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Evaluation of the optic nerve head vessel density in patients with limited scleroderma

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Abstract

Objectives: To investigate the optical coherence tomography angiography (OCTA) parameters of the optic nerve head and peripapillary retina and to assess macular and peripapillary retinal nerve fiber layer (RNFL) thickness by using spectral-domain optical coherence tomography (SD-OCT) in patients with limited scleroderma and to compare these results with those of healthy control subjects.

Materials and Methods: 42 patients with a confirmed diagnosis of limited scleroderma and 32 age- and sex-matched healthy control subjects were included in the study. OCTA was performed for the radial peripapillary capillary plexus (RPCP) whole image, inside disc, and peripapillary vessel densities in all participants with XR Avanti AngioVue OCTA (Optovue, Fremont, California, USA). OCT images were obtained with Spectralis OCT with eye-tracking dual-beam technology (Heidelberg Engineering GmbH, Heidelberg, Germany), and peripapillary RNFL thickness was evaluated with circle program. The data from the right eyes of all participants were used for statistical analysis.

Results: No significant difference was found between the radial RPCP whole image, inside disc, and peripapillary vessel density values or the RNFL parameters of the scleroderma patients when compared with the controls ($p > 0.05$ for all).

Conclusion: Decreased peripapillary vessel density on OCTA, which can be an early sign of glaucoma, could not be observed in scleroderma patients in this study. However, further long-term studies are still needed to identify glaucoma tendency in patients with scleroderma before clinically detectable glaucoma.

Keywords: glaucoma, optical coherence tomography, optical coherence tomography angiography, scleroderma

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Introduction

Prevalence of normal-tension glaucoma (NTG) and primary open-angle glaucoma (POAG) is higher in patients with scleroderma (systemic sclerosis) than in the general population. The higher risk of glaucoma in scleroderma patients is often attributed to generalized vasospasm, which is one of the main features of scleroderma.[1–5] In addition to vasospasm, ischemic changes and local infarction, which are thought to be involved in the pathogenesis of scleroderma, can also increase the risk of glaucoma.[6,7] If these ischemic changes and infarction occur in the optic nerve head and peripapillary retina as mentioned above, they may be the main cause of glaucoma predisposition.

Optical coherence tomography angiography (OCTA) is a new imaging modality and can provide noninvasive and quick mapping of the optic disc vasculature and peripapillary microvasculature. Recent studies have shown that OCTA parameters of the optic nerve head and peripapillary retina are reduced in patients with glaucoma compared with normal participants.[8–11] As is well known, chronic and progressive loss of ganglion

cell axons, which is routinely diagnosed by the presence of thinning of peripapillary retinal nerve fiber layer (RNFL), is a cardinal feature of glaucomatous optic neuropathy.[12–14] The diagnostic ability of peripapillary vessel density captured by OCTA may be lower or, at best, equal to the thickness of peripapillary RNFL, but it is unclear whether OCTA will add benefit to the standard clinical care and monitoring of scleroderma patients.[11,15] The aim of our study was to assess the vessel density of the optic nerve head and peripapillary retina using OCTA, and peripapillary and macular RNFL thickness using spectral-domain optical coherence tomography (SD-OCT) in patients with limited scleroderma and to compare these results with those of healthy controls.

Materials and methods

Patients

This prospective cross-sectional study included patients with limited scleroderma who were recruited from the outpatient clinic at a tertiary care referral center for scleroderma.[15] Patients who fulfilled the criteria for the diagnosis of scleroderma proposed by the American College of Rheumatology were evaluated for enrollment in the study.[16] Eligible patients with thickening of skin affecting the limbs distal to the elbows or knees, with or without face and neck involvement were defined as limited scleroderma and enrolled in the study.[17] The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review board (No: 2012-KAEK-15/1863). Consecutive sex- and age-matched patients with no known systemic or ocular disorders were included in the study as the control group. Written informed consent was obtained from each participant.

