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ORIGINAL RESEARCH

Corneal Epithelial Thickness in Sjogren's Disease: A Pilot Study

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Purpose: This study was to assess corneal epithelial thickness (CET) in patients with Sjogren's disease (SjD).

Methods: A retrospective chart review was conducted of SjD patients from September 2021 to January 2022. Patient demographics, unanesthetized Schirmer's test, serologic markers, and symptoms as measured by the Ocular Surface Disease Index (OSDI) were reviewed. Epithelial thickness from both eyes was measured using anterior segment OCT at the central 3mm and concentric 5mm, 7mm, and 9mm zones for the superior, temporal, inferior, and nasal corneal quadrants. Associations between corneal epithelial thickness with patient demographics, clinical characteristics, and symptoms were evaluated using regression models.

Results: Fifteen SjD patients (100% female) were included with a mean age of 58.4 years. Patients with Sjogren's disease had a significantly thinner superior corneal epithelium compared to the inferior epithelium (mean 47.7mm vs 53.1mm, $p = 0.001$). The epithelial thickness mean standard deviation (MSD) was significantly inversely correlated with the unanesthetized Schirmer test ($r = -0.39$, $p = 0.005$), suggesting that an overall variability of CET correlates with decreased aqueous tear production. SS-A, SS-B, ANA, and RF positivity were not associated with any measures of CET.

Conclusion: This pilot study suggests that there is significant superior versus inferior thinning of corneal epithelium in Sjogren's patients. There was a significant correlation between variability of corneal epithelial thickness and decreased tear production in Sjogren's patients. Further larger studies are needed to understand the relationship of CET with objective and subjective measurements of ocular surface disease.

Keywords: Sjogren's disease, corneal epithelial thickness, anterior segment OCT

Introduction

Dry eye disease (DED) is a highly prevalent disease and is estimated to account for up to 25% of eye care outpatient visits.[1] Patients with Sjogren's disease (SjD) account for about 11% of DED patients.[2] SjD is one of the most common systemic autoimmune diseases that targets salivary and lacrimal glands, thereby producing xerostomia and keratoconjunctivitis sicca, respectively.[3]

Historically, diagnosis and management of dry eye, whether it be Sjogren's associated or not, can be challenging and requires the assessment of multiple objective and subjective measures. The slit-lamp exam, including the use of fluorescein staining of the cornea, may help clinicians evaluate the presence and severity of dry eye disease. Validated questionnaires such as the Ocular Surface Disease Index (OSDI) may provide information on subjective symptoms of affected patients.[4] In addition, meibography, tear film constituent analysis, and biomarkers may be used to evaluate DED.[5–7] However, due to the often subjective, variable, and tedious nature of these assessments, efforts have been made to discover new diagnostic tools that offer an objective and efficient assessment of the ocular surface.

In recent years, anterior segment optical coherence tomography (AS-OCT) has emerged as a new diagnostic tool for anterior segment pathology including DED. The benefits of AS-OCT include that it is a non-contact, non-invasive method of measuring structures of the anterior segment including corneal epithelial thickness, in an objective, repeatable,

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and rapid manner.[8] A few studies have been published exploring the utility of corneal epithelial thickness mapping in general DED, but most did not include SjD patients. For example, a 2014 study by Cui et al found that patients with symptomatic dry eye disease had a thinner superior corneal epithelial thickness compared to controls.[9] However, their study excluded patients with SjD. A separate study by Liang et al reported that in 54 non-Sjogren's DED patients, the limbal epithelium was thinner and bulbar conjunctival epithelium was thicker in DED patients when compared to non-DED patients.[10] More recently, Edorh et al found that, similar to prior studies, the superior corneal epithelium is the first to be impacted by DED; however, the authors did not specify whether or not SjD patients were included in their study.[11]

Given the promising diagnostic utility of corneal epithelial mapping in dry eye disease, studies on SjD patients are needed to understand the potential clinical utility of AS-OCT in this subpopulation. Our goal was to characterize patterns of corneal epithelial thinning measured by AS-OCT in Sjogren's patients and to evaluate the association of AS-OCT findings with patient demographics and clinical characteristics of SjD.

