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Conjunctival microvascular alterations in dry eye disease: A comparative study of Sjögren's and non-Sjögren's subtypes

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Abstract:

PURPOSE: Conjunctival microvasculature is associated with ocular and systemic diseases. Previous studies have reported increased blood flow velocity (BFV), blood flow rate (BFR), vessel density, and diameter in dry eye disease (DED). This study aimed to compare bulbar conjunctival microvascular morphology and hemodynamics between patients with DED with and without Sjögren's dry eye (SSDE and NSDE) who had comparable symptoms, and to assess their correlations with Meibomian gland dysfunction (MGD) parameters.

MATERIALS AND METHODS: In this prospective study, conjunctival imaging for the left eyes of patients with DED was performed using a previously developed optical system incorporating Attention-UNet-based vessel segmentation and a validated two-step motion-correction pipeline. Tear film lipid layer thickness measurement and meibography were performed using the LipiView® II Ocular Surface Inferometer. Microvascular parameters, including BFV, BFR, and diameter, were quantified.

RESULTS: The mean microvessel diameter for the SSDE group (12.985 ± 2.478 μm) was significantly higher than that for NSDE (9.431 ± 3.982 μm) ($P < 0.050$). In the NSDE group, diameter correlated positively with BFR ($P < 0.050$), and BFR correlated with both upper and lower meiboscores ($P < 0.050$).

CONCLUSION: These findings reveal distinct conjunctival microvascular signatures in patients with SSDE, and support vessel diameter as a discriminator. The association between hemodynamic changes and MGD parameters in the NSDE group underscores the interplay between MGD and conjunctival microcirculation in NSDE. The differences in microvasculature identified in this study may serve as valuable biomarkers for DED subtype classification and the development of personalized treatment.

Keywords:

Bulbar conjunctiva, conjunctival microvasculature, dry eye disease, meibomian gland dysfunction, Sjögren's syndrome

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Introduction

Dry eye disease (DED) is a multifactorial disease that results in symptoms such as ocular discomfort, visual disturbances, and tear film instability, with potential damage to the ocular surface.[1] Its global prevalence was estimated as 11.59% between 1997 and 2021, with the highest prevalence (42.8%) observed in Eastern Asia.[2] The most common complaint of patients with DED is ocular discomfort, described as dryness, redness, a foreign body sensation, a heavy sensation, pain, light sensitivity, discharge, itching, and eye fatigue.[3] Common risk factors include advanced age, female sex, low humidity,

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use of systemic medications, and autoimmune disorders.[4]

Tests such as the tear film breakup time (TBUT), Schirmer's test, and fluorescein or lissamine green ocular surface staining are generally performed to diagnose DED. However, the results are often interpreted subjectively, have low accuracy, and may not be correlated. The correlation between symptoms and signs of DED is often poor.[5] Therefore, objective tests that correlate symptom severity with the various etiologies of DED are required.

The conjunctival vasculature may serve as a valuable tool in this regard. The conjunctiva, a microvascularized translucent membrane that covers the sclera of the human eye, has intricate microcirculation and serves as the basic functional unit of blood circulation.[6] Conjunctival microvasculature is associated with ocular and systemic diseases. Previous studies have reported alterations in the conjunctival microvasculature of patients with DED, including increased blood flow velocity (BFV), blood flow rate (BFR), vessel density, and vessel diameter.[7] However, no study has specifically examined how meibomian gland dysfunction (MGD)-related DED subtypes affect conjunctival microvasculature.

Conventional methods for measuring conjunctival vessels include functional slit-lamp biomicroscopy, a method in which a digital camera is attached to the front of a slit lamp for imaging.[8] Modified laser Doppler flowmetry is another method for measuring conjunctival blood flow. It utilizes confocal scanning and laser Doppler flowmetry to generate a two-dimensional microcirculation.[9] Orthogonal polarized spectral imaging can also be used to visualize the blood vessels of the peripheral microcirculation at a wavelength within the hemoglobin absorption spectrum (548 nm).[10] A custom-built optical system incorporating a two-step calibration method and a deep learning-based segmentation model has been introduced to address method limitations related to motion artifacts stemming from image displacement and low-quality images.[11]