Patients with a history of severe systemic hypertension (defined as systolic blood pressure exceeding 179 mmHg or a diastolic blood pressure exceeding 109 mmHg), pulmonary hypertension, diabetes mellitus, ocular surgery, glaucoma, or those with first-degree relatives with primary open-angle glaucoma were excluded from the study. Those with intraocular pressure (IOP) of >21 mmHg or evidence of glaucomatous changes in the optic disc were referred to the glaucoma unit, and patients who fulfilled the diagnostic criteria for POAG and NTG were excluded from the study. Criteria for diagnosing POAG are as follows: diagnosed glaucomatous optic neuropathy based on changes in the optic disc and visual field defects, open anterior chamber angle in gonioscopy, and IOP above 21 mmHg at the time of diagnosis evaluated on the basis of a 24-h IOP monitoring. In the case of NTG, IOP at the time of diagnosis was below 21 mmHg. Exclusion criteria also encompassed the presence of other retinal diseases, severe cataract, nystagmus, poor eye fixation, significant media opacity, and refractive spherical and cylindrical error ⩾1.5D that could possibly confound the measurements.

Following the recruitment of data regarding age, sex, and autoantibody profile of the patients, all underwent a comprehensive ophthalmologic examination, including the Snellen best-corrected visual acuity test, slit-lamp examination, and IOP measurement, by performing applanation tonometry and dilated indirect ophthalmoscopy. After undergoing a detailed ophthalmologic examination, all of the participants underwent OCT and OCTA measurements of both eyes with dilated pupils by the same examiner, performing at the same time interval (2–4 p.m.) of the day.

Imaging

OCTA was performed for the radial peripapillary capillary plexus (RPCP) whole image, inside disc, and peripapillary vessel densities in all participants with XR Avanti AngioVue OCTA (Optovue, Fremont, California, USA) (Version 2017.1.0.151). Three-dimensional optic disc scan covered an area of 4.5×4.5 mm^2 centered on the optic disc. Quantification of the vessel density was defined as the percentage of an area occupied by the vessels. Subjects with poor image quality were excluded based on the presence of one or more of the following criteria: a low signal strength index (<7), the presence of one or more blink artifacts, poor fixation leading to motion or doubling artifacts, and media opacity obscuring the view of the vasculature. This system uses a split-spectrum amplitude decorrelation angiography (SSADA) algorithm and operates at 70,000 A-scans per second to acquire OCTA volumes consisting of 400×400 B-scans. Using the SSADA algorithm, we were able to visualize the blood flow and microvascular architecture.

OCT images were obtained with Spectralis OCT with eye-tracking dual-beam technology (Heidelberg Engineering GmbH, Heidelberg, Germany), and peripapillary RNFL thickness was evaluated with circle program. SD-OCT

images were generated using the horizontal SD-OCT cross-sections (25 lines spaced 240 mm apart; 20° × 20°)

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 20.0 was used to analyze outcomes. The distribution pattern of the variables was tested by visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk test) tools. The *t* test was used for normally distributed data; the Mann–Whitney *U* test was used for nonnormally distributed data. The correlations between parameters were tested by Pearson's correlation tests. The data from the right eyes of all participants were used for statistical analysis. A two-tailed "*p*" value less than 0.05 was considered as statistically significant.

Results

42 eyes of 42 patients who had limited scleroderma and 32 healthy controls were included in the study according to the inclusion and exclusion criteria. There were no statistically significant differences with regard to mean age, sex, spherical equivalent of refraction, and IOP between the study groups ($p > 0.05$ for all). The autoantibody profile, and clinical and demographic characteristics of the patients are demonstrated in Table 1.

No significant difference was found among the OCTA parameters, the mean radial RPCP whole image, inside disc, and peripapillary vessel density values, compared with those of controls. None of the RNFL parameters was significantly different in patients with scleroderma in comparison with the control group ($p > 0.05$ for all). OCTA and OCT variables for scleroderma and control eyes are demonstrated in Table 2.

