Photodiagnosis and Photodynamic Therapy 43 (2023) 103657

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Optical coherence tomography angiography aspects of the retinal and optic disc microvascular morphology in erythemato-telangectatic rosacea☆

İbrahim Ethem AY [a], Seçil Soylu [b], Aynur ER [a], İrem Nur Durusu [b], Mustafa Doğan [a], Hamidu Hamisi Gobeka [a,*]

[a] Department of Ophthalmology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
[b] Department of Dermatology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

ARTICLE INFO

Keywords:
Choriocapillaris
Erythemato-telangiectatic rosacea
OCTA
Retina
Vessel density

ABSTRACT

Background: To investigate retinal and optic disc (OD) microvascular morphological changes in erythemato-telangiectatic rosacea (ETR) patients using optical coherence tomography angiography (OCTA), and compare the findings to age- and gender-matched healthy individuals.

Methods: This study included newly diagnosed 31 ETR patients (31 right eyes, group 1) who were clinically diagnosed by two experienced dermatologists. A control group had 32 healthy individuals (32 right eyes, group 2). Demographic data, including age and gender were collected, followed by a thorough ophthalmologic exam. A 6 × 6 mm macular OCTA analysis of superficial and deep capillary plexus (SCP and DCP) vessel densities (VDs), as well as foveal avascular zone (FAZ) area, FAZ perimeter (PERIM), foveal VDs 300 μm area around FAZ (FD-300), and flow areas in the outer retinal and choriocapillaris, was then performed.

Results: Mean age in groups 1 and 2 was 43.70 ± 13.02 and 43.62 ± 12.30 years, respectively (p=0.979). Male-to-female ratio in group 1 was 4:27 and 4:28 in group 2. Capillary flow analysis revealed slightly higher values in group 1 than in group 2, with the former having a significantly higher select area in the outer retinal layer (p=0.001) and flow area in the choriocapillaris (p=0.002). Despite slightly higher values in group 1, there were no significant differences in SCP and DCP VDs ($p > 0.05$), FAZ area (p=0.471), PERIM (p=0.778), or FD-300 (p=0.527).

Conclusions: ETR appears to be associated with posterior segment changes, especially retinal microvascular morphology, even in asymptomatic ocular conditions. Given the disease's high rate of misdiagnosis, understanding rosacea-induced ocular manifestations is critical for ophthalmologists

1. Introduction

Rosacea (L. *rosaceus*, rosy) is a chronic dermatological disorder characterized by vasomotor instability that manifests in various manners. It predominantly affects the microvascular system and pilosebaceous units of the central facial skin convexities. This disorder frequently causes remissions and exacerbations of transient or persistent erythema, telangiectasias, papules, pustules, phymatous changes, as well as ocular involvement [1]. The National Rosacea Society classified the disorder into four main subtypes based on its clinical and morphological manifestations: erythemato-telangiectatic (ETR), papulopustular, phymatous, or ocular rosacea (OR) [2–4]. Diagnosis can be complicated due to overlap with the cutaneous manifestations of chronic actinic damage in fair-skinned individuals [5,6].

Despite its enigmatic pathophysiology, rosacea primarily manifests as a cutaneous vascular disorder with inflammatory changes [7]. This disorder is also related to vasodilatory changes, resulting in increased vascular flow as well as erythema and telangiectasias [8]. Mild rosacea symptoms like facial flushing and erythema are frequently ignored. They can, however, impede the healing of more serious conditions [9]. Further, rosacea can cause mild irritation, dryness [10], and blurred vision, as well as potentially severe ocular surface disruption, inflammatory keratitis, corneal ulceration, and eventual perforation [1,11]. In 20% of cases, ocular symptoms may appear before typical cutaneous

☆ GSM: 0090 534 331 43 62.GSM: 0090 0090 533 973 27 87.Tel: 0090 537 511 87 04.GSM: 0090 532 177 18 38.GSM: 0090 533 655 89 86.GSM: 0090 507 977 22 69.

* Corresponding author.
E-mail address: hgobeka@gmail.com (H.H. Gobeka).

https://doi.org/10.1016/j.pdpdt.2023.103657
Received 27 May 2023; Received in revised form 13 June 2023; Accepted 16 June 2023
Available online 17 June 2023

involvement or occur simultaneously with cutaneous changes [12]. Early detection is critical because untreated rosacea can result in deformity and even blindness. This disorder has no specific test; however, its distinctive appearance, cutaneous distribution, discrete course, typical target population, and response to various therapies allow for accurate diagnosis [13]. The literature on ETR posterior segment findings is limited. Given the natural course of the disorder, we posit that retinal microvascular morphology may be affected as well.

Optical coherence tomography angiography (OCTA) is a novel non-invasive imaging technique for detailed imaging of the retinal microvasculature [14]. Although fundus fluorescein angiography (FFA) is the gold standard for visualizing the retinal microvasculature, OCTA has several advantages over FFA, including being non-invasive and not requiring intravenous dye. Besides, superficial and deep capillary plexuses (SCP and DCP) can be visualized separately using OCTA. The foveal avascular zone (FAZ), capillary non-perfusion areas, and microstructural vessel density (VD) can also be quantified with technique [15,16].