Methods

A retrospective chart review was conducted on SjD patients from the Penn Dry Eye & Ocular Surface Center at the Scheie Eye Institute from September 2021 to January 2022. This study was reviewed and approved by the University of Pennsylvania institutional review board (IRB). The guidelines outlined in the Declaration of Helsinki were followed. All patients were consented for participation in the study.

For each patient data including age, sex, race, unanesthetized Schirmer test scores, serum studies (ie, anti-Ro/SSA, anti-La/SSB, anti-nuclear antibody (ANA), and rheumatoid factor (RF) positivity), and symptoms as measured by the OSDI were extracted. Central epithelial thickness was measured in both eyes using the Optovue RTVue-XR Avanti OCT System (Visionix, Fremont, CA) and the central 3mm and concentric 5mm, 7mm, and 9mm zones were recorded for the superior (S), temporal, inferior (I), and nasal (N) quadrants.

Statistical analyses through correlation analysis and linear regression models were performed to assess the associations of corneal epithelial measurements with demographics, serologic markers, unanesthetized Schirmer test score, and dry eye symptoms among SjD patients. The inter-eye correlation was accounted for by using generalized estimating equations.

In this pilot study, the correction for multiple comparisons were not made. All statistical comparisons were performed in SAS v9.4 (SAS Institute Inc, Cary, NC), and two-sided $p < 0.05$ was considered statistically significant.

Results

Fifteen patients with Sjogren's disease were included in the study. The mean age was 58.4 years, all were female, and 80% were Caucasian. Ten (66.6%) patients were positive in SS-A or SS-B, 11 (73.3%) were RF positive, and 9 (60%) were ANA positive. Five (33.3%) patients had a positive salivary gland biopsy. Eight (53.3%) patients were on hydroxychloroquine.

Mean corneal epithelial thickness in the central 3mm and concentric 5mm, 7mm, and 9mm zones in the superior, temporal, inferior, and nasal quadrants is displayed in Figure 1. The overall mean maximum epithelial thickness was 58.2mm and the mean minimum epithelial thickness was 39.1mm. Patients with Sjogren's disease had a significantly thinner superior corneal epithelium (mean 47.7mm) compared to the inferior epithelium (mean 53.1mm, $p = 0.001$).

Race, age, SS-A, SS-B, and RF positivity were not significantly associated with tear secretion measured by Schirmer's testing or OSDI scores. ANA positivity was not significantly associated with Schirmer measurements but was associated with a lower OSDI score (43.1 vs 67.9, $p = 0.01$). (Table 1)

Pearson correlation coefficients and linear regression coefficients were calculated for all zones of corneal epithelium and associated measurements. The mean standard deviation (MSD) of the corneal epithelial thickness was inversely correlated with the aqueous tear production measured by Schirmer test ($r = -0.39$, $p = 0.0047$). All other corneal epithelium thickness measures were not significantly correlated with Schirmer or OSDI (Table 2). Corneal epithelial measurements did not differ by race and age (Table 3) and were not associated with positivity of SS-A, SS-B, ANA, and RF (Table 4 and Table 5).