The OCTA perfusion parameters and RNFL parameters of the scleroderma patients were not correlated with age, age at diagnosis, and duration of the disease ($p > 0.05$ for all). The only exception was for the radial RPCP whole-image vessel density, which showed a weak correlation with the duration of the disease ($p = 0.040$, rho = −0.37, effect size (d) = 0.608; Pearson's correlation test). The correlation between the baseline characteristics and optic disc head vessel density and the effect of antibody levels on the vessel density of the patients with limited scleroderma are denoted in Table 3.

Table 1. Clinical and demographic characteristics of scleroderma patients and control group.

Variable	Scleroderma group	Control group	P-*value*
Age (years)			
Mean ± SD	52.00 ± 8.20	51.61 ± 8.62	0.668[a]
Range	26–73	25–75	
Sex			
Male, n (%)	4 (9.52)	3 (9.38)	0.852[b]
Female, n (%)	38 (90.48)	29 (90.62)	
Spherical equivalent, D			
Mean ± SD	0.14 ± 0.22	0.41 ± 0.65	0.898[a]
Range	−0.5 to +0.5	−0.5 to +1.0	
IOP, mmHg			
Mean ± SD	15.16 ± 2.94	15.19 ± 2.48	0.712[a]
Range	10–20	10–18	
Duration of scleroderma (years)			
Mean ± SD	10.13 ± 8.61	N/A	–
Range	1–38		
Age at diagnosis (years)			
Mean ± SD	40.81 ± 10.71	N/A	–
Range	22–61		
Anti-topo I positivity	40.62%	N/A	–
ACA positivity	25%	N/A	–
ANA positivity	28.13%	N/A	–
Digital ulcers	53.13%	N/A	–

ACA, anti-centromere antibodies; ANA, antinuclear antibody; anti-topo I, anti-DNA topoisomerase I; D, diopter; IOP, intraocular pressure; N/A, not applicable; SD, standard deviation.
[a]*t* test.
[b]Pearson's Chi-square.

Discussion

In glaucoma, OCTA-derived nerve fiber layer plexus capillary density measurements are highly reproducible and, compared with RNFL thickness, are more tightly correlated with visual field

Table 2. OCT and OCTA parameters of patients with scleroderma and healthy controls.

Variable	Scleroderma Mean ± SD	Control Mean ± SD	p-*value*
Vessel density, RPCP %			
Whole image	50.79 ± 1.79	50.98 ± 2.19	0.718
Inside disc	50.72 ± 4.74	50.49 ± 4.34	0.839
Peripapillary	53.13 ± 2.26	53.60 ± 2.45	0.430
pRNFL thickness, μm			
Global	105.69 ± 9.40	103.03 ± 7.66	0.235
Temporal	77.75 ± 11.38	74.86 ± 10.24	0.304
Nasal	84.16 ± 15.70	77.31 ± 12.17	0.064
Temp Inf	149.47 ± 22.88	145.97 ± 29.06	0.601
Temp Sup	143.34 ± 15.48	137.62 ± 18.59	0.199
Nas Inf	113.63 ± 17.28	121.31 ± 21.25	0.129
Nas Sup	115.75 ± 17.12	115.31 ± 17.46	0.921
mRNFL thickness, μm			
Total	26.20 ± 2.49	25.51 ± 2.56	0.281
Inferior	33.50 ± 4.39	32.97 ± 5.13	0.658
Superior	31.78 ± 4.79	30.38 ± 3.50	0.185
Nasal	35.66 ± 4.80	34.56 ± 4.85	0.368
Temporal	18.00 ± 1.48	18.00 ± 2.31	0.998

mRNFL, macular retinal nerve fiber layer; Nas-inf, nasal-inferior; Nas-sup, nasal-superior; OCTA, optical coherence tomography angiography; pRNFL, peripapillary retinal nerve fiber layer; RPCP, radial peripapillary capillary plexus; SD, standard deviation; Temp-inf, temporal-inferior; Temp-sup, temporal-superior.

parameters.[8–10] In this study, we analyzed optic disc vasculature and peripapillary microvasculature with OCTA and RNFL thickness using OCT in limited scleroderma patients. Compared with healthy control subjects, patients with scleroderma had no significant difference in whole image, inside disc, or peripapillary vessel densities and RNFL thickness parameters. These findings may suggest that the evaluation of the optic nerve head vessel density is currently not suitable for screening susceptibility to glaucoma in patients with scleroderma.

