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Original article

Corneal Thickness Mapping in Rheumatoid Arthritis Patients Using Anterior-Segment Optical Coherence Tomography

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Abstract:

Background: Ocular manifestations of rheumatoid arthritis (RA) include dry eye (DE), episcleritis, scleritis, and peripheral ulcerative keratitis (PUK). The most common form of ocular involvement is DE. **Purpose:** To generate corneal thickness (CT) and corneal epithelial thickness (CET) maps using anterior segment optical coherence tomography (AS¬¬-OCT) in RA patients and compare those parameters with normal subjects. **Materials and Methods:** A case-control study was done on 35 eyes of 18 RA patients and 25 eyes of 14 healthy individuals recruited from Benha University Hospitals. All the included cases were subjected to full history taking and ophthalmological examination. All participants were successfully imaged using AS-OCT with subsequent automated CT and CET mapping. The disease activity score (DAS-28) was calculated for RA patients. **Results:** RA patients had significantly thinner CT in all regions ($p<0.05$, $p\leq0.001$) and their epithelium was found to be thinner in the superior and the superonasal sectors in RA with DE (RA-DE) subgroup ($p=0.002$ and $p=0.004$, respectively) than the controls. There was statistically significant positive correlation between "mean (CT, CET)" and TBUT ($r=0.352$, $p=0.006$ and $r=0.493$, $p<0.001$, respectively). There was statistically significant negative correlation between mean CET and (OSDI, disease duration, DAS, ESR) ($r=-0.603$, $p<0.001$, $r=-0.468$, $p<0.005$, $r=-0.57$, $p=0.001$ and $r=-0.547$, $p<0.001$, respectively), while the mean CT had no significant correlation with these parameters. **Conclusion:** RA patients had thinner CT than controls, which correlated with TBUT and thinner CET in RA-DE subgroup which correlated with all parameters (TBUT, OSDI, disease duration, DAS, ESR).

Keywords: Corneal Thickness Mapping; Rheumatoid Arthritis; AS-OCT.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, multisystem, autoimmune connective tissue disease sustained by environmental and genetic factors [(1)]. Women are nearly three times more likely to have the disease than men [(2)]. The disease principally affects the joints and is usually accompanied by one or more extra-articular manifestations. The eye is an important extra-articular target organ for this disease and the ocular surface, in particular, is one of the most frequently affected areas [(3)].

Ocular manifestations involved with RA which can be the initial presentation of the disease are dry eye (DE) or keratoconjunctivitis sicca (KCS), episcleritis, scleritis, peripheral ulcerative keratitis (PUK), anterior uveitis, retinal vasculitis and optic neuritis [(4)]. In fact, any component of the eye can be affected in RA. However, anterior eye involvement is the most frequently encountered in clinical practice [(5)].

The most common form of ocular involvement is DE, affecting most RA patients [(6)]. DE may present either as KCS or secretory deficiency [(7)]. The type of collagen affected, the amount of corneal hydration, and the involvement of the extracellular matrix of the cornea may vary in different types of autoimmune diseases with corneal involvement. This may be reflected on different corneal parameters, including pre-corneal tear film, corneal thickness (CT), and corneal epithelial thickness (CET) [(8)].

Tear film breakup time test (TBUT), and symptoms questionnaire ocular surface disease index (OSDI score)- are among the DE diagnostic methods currently used in routine clinical practice [(9)].

Measurement of the CT and CET is an important and sensitive indicator of corneal health and plays an important role in both diagnostic and therapeutic assessment of ocular diseases such as keratoconus, postoperative ectasia, screening and planning for refractive surgery, assessing the function of endothelial cells (Fuchs dystrophy), monitoring corneal diseases such as corneal edema, and obtaining true intraocular pressure (IOP) measurements. An ideal tool for pachymetry should be precise, reliable and non-invasive. For these reasons, several methods have been developed and demonstrated for performing such measurements [(10-13)].

Today, AS-OCT is used to image the tear film [(14);] measure the lower tear film height and area; [(15,16)] measure CT; as well as the surface CET providing a thickness map in each corneal region using an in vivo, high-definition, non-invasive technique- that provides magnified, cross-sectional images of ocular biological tissues via measuring optical reflections [(17-23)].

The aim of our study was to use AS-OCT to generate corneal thickness (CT) and corneal epithelial thickness (CET) maps in RA patients and compare those parameters with normal subjects.

Materials and Methods

This study was designed as a case-control cross-sectional study on 35 eyes of 18 RA patients and 25 eyes of 14 healthy individuals, recruited from Rheumatology and Ophthalmology Departments, Benha University Hospital, in the period between June 2021 and August 2023.

Ethical approval:

The study met the ethical criteria of the Institutional Review Board (IRB) in Faculty of Medicine Benha University (MS 5-11-2021). Written informed consent was obtained from all participants before being enrolled.