DED has several subtypes, including conditions associated with systemic autoimmune disorders such as Sjögren's syndrome (SS). SS is a chronic inflammatory autoimmune disease characterized by lymphocytic infiltration of exocrine glands, such as the salivary and lacrimal glands. This causes aqueous-deficient DED.[12] Approximately 1% of DED cases in the general population are linked to SS. However, up to 10% of patients with clinically significant DED present underlying SS.[13,14] Mild SS symptoms are often overlooked, leading to an average diagnostic delay of approximately 11 years.[15] Early detection is essential for preventing ocular and systemic complications. However, evidence-based tools for screening patients with DED for SS during initial consultations are currently lacking. This underscores the need for diagnostic aids that can prompt further rheumatological evaluation when warranted.[16]

We previously developed and validated an imaging platform that combines Attention-UNet-based vessel segmentation with a two-step motion-correction pipeline.[11] This platform reduces image displacement from 16 μm to <1 μm while achieving high segmentation accuracy and flow metric reproducibility. We applied it to quantify bulbar conjunctival BFV, BFR, and vessel diameter. The primary objective of this study was to analyze the morphological and hemodynamic features of the bulbar conjunctival microvasculature in patients with DED and distinguish between those with and without SS. The secondary objective was to explore correlations between the parameters of MGD and the conjunctival microvasculature.

Materials and Methods

Study design and patient recruitment

This prospective study included 51 patients with DED recruited from Yeouido St. Mary's Hospital between April 2020 and October 2021. Prior data on differences between the conjunctival vessels of eyes with Sjögren's syndrome dry eye (SSDE) and non-Sjögren's dry eye (NSDE) were not available at the time of the study design. *Post hoc* power analysis (G*Power 3.1; Heinrich Heine University Düsseldorf, Germany) based on the observed mean vessel diameter differences (Cohen's $d = 1.10$) yielded a power of 0.97 (97%) to detect this effect. This study was approved by the Institutional Review Board (No. SC19DESE0067) and conducted in compliance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before their participation.

Patients aged ≥20 years and diagnosed with DED by one corneal specialist (K.S.N.) were included. DED was defined as a TBUT of ≤5 s with symptoms in accordance with the consensus reached by the Asia Dry Eye Society.[17] Demographic information and ocular and medical history, including SS, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, and other systemic vascular diseases, were collected. Standardized questionnaires were used to assign ocular surface disease index (OSDI) scores (range, 0–100; normal, 0–12; mild, 13–22; moderate, 23–32; severe, ≥33).[18] The left eye of each patient was selected for evaluation. A complete ophthalmic examination was conducted with a minimum interval of 5 min in the following order: TBUT, fluorescein staining of the cornea and

conjunctiva, conjunctival microvasculature evaluation, slit-lamp examination for assessment of meibomian gland expression (MG expressibility), evaluation of the tear film lipid layer thickness (LLT), and MG loss with an ocular surface interferometer. The examination sequence is described in detail in Section 2.2.

Patients were excluded based on the following criteria: use of topical or systemic steroids; use of medications known to affect tear secretion (e.g., sulfasalazine); systemic treatments, including immunosuppressant agents, specifically for SS; presence of other ocular diseases, including diabetic and hypertensive retinopathy, or a history of ocular surgery or ocular trauma; use of topical eye drops or contact lenses; inability to understand the questionnaire or the procedures; and difficulty in measuring conjunctival microvasculature due to poor cooperation.

The patients were divided into two groups: those with SSDE and those with NSDE. SS was diagnosed by a board-certified rheumatologist who was blinded to all conjunctival microvasculature data, using only clinical history, serology, ocular staining, and salivary gland biopsy in accordance with the 2012 American College of Rheumatology criteria developed by the Sjögren's International Collaborative Clinical Alliance (SICCA).[19,20]

Ophthalmic examinations

Tear and ocular surface evaluation

TBUT was measured for each eye using a fluorescein-based measurement with slit-lamp examination. Corneal and conjunctival fluorescein staining scores were graded from 0 to 5 based on the Oxford Scheme. For all fluorescein-based measurements, a drop of topical proparacaine hydrochloride solution (Alcaine eye drops 0.5%; Alcon Ophthalmic Products Co. Ltd., Seoul, Korea) was placed on a fluorescein® sodium-impregnated paper strip (Haag-Streit International Con., Ltd, Koeniz, Switzerland) and instilled into each conjunctival sac. A yellow-barrier filter and cobalt-blue illumination from a slit lamp (Topcon SL-D701; Topcon Co., Ltd., Tokyo, Japan) were used to assess the tear film.