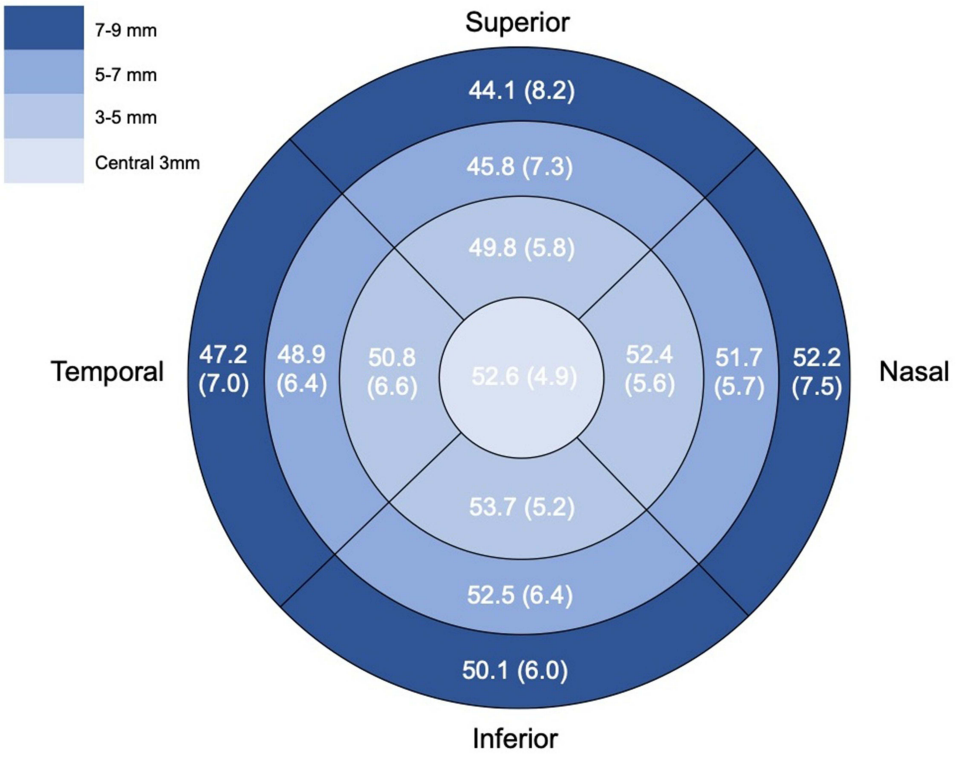

Figure 1 Mean corneal epithelial thickness in 15 Sjogren's patients. Corneal epithelial thickness measured by anterior segment OCT, notated as mean (standard deviation).

Discussion

In this pilot study of 15 patients with Sjogren's disease, we found a significantly thinner superior corneal epithelium compared to the inferior epithelium. The corneal epithelial thickness did not correlate with serology (SS-A, SS-B, ANA, or RF positivity), unanesthetized Schirmer scores, or symptoms as measured by OSDI scores. However, the mean standard deviation of epithelial thickness was inversely correlated with Schirmer scores.

Table 1 Associations of Patient Characteristics and Serologic Markers, with Tear Secretion Measured by Schirmer's Test and Symptoms Measured by Ocular Surface Disease Index (OSDI) Scores

	# of Patients	Schirmer Test Score		OSDI Score	
		Mean (SE)	P-value	Mean (SE)	P-value
Race			0.52		0.98
White	12	11.8(2.3)		49.8(5.4)	
Non-white	3	16.2(6.2)		49.5(10.7)	
SS-A			0.051		0.34
Positive	10	9.4(2.5)		46.5(5.7)	
Negative	5	19.1(3.0)		56.0(8.1)	
SS-B			0.052		0.99
Negative	5	6.4(2.7)		49.6(8.3)	
Positive	10	15.8(2.6)		49.7(5.9)	

(*Continued*)

Table 1 (Continued).

	# of Patients	Schirmer Test Score		OSDI Score	
		Mean (SE)	P-value	Mean (SE)	P-value
RF			0.06		0.66
Negative	6	8.4(2.5)		52.4(6.7)	
Positive	5	18.4(3.5)		56.8(7.4)	
ANA			0.21		0.01
Negative	11	10.7(2.4)		43.1(0.5)	
Positive	4	17.9(4.5)		67.9(7.5)	
Age					
Regression coefficient for per year increase (SE)	15	−0.32(0.12)	0.10	−0.60(0.42)	0.17

Abbreviations: SE, standard error; RF, rheumatoid factor; ANA, anti nuclear antibody.