Several studies have provided evidence for increased glaucoma prevalence (8.5–21.57%) in patients with scleroderma. Yamamoto and colleagues found a significantly higher prevalence of NTG and POAG in patients with scleroderma when compared with otherwise healthy subjects based on applanation tonometry, ophthalmoscopy with retinal photography, and automated static perimetry. The prevalence of NTG, POAG, and other subtypes of glaucoma was 3.9%, 1.3%, and 3.3%, respectively.[1] Allanore and colleagues[2] showed increased prevalence of normotensive ocular glaucomatous abnormalities including abnormal visual field, enlarged optic cup, and concentric loss of the neural rim in patients with scleroderma. Gomes and colleagues[3] found the prevalence of glaucoma to be 13.3% (11.1% POAG, 2.2% angle

Table 3. Effect of IOP, refraction error, age, age at diagnosis, disease duration, and antibody levels on the optic nerve head vessel density of the patients with limited scleroderma.

	Whole image	Inside disc	Peripapillary
IOP			
R	−0.374	−0.202	−0.059
[a]*p*	0.054	0.268	0.747
Refraction			
R	0.112	−0.086	0.208
[b]*p*	0.543	0.640	0.253
Age			
R	−0.346	−0.264	−0.183
[a]*p*	0.050*	0.145	0.316
Age at diagnosis			
R	0.017	−0.216	0.106
[a]*p*	0,928	0.242	0.572
Disease duration			
R	−0.371	−0.111	−0.219
[a]*p*	0.040*	0.552	0.237
Antibody			
ACA (+)			
Mean ± SD	50.4 ± 0.92	50.59 ± 3.52	52.59 ± 1.87
Range	48.5–51.3	45–54.2	49–54.5
ANA (+)			
Mean ± SD	51.11 ± 2.09	52.64 ± 3.,55	53.24 ± 2.11
Range	48.7–53.2	46.7–57.7	49.9–55.9
SCL70 (+)			
Mean ± SD	50.86 ± 1.32	51.15 ± 3.6	53.25 ± 1.89
Range	48.7–52.7	45.9–59	49.7–55.1
[c]*p*	0,400	0,563	0,709

ACA, anti-centromere antibodies; ANA, antinuclear antibody; IOP, intraocular pressure; SD, standard deviation.
[a]Pearson's correlation coefficient.
[b]Spearman's correlation coefficient.
[c]Kruskal–Wallis test.
*$p < 0.05$.

closure glaucoma) but did not investigate for NTG and suggested that systemic vascular disturbances were a potential reason for its occurrence. In a recent study, Szucs and colleagues[4] investigated glaucoma detection based on different diagnostic techniques including IOP measurement, peripapillary RNFL thickness, and automated static perimetry, and they found that approximately one-fifth (21.57%) of the patients suffered from a wide spectrum of glaucoma types including POAG, closed-angle, pigmentary, and NTG. These studies all suggested a glaucomatous propensity and justified long-term follow-up of scleroderma patients to assess the ophthalmological risk. Unlike the surveys mentioned here, our study is not a prevalence study. We have already excluded patients who had glaucoma or even had a family history of glaucoma and conducted the current study to investigate the possible early subclinical effects of scleroderma on the optic disc microvascular perfusion parameters that may progress to clinically apparent glaucoma. We found a weak correlation only between the radial RPCP whole-image perfusion and the duration of the disease. So if the patients with scleroderma followed for a long duration, some microvascular alterations and even glaucoma can possibly be detected.

This study is the first study in the literature which investigates optic disc microvascular alterations in patients with scleroderma using OCTA. An important limitation was the relatively small study population, which reduced the statistical power of our study. Thus, studies with larger sample size and sufficient power might produce statistically significant results. Therefore, conclusions about the insignificant differences between the groups must be interpreted with caution. Longitudinal studies with large sample sizes investigating the parameters of the optic nerve head and peripapillary retina using OCTA for a longer period of time in patients with scleroderma are still needed.