Severity of rosacea-induced ocular manifestations is frequently unrelated to the severity of rosacea-induced cutaneous manifestations [17]. Poor understanding of the clinical relationship between ocular and ETR is one of the costs of medicine's growing specialization [18]. Thus, the current study aimed to investigate retinal and optic disc (OD) microvascular morphological changes in ETR patients using OCTA, and compare the findings to age- and gender-matched healthy individuals.

2. Materials and methods

2.1. Study design and participants

This single-centered cross-sectional study was conducted at X University Faculty of Medicine, Ophthalmology Department Retina Unit. The X University Clinical Research Ethics Committee approved the study, which adhered to the principles of the Helsinki Declaration (Ethics committee date and approval code: 2022/233).

The study included newly diagnosed but naïve 31 ETR patients (31 right eyes, group 1), as well as 32 (32 right eyes, group 2) age- and gender-matched healthy individuals who visited the Ophthalmology clinic for routine exam. Rosacea was diagnosed in patients who presented to the Dermatology outpatient clinic with persistent erythema, papules, pustules, and telangiectasia without facial comedones. Two different experienced dermatologists (SS and İD) diagnosed the disease clinically, and those who were consulted to the ophthalmology department were recruited for the study.

2.2. Inclusion and exclusion criteria

The study included ETR patients without prior ocular surgery (except uncomplicated cataract surgery >6 months ago) or corneal and/or lens opacity that would interfere with posterior segment imaging. Exclusion criteria for the study included the following: (a) presence of macular edema caused by other ocular pathologies, (b) a history of ocular diseases, including uveitis, diabetic retinopathy, age-related macular degeneration, glaucoma, (c) high refractive error [>±1.5 Diopter (D)], (d) advanced cataract, as well as (e) corneal pathologies, with the exception of dry eye, which could result in poor OCTA scan quality index. Moreover, group 2 had no systemic diseases such as hypertension, diabetes mellitus, thyroid gland disease, or rheumatic disease, as well as no obvious ocular pathology other than dry eye and ≤±1.5 D refractive error.

2.3. Ophthalmological assessment

Both groups 1 and 2 had their demographic data such as age, gender, and imaging features recorded, followed by a comprehensive ophthalmological examination, all before any ETR therapeutic interventions in the group 1. This included corrected visual acuity and intraocular pressure measurements, as well as a slit-lamp biomicroscopy of the anterior and posterior segments before and after artificial mydriasis.

2.4. Optical coherence tomography angiography acquisition

One experienced technician performed all OCTA (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA) imaging procedures between 10:00 and 12:00 AM using the same device and under standard physiological conditions. The Optovue RTVue XR AVANTI software and AngioVue module were used to automatically quantify all parameters. During the procedure, the axial length and refractive errors were corrected, and the image polarization was adjusted using the 'Auto Adjust' mode. An integrated eye tracking system and projection artifact removal system (PAR) were used to eliminate and/or minimize image artifacts. Scan Quality Indicator (SQ) values <8 were excluded from the study.

The Angio-retina mode was used for 6 × 6 mm macula analysis. The SCP and DCP VDs in whole, foveal, parafoveal, and perifoveal regions were quantified by selecting the 'density' option in macular mode. The FAZ area (mm^2), FAZ perimeter (mm), and foveal VDs 300 μm around FAZ (FD-300) (%) were also quantified and recorded. A maximum circular area captured by the fovea-centered image section was manually created in the outer retinal and choriocapillaris layers, followed by an automatic quantification of capillary flow areas by the device software in flow mode (Fig. 1). The angio disc mode was used for 4.5 × 4.5 mm OD VD quantification of whole, as well as peripapillary VDs. The global retinal nerve fiber layer thickness (RNFLT) was also quantified and recorded.

2.5. Statistical analysis

Statistical analysis was performed using a statistical package for the social sciences, version 23.0 (SPSS Inc., Chicago, IL, USA). Descriptive analysis was used, with mean and standard deviation values for continuous variables and frequency (n) and percentage (%) values for categorical variables. The Shapiro-Wilks test was used to analyze data distribution. The Mann–Whitney test was used to compare abnormally distributed continuous variables, whereas the Independent samples t-test was used to compare normally distributed continuous variables of the independent samples between the two groups. Post-hoc analysis was performed using the G power software. The level of significance was set at $p < 0.05$.

3. Results

3.1. Demographic features

Group 1 had 31 ETR patients (31 right eyes), while group 2 had 32 healthy individuals (32 right eyes). Mean age in groups 1 and 2 was 43.70 ± 13.02 (range: 20.00–71.00) and 43.62 ± 12.30 (range: 20.00-68.00) years, respectively (p=0.979). In groups 1 and 2, the male-to-female ratios were 4:27 and 4:28, respectively. All study participants had best corrected visual acuity of 20/20. Furthermore, the power of the study was determined in the post-hoc analysis to be 0.98 and 0.84 with 0.05 error in the variables considered statistically significant.