Table 2 Association of Corneal Epithelial Thickness with Tear Secretion Measured by Schirmer's Test, and Symptoms Measured by Ocular Surface Disease Index (OSDI) Scores

	OSDI Score			
Epithelium Measurements	**Pearson Correlation Coefficient**	**P-value**	**Pearson Correlation Coefficient (P)**	**P-value**
Central 3mm	−0.06	0.78	−0.08	0.82
Superior 3–5mm	0.08	0.68	0.13	0.64
Superior 5–7mm	0.28	0.14	0.07	0.68
Superior 7–9mm	0.36	0.09	0.06	0.72
Temporal 3–5mm	−0.05	0.79	−0.01	0.97
Temporal 5–7mm	−0.01	0.94	−0.04	0.88
Temporal 7–9mm	0.10	0.59	0.02	0.93
Inferior 3–5mm	0.04	0.84	−0.18	0.52
Inferior 5–7mm	0.06	0.25	−0.18	0.59
Inferior 7–9mm	0.17	0.35	0.11	0.68
Nasal 3–5mm	−0.008	0.97	−0.02	0.95
Nasal 5–7mm	0.13	0.42	−0.18	0.55
Nasal 7–9mm	0.26	0.18	−0.02	0.95
Superior average	0.20	0.28	0.08	0.70
Inferior average	0.08	0.67	−0.18	0.61
Max	−0.22	0.26	−0.15	0.61
Min	0.22	0.14	0.06	0.75
Mean standard deviation	−0.39	0.0047	−0.16	0.39

Table 3 Associations of Corneal Epithelial Thickness with Race and Age

	Race			Age	
Epithelium Measurements	**White Mean (SE)**	**Non-White Mean (SE)**	**P-value**	**Regression Coefficient (SE)**	**P-value**
Central 3mm	52.5(1.4)	53.4(1.5)	0.64	0.99(0.07)	0.86
Superior 3–5mm	49.5(1.6)	51.2(1.0)	0.40	0.95(0.06)	0.37
Superior 5–7mm	45.2(1.9)	48.6(1.5)	0.28	0.90(0.08)	0.37
Superior 7–9mm	43.6(2.3)	46.4(1.7)	0.39	0.93(0.10)	0.54
Temporal 3–5mm	50.4(1.8)	52.6(1.6)	0.37	1.04(0.09)	0.63
Temporal 5–7mm	48.3(1.5)	51.8(1.0)	0.13	1.01(0.09)	0.95
Temporal 7–9mm	46.1(1.7)	52.4(1.3)	0.08	0.96(0.12)	0.80
Inferior 3–5mm	53.8(1.4)	53.4(2.4)	0.89	0.98(0.09)	0.84
Inferior 5–7mm	52.7(1.7)	51.6(2.1)	0.70	0.97(0.10)	0.76
Inferior 7–9mm	50.3(1.7)	49.6(2.1)	0.81	0.997(0.07)	0.97
Nasal 3–5mm	52.3(1.5)	52.6(1.8)	0.91	0.92(0.07)	0.16
Nasal 5–7mm	51.0(1.5)	54.6(1.6)	0.16	0.91(0.07)	0.23
Nasal 7–9mm	51.3(2.0)	56.6(0.7)	0.10	0.89(0.10)	0.37
Superior average	47.2(1.7)	49.8(0.6)	0.25	0.92(0.07)	0.33
Inferior average	53.2(1.6)	52.4(2.1)	0.77	0.97(0.09)	0.76
Max	58.1(1.9)	59.0(2.0)	0.74	0.90(0.11)	0.25
Min	38.5(2.9)	42.0(3.8)	0.52	0.96(0.18)	0.83
MSD	4.0(0.5)	2.8(0.8)	0.32	0.99(0.05)	0.81

Abbreviations: SE, standard error; MSD, mean standard deviation.