Meibomian gland evaluation

A drop of topical anesthetic was instilled into the conjunctival sac to evaluate MG expressibility, and the upper eyelid was squeezed with cotton swabs by a single investigator (K.S.N). The ability of eight MGs situated in the central region of the upper eyelid to secrete meibum was evaluated following the application of mechanical pressure using a handheld Meibomian Gland Evaluator™ (TearScience Inc., Morrisville, NC, USA).[21] Scores ranging from 0 to 8 were assigned based on the number of expressible glands among the eight central glands. Tear film LLT was measured using an ocular surface interferometer LipiView® II (TearScience Inc., Morrisville, NC, USA). Among the maximum, minimum, and average LLT from all frame averages obtained, only the average LLT was used in this study. The MGs were observed with LipiView® II by everting the upper and lower eyelids. The meiboscore, which showed partial or complete loss of the MGs, was scored from grade 0 to grade 3 for each upper and lower eyelid using Lipiview® II meibography: Grade 0 (no gland dropout), Grade 1 (<1/3), Grade 2 (1/3–2/3), and Grade 3 (>2/3 gland dropout of the total MG area).[15]

Conjunctival microvasculature evaluation

Conjunctival blood flow analysis was performed in the left eye. The conjunctival microvasculature was evaluated after fluorescein staining but before the MG and tear film lipid evaluations to minimize the potential impact of desiccating stimuli or pressure exerted during MG evaluation. This testing sequence ensured that any hemodynamic alterations in the conjunctival microvasculature due to external factors were minimized during blood flow analysis.

Participants were instructed to maintain head and face position during the examination and fix their gaze on a target point located 1 meter ahead at a 45° angle to the right. A single expert technician selected the most visible bulbar vessel in the temporal area of the left eye using an observability index combining vessel length and temporal contrast variance. All image analyses were performed by an investigator (D.Y.K) blinded to SS status.

Imaging was performed as previously described.[11] The design of this system is shown in Figure 1. The system provided a magnification of ×3.798 and a field of view of 2.00 mm × 1.68 mm. The processing pipeline combined Attention-UNet-based vessel segmentation with a validated two-step motion-correction process. The first step corrected large movements through coarse registration. The second step involved template matching to refine the alignment. This approach reduced the mean displacement from approximately 16 μm to <1 μm in our prior pilot study. Video was captured at 25 frames per second for 3 s, and the frames were averaged into a high signal-to-noise composite before segmentation. Segmentation on motion-corrected images was performed using the Attention-UNet model. BFV was measured by spatial–temporal analysis of red blood cell shifts along the vessel centerline, and vessel diameter and BFR were quantified from the segmented structures.

Statistical analysis

Statistical analyses were performed using SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA). Normality for all parameters was assessed using the