3.2. Optical coherence tomography angiography analysis

3.2.1. Macular capillary plexus vessel densities

In comparison to group 2, group 1 was associated with relatively higher SCP and DCP VDs in all regions except foveal region; however, the difference was not statistically significant ($p > 0.05$) (Table 1).

3.2.2. Foveal avascular zone parameters

Despite having slightly higher values in group 1, there were no statistically significant differences between the two groups in any of the FAZ parameters, including FAZ area (p=0.471), PERIM (p=0.778), and

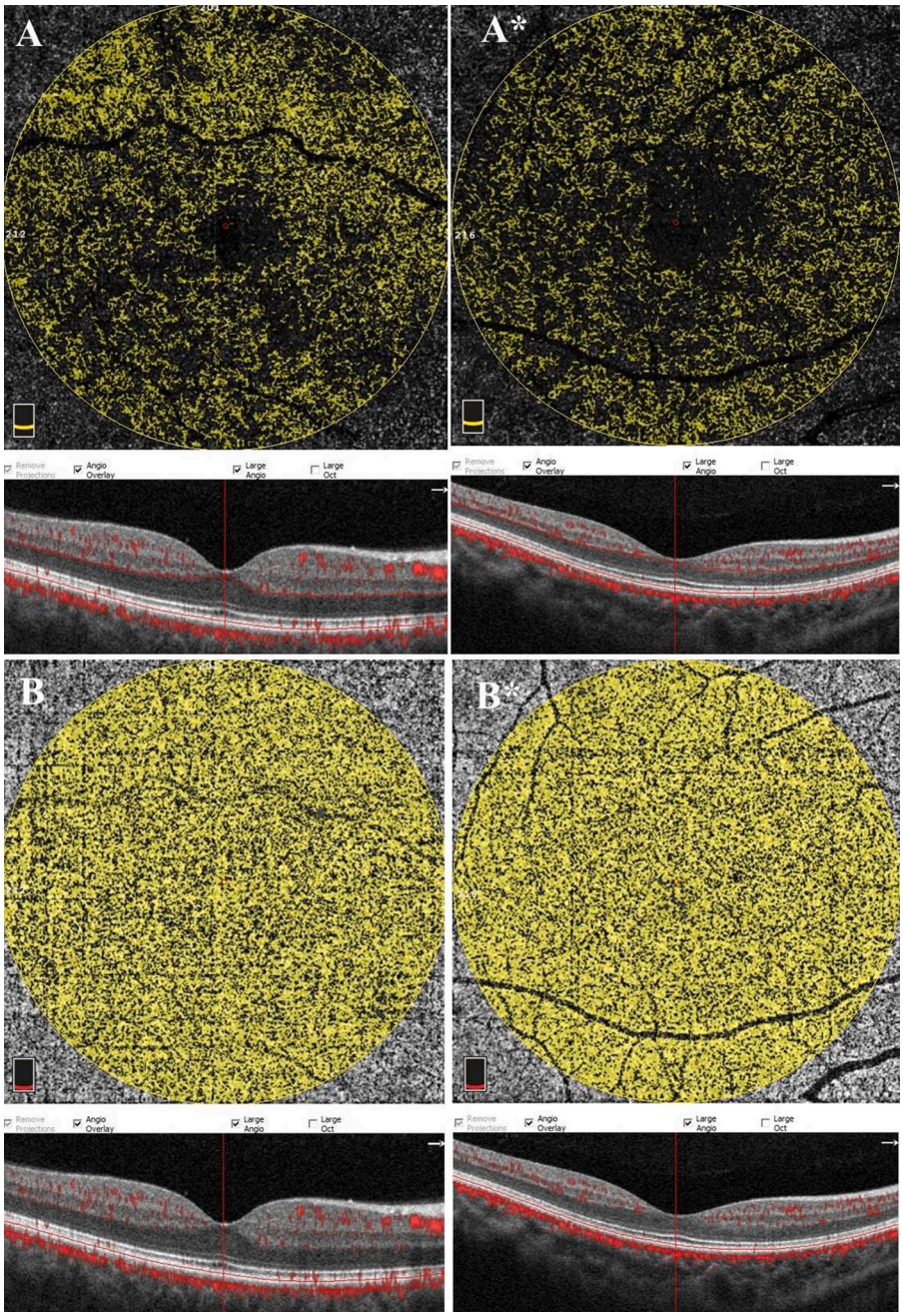

Fig. 1. En-face optical coherence tomography angiograms (6.0 × 6.0 mm scan size and 20.749 mm^2 flow area with scan quality index=9/10) displaying significantly increased vascular flow in the outer retina (p=0.001) (A/A*) and choriocapillaris (p=0.002) (B/B*) segments of the right eyes of erythematotelangiectatic rosacea patient (*letters without asterisks*) when compared to healthy individual (*letters with asterisks*). The corresponding OCT cross-sections through the central fovea of both the patient and the healthy individual are shown beneath each figure part.

