that extend beyond the angiography defined lesion.
- **In the OCT (E):** hyperreflective fusiform lesion (red arrow) associated with increase thickness of the retina (macular edema), with loss foveal contour, with sensory detachment (green arrow).

DISCUSSION

This study was done on 30 patients aged 50 years or more and having any type of AMD

In the present study, the ages of patients ranged from 50 to 75 years, Male patients mean age was (65.16 ± 6.08) and female patient mean age was (63.11 ± 6.13), 18 patients were females and 12 patients were males. The female to male ratio among studied patients was

60% to 40%, Women tend to have higher prevalence rates than men, and this was in agreement with **Lea Querques et al.** ⁽⁹⁾.

Lea Querques et al. ⁽⁹⁾ found that a total of 58 eyes of 29 patients (21 women and 8 men; mean age: 73 ± 9 years; range, 56 ± 72 years.

Number of patients less than 60 years was 9 patients(30%) and number of patient more than 60 years was 21 patients (70%) this mean that the prevalence of AMD is increased as the age increase this was in agreement with a meta-analysis performed in 2004 by **Friedman et al.** ⁽¹⁰⁾.

Friedman et al. ⁽¹⁰⁾ study conducted on 25000 subjects and found that the prevalence rate increases sharply with age from less than 0.5% in subjects 50 to 60 years, to 12% and 16% in men and women aged 80 years or more respectively.

In the present study, from the mean VA in each class of AMD we noticed that there was marked visual impairment in cases having disciform scar (1.50 ± 0.00), CNV (1.28 ± 0.17) and G A (1.28 ± 0.10) than those having drusen (0.83 ± 0.16) this was in agreement with **Lim et al.** ⁽¹¹⁾, who documented that Most visual loss occurs in the late stages of the disease due to one of two processes a) Neovascular ('wet') AMD b) Geographic atrophy ('late dry').

In the present study: the eyes having drusen were 24 eyes (48%), eyes having CNV were 16 eyes (32%), eyes having G A were 5 eyes(10%),eyes having PED were 3 eyes (6%) and eyes having disciform scar were 2 eyes (4%).

FAF in cases having drusen: were normal in (4 eyes) of cases with drusen although they appeared as hyperfluorescent spots on FFA and as focal undulation in the hyperreflective RPE layer on OCT, FAF were increased in (11eyes) which corresponding to undulation corresponding to undulation and irregularities in the overlying RPE without significant alternation in the overlying IS-OS junction and ELM, and mixed pattern of increase and decrease in (9 eyes) ,decreased FAF this was corresponding to irregularities and disruption in the overlying RPE , IS-OS junction and ELM (window defect), this agreement with **Steffen et al.** ⁽¹²⁾ and **Bindewald et al.** ⁽¹³⁾ who reported that alterations of the FAF signal are not necessarily associated with corresponding funduscopically or angiographically visible drusen or irregular pigmentations, which might indicate that FAF findings represent an independent measure of disease stage and activity.

In the present study, cases that having CNV which appeared as lacy filling with early focal hyperfluorescence that increased gradually throw out the angiograph (leakage of the dye) on FFA ,and appeared as a hyper-reflective, fusiform area of thickening above and adjacent to the RPE with disrupted or intact RPE on OCT , showed decreased FAF signal in most of cases (14 eyes), this agreement with **Dandekar et al.** ⁽¹⁴⁾ who reported long-standing CNV, more areas with decreased intensity were typically detected which was explained by photoreceptor loss and scar formation with increased melanin deposition with increased melanin deposition. But it does not agrees with **McBain et al.** ⁽¹⁵⁾, who reported speculated that typical low FAF signals at the site of the CNV are related to absorption phenomena caused by the CNV growing in the subretinal space, rather than being related to severe damage to the RPE.

In the other cases, CNV showed normal FAF signal (2eyes), this was agreement with **Dandekar et al.** ⁽¹⁴⁾, they demonstrated that in early CNV, patches of continuous or normal autofluorescence were present, corresponding with areas of hyperfluorescence on the comparative fluorescein angiograms. According to the authors, this would imply that the new vessel complex, regardless if classic or occult type, would be external (scleral) to the RPE in the majority of cases.