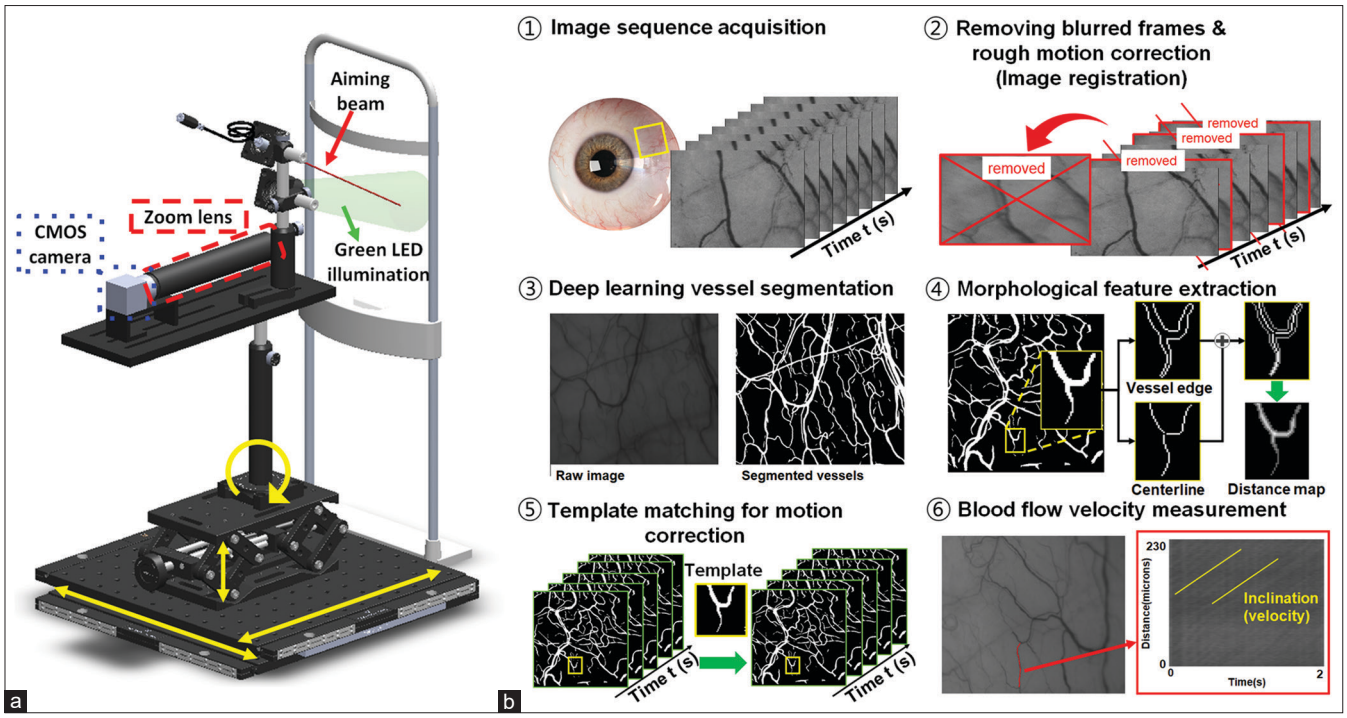

Figure 1: Experimental optical setup and image analysis procedures. (a) Custom-built optical imaging system for human conjunctival microcirculation. (b) Quantification of the blood flow velocity from acquired conjunctival vessel images

Kolmogorov–Smirnov test; a non-parametric test was used for statistical analysis because none of the parameters followed a normal distribution ($P < 0.050$). Sex differences between the SSDE and NSDE groups were compared using Fisher's exact test. The Mann–Whitney *U*-test was used to compare age, medical conditions (including HTN, DM, dyslipidemia, and other vascular diseases), ocular symptoms, and ocular clinical findings between the two groups. Multivariable logistic regression analysis was performed to determine whether conjunctival microvascular parameters independently distinguish SSDE from NSDE after adjusting for potential confounders, including sex, age, and systemic diseases. Spearman's rank correlation coefficients were calculated to explore the relationships between the bulbar conjunctival microvascular parameters and other variables. All subgroup correlation analyses were performed *post hoc* and considered exploratory. No adjustment for multiple comparisons was performed. A $P < 0.050$ denoted statistical significance. Graphical representations of the results were generated using GraphPad Prism (version 10.3.0; Graphpad Software Inc., La Jolla, California, USA).

Results

Demographics of the study population

The study included 51 eyes of 51 patients with DED, including 17 patients with SS diagnosed at the Rheumatology Department, and 34 without SS. The demographic characteristics of the patients are presented in Table 1. No differences in sex ($P = 0.161$) or age ($P = 0.522$) were observed between the two groups. There were no differences in other medical issues, including HTN, DM, or dyslipidemia ($P = 0.276$, $P = 0.475$, $P = 0.141$, respectively). Other vascular or systemic diseases were not found in any of the patients.

Clinical data of ocular surface and meibomian gland function parameters

The SSDE and NSDE groups showed no significant differences in OSDI score ($P = 0.095$), TBUT ($P = 0.673$), corneal and conjunctival staining scores ($P = 0.370$), MG expressibility ($P = 0.301$), average LLT ($P = 0.390$), or meiboscore of the upper ($P = 0.351$) and lower ($P = 0.986$) eyelids [Table 2]. No significant differences would result from the exclusion criteria of topical or systemic medication for SS; patients with severe symptoms and signs of SS are usually receiving treatment.