FD-300 (p=0.527) (Table 2).

3.2.3. Capillary flow analysis

Both the outer retinal and choriocapillaris flow analyses revealed slightly higher values in group 1 than in group 2. Furthermore, in group 1, select area in the outer retinal layer (p=0.001) and flow area in the choriocapillaris layer (p=0.002) were statistically significantly higher than in group 2 (Table 3).

3.2.4. Optic disc vessel density and retinal nerve fiber layer

The differences in whole and peripapillary OD VDs, as well as global RNFL, between the two groups were not statistically significant (p > 0.05), (Table 4).

4. Discussion

Rosacea is currently thought to be a syndrome or typology with a wide range of cutaneous manifestations, typically manifesting in middle age and affecting 2–10% of the population. Despite being recognized as a common cutaneous disorder, rosacea has long been misunderstood and misdiagnosed. It is presently considered as a unique medical condition that necessitates prompt evaluation and therapeutic interventions [19]. ETR is the most common rosacea subtype, defined by flushing and persistent central facial erythema with periocular skin sparing. Rosacea flushing differs from physiological flushing in that it lasts >10 minutes. Subcutaneous microvasculature may swell and become visible as the symptoms appear and fade [17].

ETR, in particular, has a strong female preponderance and is frequently identified beyond the age of 30, which is also consistent with the current study. Rosacea-related ocular involvement ranges from less

Table 1
Comparative analysis of macular capillary plexus vessel densities.

Parameters		Participants	Mean ±SD	Median	Min-Max	*p* value
SCP VD (%)	Whole	Group 1	52.02 ± 3.05	52.10	42.90-57.00	0.794*
		Group 2	51.81 ± 3.29	52.75	41.30-58.50	
	Foveal	Group 1	20.00 ± 7.75	20.80	2.60-36.30	0.296**
		Group 2	22.99 ± 9.25	24.20	8.60-53.90	
	Parafoveal	Group 1	54.23 ± 4.18	55.20	45.20-61.00	0.944**
		Group 2	53.84 ± 5.08	55.40	32.40-59.50	
	Perifoveal	Group 1	53.07 ± 3.70	53.60	44.00-64.80	0.253*
		Group 2	52.08 ± 3.11	52.45	43.20-59.00	
DCP VD (%)	Whole	Group 1	55.45 ± 6.21	56.80	40.60-65.40	0.606**
		Group 2	54.47 ± 6.55	56.15	37.60-62.50	
	Foveal	Group 1	37.96 ± 8.70	39.70	21.10-52.20	0.830*
		Group 2	38.40 ± 7.42	39.10	21.30-53.00	
	Parafoveal	Group 1	58.37 ± 4.18	59.60	47.10-63.30	0.293**
		Group 2	56.94 ± 5.73	59.25	34.80-63.70	
	Perifoveal	Group 1	56.95 ± 6.91	59.20	39.90-67.60	0.514**
		Group 2	55.89 ± 6.87	57.20	38.50-64.00	

Group 1: Erythemato-telangiectatic rosacea patients, Group 2: Healthy individuals, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, VD: Vessel density, SD: Standard deviation, %: Percentage,
* Independent t test,
** Mann Whitney U test.

Table 2
Analysis of FAZ parameters.

FAZ parameters	Participants	Mean±SD	Median	Min-Max	*p* value
FAZ area (mm^2)	Group 1	0.29 ± 0.12	0.29	0.11-0.55	0.471*
	Group 2	0.27 ± 0.10	0.26	0.09-0.43	
PERIM (mm)	Group 1	20.48 ± 4.19	21.14	13.49-28.82	0.778**
	Group 2	19.85 ± 4.03	19.94	11.57-25.01	
FD-300 (%)	Group 1	55.88 ± 4.71	55.97	45.68-66.31	0.527**
	Group 2	54.48 ± 5.66	55.28	32.39-61.50	

Group 1: Erythemato-telangiectatic rosacea patients, Group 2: Healthy individuals, FAZ: Foveal avascular zone, PERIM: FAZ perimeter, FD-300: Foveal vessel density 300 μm around FAZ, mm^2: Millimeter square, mm: Millimeter, %: Percentage, SD: Standard deviation,
* Independent t test,
** Mann Whitney U test.

than 10% to more than 50% [20]. The ocular manifestations have been shown to occur up to 20% of the time prior to any dermatologic manifestations. There is no correlation between the severity of rosacea papules, pustules, flushing, and nodular facial signs and the severity of ocular manifestations [21,22]. A significant correlation has been reported between the severity of facial telangiectasia and OR findings. But, due to the small sample size, researchers were unsure about the relationship [21]. Moreover, ocular manifestations have long been known to be bilateral and involve the eyelids, conjunctiva, and corneal tissues [8,21,23]. Rosacea has also been associated to vitritis in a few instances [24].

Table 3
Capillary flow analysis.