Table 4 Association of Corneal Epithelial Thickness with SS-A and SS-B Positivity

	SS-A			SS-B		
Epithelium Measurements	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**
Central 3mm	53.7(1.7)	50.6(0.4)	0.12	51.9(2.6)	53.0(1.1)	0.70
Superior 3–5mm	51.0(1.9)	47.5(0.8)	0.14	49.0(3.1)	50.2(1.3)	0.72
Superior 5–7mm	45.8(2.4)	45.6(1.7)	0.93	43.1(3.7)	47.2(1.4)	0.33
Superior 7–9mm	43.6(2.7)	45.0(2.0)	0.67	40.0(4.1)	46.2(1.6)	0.20
Temporal 3–5mm	52.3(2.1)	47.9(1.1)	0.11	50.1(3.5)	51.1(1.4)	0.79
Temporal 5–7mm	50.4(1.8)	46.0(0.7)	0.06	47.7(2.7)	49.5(1.4)	0.56
Temporal 7–9mm	48.7(2.0)	44.2(1.7)	0.13	45.8(3.1)	47.9(1.7)	0.56
Inferior 3–5mm	54.8(1.7)	51.6(0.8)	0.13	51.5(1.9)	54.9(1.5)	0.19

(*Continued*)

Table 4 (Continued).

	SS-A			SS-B		
Epithelium Measurements	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**
Inferior 5–7mm	53.6(2.1)	50.4(1.3)	0.22	49.2(1.2)	54.3(2.0)	0.07
Inferior 7–9mm	51.3(1.9)	47.9(1.8)	0.23	47.3(1.8)	51.6(1.9)	0.14
Nasal 3–5mm	53.8(1.7)	49.6(1.0)	0.08	52.1(2.6)	52.5(1.5)	0.88
Nasal 5–7mm	52.9(1.7)	49.3(1.1)	0.12	49.8(1.6)	52.6(1.7)	0.25
Nasal 7–9mm	53.2(2.4)	50.2(2.0)	0.35	49.2(3.1)	53.7(1.9)	0.35
Superior average	48.3(2.1)	46.5(1.2)	0.48	45.9(3.3)	48.6(1.3)	0.46
Inferior average	54.1(1.9)	51.1(1.1)	0.21	50.2(1.6)	54.6(1.7)	0.10
Max	60.2(2.2)	54.6(0.6)	0.0501	59.2(3.4)	57.7(1.6)	0.70
Min	39.2(3.6)	39.0(2.7)	0.97	34.7(3.7)	41.4(2.2)	0.30
MSD	4.2(0.7)	3.0(0.3)	0.14	4.8(1.1)	3.3(0.3)	0.22

Abbreviations: SE, standard error; MSD, mean standard deviation.

Table 5 Association of Corneal Epithelial Thickness with Rheumatoid Factor (RF) and Anti-Nuclear Antibody (ANA) Positivity

	RF			ANA		
Epithelium Measurements	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**
Central 3mm	53.5(2.1)	51.2(0.5)	0.36	52.3(1.3)	53.4(2.5)	0.71
Superior 3–5mm	51.1(2.6)	48.6(0.7)	0.38	49.4(1.5)	50.8(2.9)	0.69
Superior 5–7mm	46.1(3.3)	46.6(1.5)	0.89	45.6(2.2)	46.3(1.8)	0.81
Superior 7–9mm	43.5(3.7)	46.8(1.5)	0.43	43.6(2.6)	45.4(1.5)	0.55
Temporal 3–5mm	52.8(2.3)	49.4(1.0)	0.21	50.5(1.7)	51.5(3.3)	0.79
Temporal 5–7mm	50.7(1.3)	47.4(1.1)	0.10	49.3(1.6)	47.8(2.0)	0.56
Temporal 7–9mm	49.2(1.5)	45.7(1.8)	0.17	48.0(1.9)	45.0(2.1)	0.33
Inferior 3–5mm	53.1(1.9)	52.7(0.7)	0.85	53.9(1.6)	53.3(1.5)	0.77
Inferior 5–7mm	51.9(2.0)	51.0(1.3)	0.70	53.3(1.9)	50.5(1.4)	0.28
Inferior 7–9mm	50.9(2.6)	49.1(1.4)	0.54	50.3(1.9)	49.6(2.0)	0.79
Nasal 3–5mm	52.8(2.3)	50.6(0.7)	0.37	52.2(1.4)	52.9(2.8)	0.83
Nasal 5–7mm	52.0(1.6)	50.0(1.0)	0.30	52.4(1.7)	49.8(1.1)	0.24
Nasal 7–9mm	53.6(2.4)	51.1(1.8)	0.42	52.5(2.3)	51.4(2.2)	0.73
Superior average	48.3(2.9)	47.6(1.1)	0.81	47.3(1.8)	48.5(2.1)	0.68
Inferior average	52.4(1.9)	51.9(1.0)	0.81	53.5(1.8)	51.9(1.4)	0.48

(*Continued*)

Table 5 (Continued).