Bulbar conjunctival microvasculature parameters

The bulbar conjunctival microvasculature parameters for both groups are compared in Figure 2. Vessel diameters of the bulbar conjunctival microvasculature were significantly larger for the SSDE group (12.985 ± 2.478 μm) than for the NSDE group (9.431 ± 3.982 μm) ($P = 0.003$, Mann–Whitney U test). The SSDE group had higher BFR (21.238 ± 14.240 pl/s) and lower BFV (0.158 ± 0.103 mm/s) than the NSDE group (18.910 ± 23.632 pl/s and 0.203 ± 0.225 mm/s,

respectively), but these differences were not statistically significant (P = 0.154 and P = 0.962, respectively). The multivariable logistic regression model adjusted for sex, age, and systemic diseases (including HTN, DM, and dyslipidemia) revealed bulbar conjunctival microvessel diameter as the only remaining independent predictor of SSDE (odds ratio [OR] = 1.72; 95% confidence interval [CI]: 1.16–2.66; P = 0.007).

Table 1: Demographic characteristics of patients

	SSDE (n=17), n (%)	NSDE (n=34), n (%)	P
Sex			
Male	0	6 (17.65)	0.161*
Female	17 (100)	28 (82.35)	
Age	53.846±8.424	54.543±13.148	0.522**
HTN	4 (23.53)	4 (11.77)	0.276**
DM	0	1 (2.94)	0.475**
Dyslipidemia	4 (23.53)	0	0.141**
Other vascular disease	0	0	

*Fisher's exact test, **Mann–Whitney U-test. DM=Diabetes mellitus, HTN=Hypertension, NSDE=Nonsjögren dry eye disease, SSDE=Sjögren syndrome dry eye disease

Table 2: Ocular surface and meibomian gland function parameters for patients with and without Sjögren's syndrome

	SSDE	NSDE	P*
OSDI	42.838±24.716	35.038±18.439	0.095
TBUT (s)	1.692±1.032	1.971±1.362	0.673
Corneal and conjunctival staining score	1.923±1.037	1.600±0.901	0.370
MG expressibility	2.538±2.570	2.086±2.556	0.301
Average LLT (nm)	91.071±26.675	86.387±19.620	0.390
Upper lid meiboscore	2.214±0.787	2.250±0.987	0.351
Lower lid meiboscore	1.857±0.900	1.903±0.962	0.986

*Mann–Whitney U-test. LLT=Lipid layer thickness, MG=Meibomian gland, NSDE=Nonsjögren dry eye disease, OSDI=Ocular surface disease index, SS=Sjögren's syndrome, SSDE=Sjögren's syndrome dry eye disease, TBUT=Tear breakup time

Correlations between vessel diameter and blood flow rate

BFR increased with increasing conjunctival microvasculature diameter for the NSDE group (ρ = 0.807, P < 0.001). The correlation was weaker and not significant for the SSDE group (ρ = 0.390, P = 0.188). The correlations between the logarithm of the BFR (log-transformation applied for clearer visualization) and the diameter are shown in Figure 3. The ρ and P values remained unchanged after transformation.

Correlations between bulbar conjunctival microvasculature parameters, and ocular surface and meibomian gland function parameters

BFR, BFV, and vessel diameter were not significantly correlated with the OSDI, TBUT, or staining scores in either group [Table 3]. In the NSDE group, BFV correlated positively with the lower meiboscore (ρ = 0.447, P = 0.012) and showed a trend toward a positive association with the upper meiboscore (ρ = 0.348, P = 0.070). Conversely, BFV was nonsignificantly negatively correlated with the lower meiboscore (ρ = −0.416, P = 0.354) but significantly negatively correlated with the upper meiboscore (ρ = −0.757, P = 0.049) for the SSDE group.

Discussion

Summary of findings

This study is the first to determine the differences in the bulbar conjunctival microvasculature between SSDE and NSDE using a custom-built optical system with a two-step calibration method and a deep learning-based segmentation model. The findings suggest a new approach for inflammatory DED. We investigated how SS, a systemic condition closely associated with DED, affects the conjunctival microvasculature. Vessel diameters significantly increased for the SSDE group, whereas no significant differences were observed for other