	Participants	Mean±SD	Median	Min-Max	*p* value
Outer retinal layer					
Select area (mm^2)	Group 1	28.28 ± 0.06	28.29	28.19-28.36	0.001**
	Group 2	28.12 ± 0.20	28.21	27.77-28.36	
Flow area (mm^2)	Group 1	9.53 ± 0.22	9.51	6.51-16.39	0.098*
	Group 2	8.58 ± 2.18	8.06	5.19-13.45	
Choriocapillaris layer					
Select area (mm^2)	Group 1	28.26 ± 0.06	28.23	28.19-28.36	0.545**
	Group 2	28.15 ± 0.21	28.26	27.77-28.36	
Flow area (mm^2)	Group 1	20.05 ± 1.11	20.21	17.25-21.48	0.002**
	Group 2	19.22 ± 1.01	19.57	16.51-20.66	

Group 1: Erythemato-telangiectatic rosacea patients, Group 2: Healthy individuals, mm^2: Millimeter square, SD: Standard deviation,
* Independent t test,
** Mann Whitney U test.

Rosacea, especially ETR, is often misdiagnosed, undertreated, and underreported. As there are no undisputed histopathological or laboratory defining features of the disorder, the diagnosis is typically predicated on gathering of clinical signs. The reason for rosacea underdiagnosis could be a lack of definitive diagnostic criteria among ophthalmologists [24]. Because dermatologists and ophthalmologists do not see the same patients, their assessments differ greatly, even though they both treat patients using monocular visual acuity. There have been no comprehensive epidemiological studies. Since the ocular manifestations are so ambiguous, the disorder is frequently misdiagnosed. When both ophthalmologists and dermatologists evaluate the same patient for both ocular and cutaneous involvement, the likelihood of ETR diagnosis is increased, allowing for early intervention to protect eyes, particularly those with posterior segment involvement. This condition appears to be very obvious, as evidenced by the current study's discovery of microvascular morphological changes in the posterior segment, particularly at the macular and choroid layer levels. This suggests that in ETR patients with otherwise asymptomatic healthy eyes, early changes in the microvascular system may be detectable.

Patients with ocular rosacea may have minimal facial symptoms but extensive ocular manifestations, particularly those involving the anterior segment [12]. However, when it comes to microvascular morphological changes in the ocular posterior segment, the inverse may be true for ETR with classic cutaneous problems [25]. Aside from environmental triggers and genetic predisposition, the main abnormalities associated with rosacea are thought to be neurovascular dysregulation and abnormal innate immune response, which can lead to cutaneous inflammatory changes [26], as evidenced by the presence of interleukin-1a and b, gelatinase B, and collagenase-2 in tear fluids [27–30]. Tumor necrosis factor-alpha levels in the serum have been found to increase in these patients, as well as conjunctival epithelial cell overexpression of intercellular adhesion molecule 1 and HLA-DR [31,32]. Further, rosacea patients are hypersensitive to common environmental stimuli, including sunlight, extreme climatic conditions, spicy foods, hot drinks, psychological pain, and so on [33,34]. These factors are involved in the induction of the inflammatory and immune systems,

Table 4
Optic disc vessel density and retinal nerve fiber layer analysis.

		Participants	Mean±SD	Median	Min-Max	*p* value
Optic disc vessel density (%)						
Whole	Group 1	49.93 ± 2.59	49.90	43.80-54.90	0.919*	
	Group 2	49.87 ± 2.59	50.00	42.00-56.90		
Peripapillary	Deep	Group 1	53.06 ± 6.26	52.60	38.00-72.30	0.564**
		Group 2	52.17 ± 2.79	52.10	44.80-57.60	
	Superficial	Group 1	52.00 ± 4.19	53.10	39.70-57.00	0.149**
		Group 2	51.49 ± 3.17	51.95	40.20-58.60	
Retinal nerve fiber layer thickness (μm)						
Global	Group 1	112.87 ± 14.32	114.00	59.00-138.00	0.441**	
	Group 2	115.97 ± 11.06	115.00	89.00-135.00		

Group 1: Erythemato-telangiectatic rosacea patients, Group 2: Healthy individuals, SD: Standard deviation, %: Percentage; μm: Micrometer,
* Independent t test,
** Mann Whitney U test.

as well as the upregulation of Toll-like receptor 2 in keratinocytes [32]. The latter increases the activity of the enzyme serine protease KLK5, which is involved in cathelicidin synthesis. Cathelicidin also increases vascular endothelial growth factors levels in epidermal keratinocytes, causing vascular endothelial changes and, eventually, angiogenesis [35]. Furthermore, as revealed by the skin outcomes of rosacea patients, an IL-18 stands out as another hypothesis that could be associated to retinal damage in rosacea. In essence, the levels of IL-18 and vascular endothelial growth factors are inversely related. Given that intraocular VEGF levels rise in cases of retinal ischemia, resulting in neovascularization and cystoid macular edema, the potential link between rosacea and retinal involvement is worth investigating [36].