	RF			ANA		
Epithelium Measurements	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**	**Positive Mean (SE)**	**Negative Mean (SE)**	**P-value**
Max	58.5(2.9)	55.2(0.6)	0.29	58.1(1.7)	58.5(3.5)	0.93
Min	40.7(4.5)	40.6(2.8)	0.99	39.1(3.3)	39.0(3.1)	0.97
MSD	3.6(0.7)	2.9(0.3)	0.36	3.8(0.6)	3.9(0.7)	0.91

Abbreviations: SE, standard error; MSD, mean standard deviation.

Superior corneal epithelial thinning has been implicated as the first affected area in DED patients. For example, Edorh et al found that superior epithelial thinning at a cutoff of less than 50 microns had 81% sensitivity and 79% specificity towards differentiating DED patients from healthy patients.[11] In our study, 62.1% of eyes had a superior corneal epithelial thickness of less than 50 microns. A separate study by Cui et al noted that the superior corneal epithelium was significantly thinner in comparison to healthy eyes and that the superior epithelium was thinner in higher grade compared to lower grade DED patients.[9] Similarly, in a study by Reinstein et al, the superior corneal epithelium was 5.9 microns thinner at the 3mm radius compared to the inferior corneal epithelium.[12] Similar to these studies, superior quadrant thickness in our study was thinner at each concentric zone and on average thinner than the inferior quadrant by 5.4 microns. The mean superior quadrant epithelial thickness was 47.7mm, concordant with the sub-50 mm diagnostic cutoff proposed by Edorh et al for dry eye patients.[11] The superior cornea has been suggested to be more prone to damage due to the frictional forces from eyelid blinking, which may be more pronounced in dry eye patients.[13,14] It has also been proposed that it is the possible the central corneal epithelium is spared due to its distance from the limbus, and relatively more immune privilege.[15]

In patients with Sjogren's disease, mapping the corneal epithelium offers a potential opportunity for ophthalmologists to closely objectively monitor the progression of disease and guide treatment decisions. Recent studies have also demonstrated that corneal epithelial mapping may be a useful tool to measure response to treatment.[15,16] In addition to aiding in diagnosis and treatment, corneal epithelial mapping may also provide important insights into the underlying mechanisms of Sjogren's disease. By studying the characteristics of the corneal epithelium in patients with the disease, researchers can gain a better understanding of the pathophysiology of dry eye syndrome and other corneal complications.

In our study, corneal epithelial thickness in each of the measured sectors did not correlate to serology, tear production measured by Schirmer testing, or symptoms measured by OSDI scores. However, the mean standard deviation of corneal epithelial thickness did negatively correlate with tear secretion as measured by Schirmer's testing. This suggests that an overall variability of corneal epithelium thickness correlates with poor tear secretion, which has not been reported in the past. Future studies are needed to validate this finding.

Limitations of this pilot study include a small sample size and the lack of a control group. More subtle changes and correlations between corneal epithelial thickness and clinical parameters that require a larger sample size to detect may be missed. Despite these limitations, our study allows comparisons to be drawn with other DED corneal epithelial mapping studies that may illuminate similarities and differences of Sjogren's disease patients compared to the DED population as a whole.

In conclusion, this small retrospective study demonstrated a significant correlation between decreased Schirmer measurements and a higher MSD of CET in SjD patients. Further, larger studies that including various subpopulations of DED patients are needed to better understand the relationship of CET with objective and subjective measurements of dry eye disease.

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