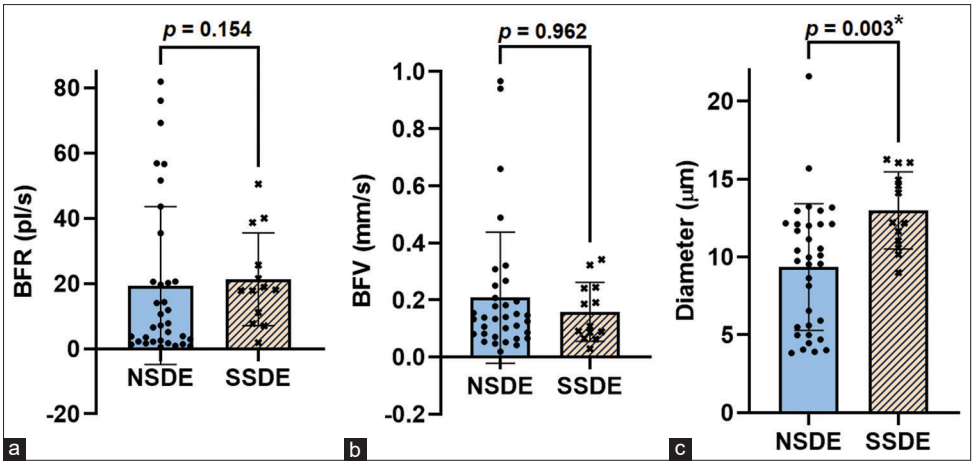

Figure 2: Comparison of bulbar conjunctival microvasculature parameters between NSDE and SSDE groups, including (a) blood flow rate, (b) blood flow velocity, and (c) vessel diameter. Analyzed using Mann–Whitney U-test. *Statistically significant results (P < 0.05). BFR = Blood flow rate, BFV = Blood flow velocity, NSDE = Non-Sjögren dry eye disease, SSDE = Sjögren's syndrome dry eye disease

Table 3: Correlations between bulbar conjunctival microvascular parameters, ocular surface, and meibomian gland function parameters in nonsjögren dry eye disease and Sjögren's syndrome dry eye disease groups

	BFR		BFV		Diameter	
	ρ	*P*	ρ	*P*	ρ	*P*
NSDE						
OSDI	0.018	0.919	−0.119	0.504	0.078	0.661
TBUT (s)	0.105	0.554	0.014	0.935	0.276	0.114
Corneal and conjunctival staining score	−0.026	0.885	−0.050	0.778	0.024	0.894
MG expressibility	0.231	0.188	0.209	0.236	0.075	0.672
Average LLT (mm)	−0.013	0.946	0.123	0.509	−0.211	0.254
Upper lid meiboscore	0.250	0.199	0.348	0.070	−0.078	0.691
Lower lid meiboscore	0.253	0.170	0.447	0.012*	−0.057	0.760
SSDE						
OSDI	−0.380	0.201	−0.363	0.223	−0.248	0.415
TBUT (sec)	−0.207	0.496	0.072	0.814	−0.248	0.413
Corneal and conjunctival staining score	0.392	0.185	0.263	0.386	0.254	0.403
MG expressibility	−0.006	0.985	0.070	0.820	−0.132	0.668
Average LLT (mm)	0.490	0.264	0.490	0.264	−0.401	0.373
Upper lid meiboscore	−0.401	0.373	−0.757	0.049*	0.23	0.631
Lower lid meiboscore	−0.151	0.746	−0.416	0.354	−0.208	0.655

*Statistically significant (*P*<0.050). Analyzed using Spearman's rank correlation. BFR=Blood flow rate, BFV=Blood flow velocity, LLT=Lipid layer thickness, MG=Meibomian gland, NSDE=Non-Sjögren dry eye disease, OSDI=Ocular surface disease index, SSDE=Sjögren's syndrome dry eye disease, TBUT=Tear breakup time

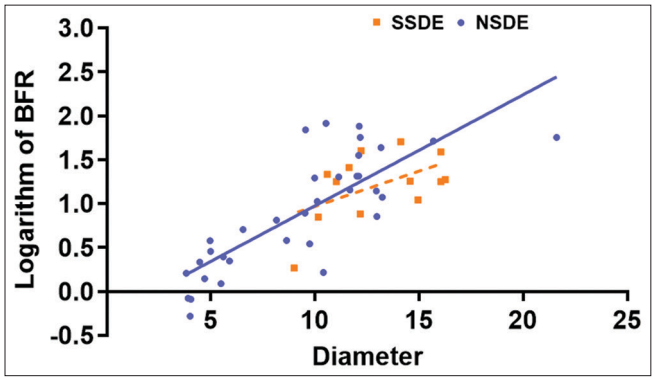

Figure 3: Correlation between vessel diameter and logarithm of blood flow rate (BFR) for the SSDE and NSDE groups. The logarithm of BFR was positively correlated with diameter for the NSDE group with statistical significance (r = 0.867, P < 0.001). Analyzed using Spearman's rank correlation. BFR = Blood flow rate, NSDE = Non-Sjögren dry eye disease; SSDE = Sjögren's syndrome dry eye disease