To our knowledge, the majority of the literature has reported rosacea-induced ocular manifestations, particularly those involving the anterior segment [8,23]. However, the natural course of other rosacea subtypes, in this case, ETR, prompted us to wonder if there could be any associated ocular microvascular morphological changes, particularly in the retina and OD. Based on the current study findings it seems primarily that this disorder appears to be more associated with retinal microvascular morphological changes rather than OD VDs and RNFLT changes. This was supported by the discovery that ETR patients had higher SCP and DCP VDs, as well as FAZ parameters such as FAZ area, PERIM, and FD-300, when compared to healthy individuals, though the difference was not statistically significant. More importantly, both the outer retinal and choriocapillaris flow analyses revealed slightly higher values in ETR patients compared to healthy individuals, with the former having statistically significantly higher select area in the outer retinal layer and flow area in the choriocapillaris layer. The pathophysiology described above may help to explain how these microvascular changes occur naturally, even before manifested ocular involvement.

With recent technological advancements in retinal microvascular imaging, OCTA has risen to prominence in ophthalmology clinics. Its advantages, such as the ability to perform repetitive measurements, have propelled it to prominence in the evaluation of retinal microvascular diseases [37]. This technique generates images by optically tracking the movement of erythrocytes in the microvascular structure [38]. Few, if any, studies have investigated posterior segment changes in relation to rosacea, particularly using OCT. In this context, a comparison of choroidal thickness in ETR and papulopustular rosacea revealed no significant differences in choroidal thickness relative to healthy controls [39]. Thus, we fervently believe that the current study is the first of its kind to use OCTA technology to determine whether there are any associated retinal and OD microvascular morphological changes in ETR patients. The presence of high blood flow in the outer retina and choriocapillaris suggests that the disease may affect the retinal microvasculature. OCTA appears to be an effective tool for determining the microvascular status of the retina and OD in rosacea, particularly ETR without ocular involvement. Furthermore, VD data may indicate that microvascular morphological changes can occur prior to clinical onset of posterior segment inflammation.

Given the possibility of symptoms deteriorating over time, the chronic condition of rosacea necessitates long-term care. Due to variation in presentations, subtypes, exacerbations, and remissions of this disorder, existing treatments and durations should also be personalized rather than being applied as absolute therapeutic regimens [40]. Additionally, patients must be thoroughly instructed on the clinical manifestations of the disorder and the importance of regular monitoring [8]. Controlling symptomatic outbreaks, as well as ocular and facial manifestations of the disease, necessitates visits to both an ophthalmologist and a dermatologist on a regular basis [2].

The current study has several limitations, including its cross-sectional design, a small number of study participants, and the fact that all ETR patients were investigated regardless of whether they were in the active or remission phase of the disease. Also, medical history of the patients was not taken into account. Further large-scale prospective studies involving patients with different rosacea subtypes at various disease phases and with consideration for which therapeutic intervention they are receiving could yield clinically useful results. Nonetheless, as the one of its kind, we strongly believe that the current study, in which for the first time the OCTA technique was used to investigate retinal and OD microvascular morphological changes, may serve as a beacon for future research, particularly in unraveling the mystery of posterior segment involvement in otherwise ETR patients without clinically visible ocular manifestations.

5. Conclusions

Conclusively, ETR could be associated with ocular posterior segment changes, especially retinal microvascular morphology, even in asymptomatic ocular conditions. Given the disease's high rate of misdiagnosis, understanding rosacea-induced ocular manifestations is critical for ophthalmologists, regardless of how difficult it may be to accurately diagnose and treat. Comprehensive ophthalmologic and dermatologic evaluations may be beneficial for earlier detection of both ocular and dermatologic manifestations and, eventually, prompt therapy may be valuable in avoiding further complications.

Funding & conflicts of interest

The authors declare that they have received no public or private financial support or involvement in the products, methods, or materials mentioned in this manuscript, and there is no conflict of interest to disclose.

Financial interest

All authors certify that they have no association or participation with any organization or individual with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all participants included in the study.

Data availability

The manuscript contains all data. The datasets used and/or analyzed during the current study, however, are available upon reasonable request from the corresponding author.

CRediT authorship contribution statement

İbrahim Ethem AY: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Seçil Soylu:** Visualization, Methodology, Formal analysis. **Aynur ER:** Methodology, Investigation, Formal analysis. **İrem Nur Durusu:** Methodology, Investigation, Formal analysis, Data curation. **Mustafa Doğan:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Visualization, Project administration. **Hamidu Hamisi Gobeka:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interests

The authors declare they have no conflict of interest.

Acknowledgments

None.