In conclusion, we comprehensively illustrated the microvascular characteristics of the optic nerve head and peripapillary retina in patients with limited scleroderma and found no significant difference in the radial RPCP whole image, inside disc, and peripapillary vessel density values and RNFL parameters compared with those of controls.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Informed consent

The study followed the tenets of the Declaration of Helsinki and was approved by the review board of Keçiören Training and Research Hospital (No: 2012-KAEK-15/1863). Informed written consent was obtained from each patient.

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References

1. Yamamoto T, Maeda M, Sawada A, *et al*. Prevalence of normal-tension glaucoma and primary open-angle glaucoma in patients with collagen diseases. *Jpn J Ophthalmol* 1999; 43: 539–542.
2. Allanore Y, Parc C, Monnet D, *et al*. Increased prevalence of ocular glaucomatous abnormalities in systemic sclerosis. *Ann Rheum Dis* 2004; 63: 1276–1278.
3. Gomes Bde A, Santhiago MR, Magalhães P, *et al*. Ocular findings in patients with systemic sclerosis. *Clinics* 2011; 66: 379–385.
4. Szucs G, Szekanecz Z, Aszalos Z, *et al*. A wide spectrum of ocular manifestations signify patients with systemic sclerosis. *Ocul Immunol Inflamm*. Epub ahead of print 2 October 2019. DOI: 10.1080/09273948.2019.1657467.
5. Broadway DC and Drance SM. Glaucoma and vasospasm. *Br J Ophthalmol* 1998; 82: 862–870.
6. Sakkas LI. New developments in the pathogenesis of systemic sclerosis. *Autoimmunity* 2005; 38: 113–116.
7. Matucci-Cerinic M, Kahaleh B and Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum* 2013; 65: 1953–1962.
8. Liu L, Tan O, Ing E, *et al*. Sectorwise visual field simulation using optical coherence tomographic angiography nerve fiber layer plexus measurements in glaucoma. *Am J Ophthalmol* 2020; 212: 57–68.

9. Lee EJ, Lee KM, Lee SH, *et al*. OCT angiography of the peripapillary retina in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2016; 57: 6265–6270.
10. Richter GM, Chang R, Situ B, *et al*. Diagnostic performance of macular versus peripapillary vessel parameters by optical coherence tomography angiography for glaucoma. *Transl Vis Sci Technol* 2018; 7: 21.
11. Triolo G and Rabiolo A. Optical coherence tomography and optical coherence tomography angiography in glaucoma: diagnosis, progression, and correlation with functional tests. *Ther Adv Ophthalmol* 2020; 12: 2515841419899822.
12. Lin PW, Chang HW, Lin JP, *et al*. Analysis of peripapillary retinal nerve fiber layer and inner macular layers by spectral-domain optical coherence tomography for detection of early glaucoma. *Int J Ophthalmol* 2018; 11: 1163–1172.
13. Gür Güngör S and Ahmet A. Are all retinal nerve fiber layer defects on optic coherence tomography glaucomatous. *Turk J Ophthalmol* 2017; 47: 267–273.
14. Mukherjee C, Al-Fahad Q and Elsherbiny S. The role of optical coherence tomography in therapeutics and conditions, which primarily have systemic manifestations: a narrative review. *Ther Adv Ophthalmol* 2019; 11:2515841419831155.
15. Kılınç Hekimsoy H, Şekeroğlu MA, Koçer AM, *et al*. Analysis of retinal and choroidal microvasculature in systemic sclerosis: an optical coherence tomography angiography study. *Eye* 2020; 34: 763–770.
16. van den Hoogen F, Khanna D, Fransen J, *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737–2747.
17. Wirz EG, Jaeger VK, Allanore Y, *et al*. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database. *Ann Rheum Dis* 2016; 75: 1285–1292.