parameters, including BFR and BFV. Vessel diameter was the only predictor of SSDE in the multivariable logistic regression analysis, which was adjusted for other confounding factors. The conjunctival microcirculatory changes were similar for both groups, whereas the morphological changes were more significant for the SS group. This result indicates that the morphological changes in the conjunctival microvasculature are more pronounced in patients with systemic inflammatory disease than in those without. These changes are more characteristic of systemic inflammatory conditions than microcirculatory changes in DED alone.

BFR, one of the microcirculation parameters, tended to increase with vessel diameter. This tendency was stronger for NSDE than for SSDE. This indicates a strong correlation between the microcirculatory and morphological changes in the conjunctival microvasculature of eyes with NSDE. The morphological changes in eyes with SSDE may be attributed to factors independent of microcirculation, potentially involving an autoinflammatory mechanism. BFV exhibited a strong positive correlation with the meiboscore for NSDE, indicating a significant association between conjunctival microcirculation and MGD. Conversely, the meiboscores were negatively associated with BFV for SSDE. Therefore, MGD may be independent of BFV alterations.

We found no significant differences in clinical symptoms or DED parameters between the groups. This finding may be attributed to the exclusion of patients with SS who were receiving systemic treatment, including systemic steroids or immunosuppressants, to eliminate the confounding effects of systemic medications. This resulted in the predominant inclusion of mild SSDE cases. Vessel diameter differentiated patients with and without SS despite the lack of differences in DED symptoms and signs.

Comparison with prior literature

The conjunctiva is a translucent, highly microvascularized membrane that covers the sclera of the human eye. The palpebral conjunctiva and eyelids share a common arterial blood supply from the terminal branches of the ophthalmic artery, whereas the bulbar conjunctiva receives blood from the anterior ciliary arteries. The branches of the anterior ciliary arteries on the bulbar conjunctiva form anastomoses with recurrent vessels from the palpebral conjunctiva in the fornices.[22] Microcirculation, which refers to the microvessels between

the arterioles and venules, serves as the basic functional unit of blood circulation.[6] Changes in the conjunctival microvasculature have been observed in various ocular and systemic diseases due to these anatomical features.

Several systemic conditions, including diabetic retinopathy,[23] untreated HTN,[24] and unilateral ischemic stroke,[25] are associated with conjunctival microvascular parameters. We hypothesized that DED associated with a systemic autoimmune disorder (SSDE) has distinct morphological or hemodynamic features compared with NSDE. However, no statistically significant differences in BFR or BFV of the conjunctival microvasculature were observed between the SSDE and NSDE groups. These findings suggest that BFR and BFV are increased in patients with DED, regardless of systemic autoimmune status. This has been previously reported in patients with DED relative to healthy controls,[7] and a decrease after anti-inflammatory treatment was also reported.[26] Prior studies[7] have documented increased conjunctival vessel diameter in DED. However, we observed greater vessel diameter enlargement in autoimmune-associated DED. This study was cross-sectional, and its findings cannot be used to determine whether vessel diameter progressively increases after SSDE onset. In contrast, longitudinal studies of contact lens wearers have shown that microcirculation changes faster than the morphology, with an initial increase in BFR and BFV followed by increased vessel diameter and density.[8,27,28]

Pathophysiological implications and clinical relevance

SS is a chronic inflammatory autoimmune disease that is histologically characterized by lymphocytic infiltration and loss of secretory function in the lacrimal gland. This leads to keratoconjunctival SICCA (DED).[29-31] It is characterized by aqueous-deficient DED.[32] The density and function of sensory nerve fibers are reduced in these patients, which suppresses the tear reflex and tear production.[12] The conjunctiva in SS often shows higher occurrence of squamous metaplasia, loss of goblet cells, and mucous aggregates than that of healthy individuals or patients with DED due to other causes.[12] These conjunctival changes were accompanied by significant alterations in the morphology of the conjunctival microvasculature, indicating the impact of SS on conjunctival microvasculature structure. Yang *et al*. used optical coherence tomography angiography to assess the retinal and conjunctival microvasculature in both healthy controls and patients with SS. They found a significant increase in temporal conjunctival vessel density in patients with SS, which highlights the structural changes in the conjunctival microvasculature.[33]