References

[1] A.C. Vieira, A.L. Höfling-Lima, M.J. Mannis, Ocular rosacea-a review, Arq. Bras. Oftalmol. 75 (2012) 363–369, https://doi.org/10.1590/s0004-27492012000500016.
[2] M. Gooderham, Rosacea and its topical management, Skin Therapy Lett. 14 (2009) 1–3.
[3] G.H. Crawford, M.T. Pelle, W.D. James, Rosacea: I. Etiology, pathogenesis, and subtype classification, J. Am. Acad. Dermatol. 51 (2004) 327–341, https://doi.org/10.1016/j.jaad.2004.03.030.
[4] J. Wilkin, M. Dahl, M. Detmar, L. Drake, A. Feinstein, R. Odom, et al., Standard classification of rosacea: report of the national rosacea society expert committee on the classification and staging of rosacea, J. Am. Acad. Dermatol. 46 (2002) 584–587, https://doi.org/10.1067/mjd.2002.120625.
[5] E.K. Akpek, A. Merchant, V. Pinar, C.S. Foster, Ocular rosacea: patient characteristics and follow-up, Ophthalmology 104 (11) (1997) 1863–1867. PMID: 9373118.
[6] E.J. van Zuuren, Z. Fedorowicz, B. Carter, M.M. van der Linden, L. Charland, Interventions for rosacea, Cochrane Database Syst. Rev. 2015 (2015), CD003262, https://doi.org/10.1002/14651858.CD003262.pub5.
[7] K. Yamasaki, R.L. Gallo, The molecular pathology of rosacea, J. Dermatol. Sci. 55 (2009) 77–81, https://doi.org/10.1016/j.jdermsci.2009.04.007.
[8] R. Odom, M. Dahl, J. Dover, Z. Draelos, L. Drake, M. Macsai, Pet al; national rosacea society expert committee on the classification and staging of rosacea. Standard management options for rosacea, part 2: options according to subtype, Cutis 84 (2009) 97–104.
[9] Culp B., Scheinfeld N. Rosacea: a review. P T 2009;34:38-45.
[10] T. Ozturk, M. Kayabasi, O. Ozbagcivan, Z. Ayhan, C.A. Utine, Common ocular findings in patients with acne rosacea, Int. Ophthalmol. 42 (2022) 1077–1084, https://doi.org/10.1007/s10792-021-02093-5.
[11] S.A. Buechner, Rosacea: an update, Dermatology 210 (2005) 100–108, https://doi.org/10.1159/000082564.
[12] V.C. Ghanem, N. Mehra, S. Wong, M.J. Mannis, The prevalence of ocular signs in acne rosacea: comparing patients from ophthalmology and dermatology clinics, Cornea 22 (2003) 230–233, https://doi.org/10.1097/00003226-200304000-00009.
[13] A.M. Kligman, Ocular rosacea. Current concepts and therapy, Arch. Dermatol. 133 (1997) 89–90, https://doi.org/10.1001/archderm.133.1.89.
[14] T.E. de Carlo, A. Romano, N.K. Waheed, J.S. Duker, A review of optical coherence tomography angiography (OCTA), Int. J. Retina Vitreous 1 (2015) 5, https://doi.org/10.1186/s40942-015-0005-8.
[15] S.T. Garrity, N.A. Iafe, N. Phasukkijwatana, X. Chen, D. Sarraf, Quantitative analysis of three distinct retinal capillary plexuses in healthy eyes using optical coherence tomography angiography, Investig. Ophthalmol. Vis. Sci. 58 (2017) 5548–5555, https://doi.org/10.1167/iovs.17-22036.
[16] K.V. Chalam, K. Sambhav, Optical coherence tomography angiography in retinal diseases, J. Ophthalmic Vis. Res. 11 (2016) 84–92, https://doi.org/10.4103/2008-322X.180709.
[17] Y. Tüzün, R. Wolf, Z. Kutlubay, O. Karakuş, B. Engin, Rosacea and rhinophyma, Clin. Dermatol. 32 (2014) 35–46, https://doi.org/10.1016/j.clindermatol.2013.05.024.
[18] P. Borrie, Rosacea with special reference to its ocular manifestations, Br. J. Dermatol. 65 (1953) 458–463, https://doi.org/10.1111/j.1365-2133.1953.tb13185.x.
[19] L. Millikan, Recognizing rosacea, Postgrad. Med. 105 (1999) 149–150, https://doi.org/10.3810/pgm.1999.02.549.
[20] B.M. Rainer, A.H. Fischer, D. Luz Felipe da Silva, S. Kang, A.L. Chien, Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study, J. Am. Acad. Dermatol. 73 (2015) 604–608, https://doi.org/10.1016/j.jaad.2015.07.009.
[21] A. Keshtcar-Jafari, M. Akhyani, A.H. Ehsani, M. Ghiasi, V. Lajevardi, O. Baradran, et al., Correlation of the severity of cutaneous rosacea with ocular rosacea, Indian J. Dermatol. Venereol. Leprol. 75 (2009) 405–406, https://doi.org/10.4103/0378-6323.53146.
[22] K.E. Donaldson, C.L. Karp, M.T. Dunbar, Evaluation and treatment of children with ocular rosacea, Cornea 26 (2007) 42–46, https://doi.org/10.1097/ICO.0b013e31802e3a54.