There were area of increased FAF signal which surround the CNV that was extended beyond the edges of angiographically defined lesion and was corresponding to thickened RPE (multilayered RPE) on OCT, this agrees with **Steffen et al.** ⁽¹²⁾, they reported that slightly increased FAF was seen at the rim of the lesion.

In the present study, cases that having GA (5 eyes) which appeared as hyperfluorescent area on FFA, and as atrophy and sever disruption in the outer retina on OCT, shows marked decreased FAF. This agrees with **Steffen et al.** ⁽¹²⁾, they reported. With disappearance of RPE, LF is also absent resulting in a corresponding marked decrease in FAF intensity The sever reduction of FAF in atrophic area correlates with disruption of the choroidal hyper reflectivity and abrupt transition from hypo reflective to hyper reflective area in the choriocapillaris on OCT. this agrees with **Steffen et al.** ⁽¹²⁾, they reported that the atrophic lesion measured in the FAF image showed closest agreement with the disruption of the choroidal hyper reflectivity seen on OCT and correlates with abrupt transition from hypo reflective to hyper reflective area in the choriocapillaris. This explained by loss of RPE layer which enhance choroidal transmission over the atrophic area.

The margin of geographic atrophy showed increased FAF. This finding is in agreement with **Steffen et al.** ⁽¹²⁾ and **Bindewald et al.** ⁽¹³⁾ they reported that high FAF intensity levels surrounding the atrophic patches and distinct patterns of abnormal FAF in the junctional zone of atrophy. These distinct FAF abnormalities do not show up on funduscopy or any other imaging method and confirm histopathologic

studies that have shown LF and melanolipofuscin-filled RPE cells in the junctional zone between atrophic and normal retina. Studies of photoreceptor function have underscored the importance of abnormal FAF intensities around atrophy and the pathophysiological role of increased RPE LF accumulation in patients with GA due to AMD.

In the present study, in cases that having PED (3 eyes): It was noticed that the PED which appears on FA as an area of increasing fluorescence with well-defined margin and late intense localized fluorescence (pooling of the dye) and on OCT as a broad elevation of the RPE showed increased FAF corresponding exactly with the detached area with ring of decreased FAF around it. This agrees with, **Karadimas and Bouzas**⁽¹⁶⁾ who documented that the new PED typically shows a mild, diffuse, increased FAF corresponding exactly with the detached area with ring of decreased FAF and **Steffen et al.**⁽¹²⁾, who reported that Most PEDs shows a corresponding marked, evenly distributed increase of the FAF signal over the lesion surrounded by a well-defined, less autofluorescent halo delineating the entire border of the lesion ,and later they may show a decreased FAF which may or may not corresponding to areas of RPE atrophy or fibrovascular scaring. The fluorescent material inside the PED may not be directly derived from RPE LE, but rather from fluid and degraded photoreceptor that contain fluorophores which show up in the excitation and emission range applied for FAF imaging .the area of increased FAF around PED may be caused by multilayered RPE and the area of decreased FAF around PED may reflect beginning organization of the PED or may be due to absorption effect of sub-neurosensory extracellular fluid.

In the present study, cases that having disciform scar (2eyes) were appeared as early hypofluorescence that demonstrate late staining with no evidence of dye leakage on FFA, and as a dense hyper reflective plaque with disruption of RPE adjacent to it and thickened RPE around it on OCT has a corresponding decreased FAF surrounded by a rim of increased FAF this finding has been observed and reported by **Steffen et al.**⁽¹²⁾, who reported that decreased FAF is observed in areas of scaring and fibrosis.

CONCLUSION

FAF imaging is a non-invasive imaging method which contributes to our understanding of the AMD pathophysiology and prognostic markers for disease progression both in early and advanced AMD the FAF.

FAF provides the opportunity to evaluate the retinal functional status. Since OCT obtains a detailed picture of the retinal anatomy, several studies have evaluated the structure/function in patients with AMD and correlated the two techniques.

There was a significant association between OCT and autofluorescence findings as in cases of GA, there

were marked hyperfluorescence at the edges of the plaques of GA correlated with hyperreflective changes in the outer retinal layers identified by OCT that did not occur in healthy retinas with normal autofluorescence and OCT.

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