Microvascular alterations have also been documented for systemic autoimmune diseases, especially in nailfold capillaries. Nailfold videocapillaroscopy (NVC) is the optimal technique for examining microvascular and cardiovascular abnormalities under these conditions.[34] The characteristic features of microvascular damage include a decrease in microvascular density and subsequent slowing of blood flow.[34] Structural changes accompanied by a decrease in nailfold capillary density are particularly evident in patients with early and active rheumatic diseases. Capillary diameters increase with these changes. We observed similar structural changes in the conjunctival microvasculature of patients with SSDE, including vessel diameter enlargement.

Interestingly, the SSDE group in our study showed a significant increase in vessel diameter without a corresponding significant increase in BFV. Furthermore, the BFV in the SSDE group showed a tendency towards further decrease relative to the NSDE group, although this difference was not statistically significant. This pattern may be consistent with chronic inflammatory processes in autoimmune diseases that lead to more persistent or potentially irreversible morphological changes, such as dilation of the conjunctival microvasculature. This contrasts with microcirculatory changes observed in other conditions, such as in contact lens wearers, in whom hemodynamic alterations precede morphological ones, as discussed in the previous section.[8,27,28] This suggests that an isolated increase in BFV might represent a more acute and potentially reversible microvasculature response to inflammation. Therefore, distinguishing between morphological and hemodynamic changes could help inform whether the inflammatory status in DED is more likely to be chronic or acute, and may explain why vessel diameter emerged as an independent predictor of SSDE in our cohort.

The relationships between the nailfold and conjunctival microvasculature have not been characterized. However, these changes in the conjunctival microvasculature may suggest similarities or related mechanisms observed in NVC.

Methodological limitations

One limitation of this study was the imprecision in measuring vessel density, a key aspect of morphological change. This led to its exclusion from the analysis. Accurate measurements of vessel density may confirm whether morphological changes are more pronounced in SS, an autoinflammatory disease. The inclusion of left eyes only and the lack of assessment of inter-eye variability may also limit the generalizability of our findings. The absence of a pre-study sample size calculation may have limited our ability to detect smaller effects. Therefore, the non-significant findings for BFR and BFV should be interpreted with caution. All subgroup correlation analyses were *post hoc*, which

may have increased the risk of type I error. Patients with severe DED, regardless of their SS status, were excluded due to inadequate measurements of the conjunctival microvasculature, making it challenging to obtain accurate data. This exclusion stems from the initial study criteria, which excluded patients using medications for SS. This limited the participant pool to those with mild symptoms. This study proposes parameters for suspected SS in patients with mild DED, which are important for early diagnosis.

The prevalence of systemic diseases such as DM and HTN did not differ significantly between the SSDE and NSDE groups. The multivariable logistic regression analysis adjusted for sex, age, and systemic diseases identified vessel diameter as an independent predictor of SSDE. However, the potential influence of unmeasured confounders cannot be fully excluded.[35] The presence of these systemic diseases may have influenced the findings. Future studies should consider more targeted exclusion criteria or conduct subgroup analyses to further isolate the effects of these systemic conditions from the microvascular changes observed in dry eye subtypes.

Conclusions

This study revealed characteristic morphological differences in the conjunctival microvasculature between patients with SSDE and NSDE, emphasizing larger vessel diameters in SSDE, an autoinflammatory disease. This demonstrates the correlations between the conjunctival microvasculature diameter and BFR, and between BFV and the meiboscore for patients with NSDE. The results emphasize the importance of detailed morphological and microcirculatory assessments for better understanding of DED conditions. Therefore, monitoring enlargement of the conjunctival microvasculature diameter in patients with DED through non-invasive methods may help establish criteria for rheumatologic evaluation for SS. This may facilitate early diagnosis and improve patient outcomes. Patients with SS often present first with dry eye symptoms at ophthalmology clinics before being referred to a rheumatologist for a definitive diagnosis. The ability of ophthalmologists to detect these morphological changes early through noninvasive imaging can play a crucial role in identifying patients who may benefit from further rheumatologic evaluation. Further longitudinal studies with larger cohorts are required to validate these findings. Including participants with severe DED in future studies would help examine the full spectrum of the condition and its potential impact on outcomes.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors declare that there are no conflicts of interests in this paper.

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