[23] M.A. Friedberg, C.J. Rapuano, D.Y. Kunimoto, et al., The Wills Eye Manual: Office and Emergency Room Diagnosis and Treatment of Eye Disease, 4th ed., Lippincott Williams & Wilkins, Philadelphia, PA, 2004, pp. 103–104.
[24] D.J. Browning, AD. Proia, Ocular rosacea, Surv. Ophthalmol. 31 (1986) 145–158, https://doi.org/10.1016/0039-6257(86)90034-2.
[25] T. Rosen, M.S. Stone, Acne rosacea in blacks, J. Am. Acad. Dermatol. 17 (1987) 70–73, https://doi.org/10.1016/s0190-9622(87)70173-x.
[26] F.C. Powell, S.N. Raghallaigh, J.L. Bolognia, J.Y. Schaffer, L. Cerroni, Rosacea and related disorders. Dermatology, Elsevier Ltd, 2018, pp. 604–614.
[27] K. Barton, D.C. Monroy, A. Nava, S.C. Pflugfelder, Inflammatory cytokines in the tears of patients with ocular rosacea, Ophthalmology 104 (1997) 1868–1874, https://doi.org/10.1016/s0161-6420(97)30014-1.
[28] A.A. Afonso, L. Sobrin, D.C. Monroy, M. Selzer, B. Lokeshwar, S.C. Pflugfelder, Tear fluid gelatinase B activity correlates with IL-1alpha concentration and fluorescein clearance in ocular rosacea, Investig. Ophthalmol. Vis. Sci. 40 (1999) 2506–2512.
[29] M. Määttä, O. Kari, T. Tervahartiala, S. Peltonen, M. Kari, M. Saari, et al., Tear fluid levels of MMP-8 are elevated in ocular rosacea–treatment effect of oral doxycycline, Graefes Arch. Clin. Exp. Ophthalmol. 244 (2006) 957–962, https://doi.org/10.1007/s00417-005-0212-3.
[30] L. Sobrin, Z. Liu, D.C. Monroy, A. Solomon, M.G. Selzer, B.L. Lokeshwar, et al., Regulation of MMP-9 activity in human tear fluid and corneal epithelial culture supernatant, Investig. Ophthalmol. Vis. Sci. 41 (2000) 1703–1709.
[31] P.J. Pisella, F. Brignole, C. Debbasch, P.A. Lozato, C. Creuzot-Garcher, J. Bara, et al., Flow cytometric analysis of conjunctival epithelium in ocular rosacea and keratoconjunctivitis sicca, Ophthalmology 107 (2000) 1841–1849, https://doi.org/10.1016/s0161-6420(00)00347-x.
[32] K. Yamasaki, K. Kanada, D.T. Macleod, A.W. Borkowski, S. Morizane, T. Nakatsuji, et al., TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes, J. Investig. Dermatol. 131 (2011) 688–697, https://doi.org/10.1038/jid.2010.351.
[33] T. Jansen, R. Romiti, A. Kreuter, P. Altmeyer, Rosacea fulminans triggered by high-dose vitamins B6 and B12, J. Eur. Acad. Dermatol. Venereol. 15 (2001) 484–485, https://doi.org/10.1046/j.1468-3083.2001.00308.x.
[34] E.L. Gutierrez, C. Galarza, W. Ramos, M. Mendoza, M.E. Smith, A.G. Ortega-Loayza, Influence of climatic factors on the medical attentions of dermatologic diseases in a hospital of Lima, Peru, An Bras. Dermatol. 85 (2010) 461–468, https://doi.org/10.1590/s0365-05962010000400007.
[35] J.R. Smith, V.B. Lanier, R.M. Braziel, K.M. Falkenhagen, C. White, J.T. Rosenbaum, Expression of vascular endothelial growth factor and its receptors in rosacea, Br. J. Ophthalmol. 91 (2007) 226–229, https://doi.org/10.1136/bjo.2006.101121.
[36] D. Rodrigues-Braz, M. Zhao, N. Yesilirmak, S. Aractingi, F. Behar-Cohen, J. L. Bourges, Cutaneous and ocular rosacea: common and specific physiopathogenic mechanisms and study models, Mol. Vis. 27 (2021) 323–353.
[37] M. Arya, R. Rashad, O. Sorour, E.M. Moult, J.G. Fujimoto, N.K. Waheed, Optical coherence tomography angiography (OCTA) flow speed mapping technology for retinal diseases, Expert Rev. Med. Devices 15 (2018) 875–882, https://doi.org/10.1080/17434440.2018.1548932.

[38] A. Wylęgała, S. Teper, D. Dobrowolski, E. Wylęgała, Optical coherence angiography: a review, Medicine 95 (2016) e4907, https://doi.org/10.1097/MD.0000000000004907.
[39] T. Şahin, A. Öztekin, S. Cevher, Does rosacea, a localized skin disease, affect the choroidal thickness? J. Cosmet Dermatol. 21 (2022) 387–391, https://doi.org/10.1111/jocd.14428.
[40] R. Odom, M. Dahl, J. Dover, Z. Draelos, L. Drake, M. Macsai, et al., National rosacea society expert committee on the classification and staging of roasacea. Standard management options for rosacea, part 1: overview and broad spectrum of care, Cutis 84 (2009) 43–47.