Inclusion criteria:

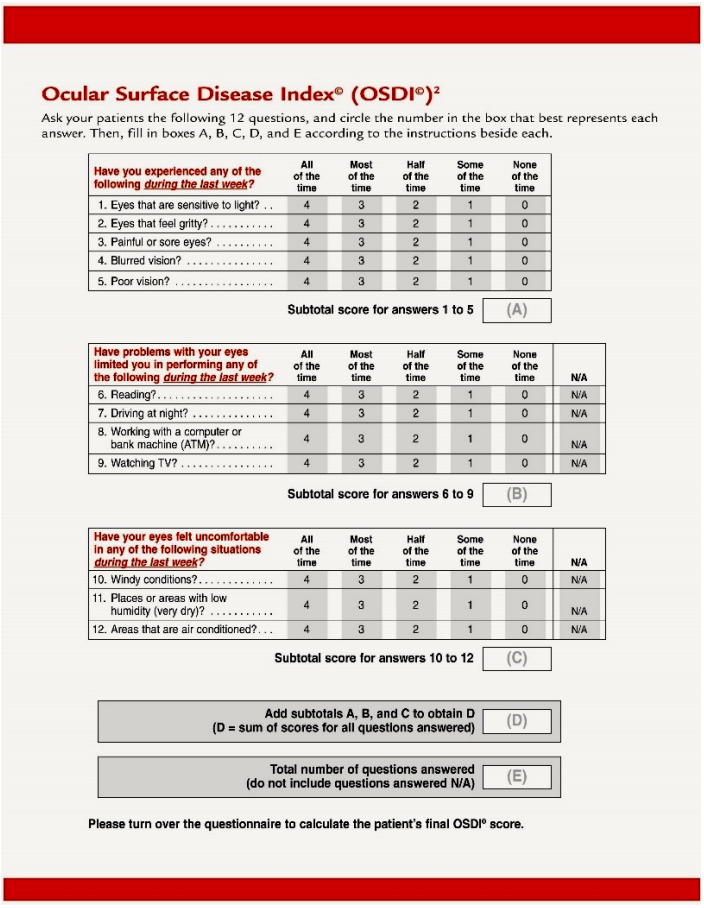
Both sexes were eligible, with age above 18 years. Rheumatoid arthritis patients with definite RA diagnosed according to the 2010 American College of Rheumatology/the European League Against Rheumatism (ACR/EULAR RA) classification criteria for RA [(24)].

Exclusion criteria:

Subjects with previous refractive, ocular surgery and ocular trauma, corneal pathology other than corneal manifestation of RA or DE, history of recent use of DE medications, prolonged use of topical medications, contact lens wear within 3 months before the study, and presence of other autoimmune systemic disorders- were excluded.

All participants were subjected to a comprehensive history and ophthalmic examination. Clinical diagnosis of DE was made based on the results of TBUT and the validated Arabic version (translation) of the OSDI (figure 1 and 2) [(25)]. TBUT evaluates tear film stability using 2% fluorescein dye. After the dye has been distributed throughout the tear film by blinking, the patient stares straight ahead without blinking. Under slit-lamp examination with cobalt blue light the time between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein-stained tear film (dry spot) is measured. A TBUT less than 10 seconds is considered abnormal.

All subjects filled the OSDI questionnaire forms. Ocular surface disease index is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with DE. The 12 items are graded on a scale of 0 to 4. The total score is then calculated using the following formula: OSDI (Sum of scores for all questions answered) ×100 / (total number of questions answered) × 4. Thus, the OSDI is scored on a scale of 0–100, with higher scores representing greater disability. A specific scale is designed- according to the score and the number of questions answered- to detect the severity of DE as normal, mild, moderate, or severe- using different shades of red in the scale for easier detection [(26)].



Ocular Surface Disease Index© (OSDI©)²

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D (D = sum of scores for all questions answered) (D)

Total number of questions answered (do not include questions answered N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

Figure (1): The OSDI questionnaire [(26)].

مؤشر امراض سطح العين

هل واجهت ايا مما يلى خلال الاسبوع الماضى؟	دائما	غالبا	احيانا	نادرا	مطلقا	
١. حساسية او انزعاج من تعرض العين للضوء	(٤)	(٣)	(٢)	(١)	(٠)	
٢. شعور بجسم غريب او شد فى العينين	(٤)	(٣)	(٢)	(١)	(٠)	
٣. الم او تهيج واحتقان فى العينين	(٤)	(٣)	(٢)	(١)	(٠)	
٤. رؤية ضبابية	(٤)	(٣)	(٢)	(١)	(٠)	
٥. رؤية متدهورة	(٤)	(٣)	(٢)	(١)	(٠)	
المجموع الفرعي للاجابات من ١ الي ٥	(أ)					
هل عانيت من مشاكل في عينك خلال الاسبوع الماضي؟	دائما	غالبا	احيانا	نادرا	مطلقا	لا ينطبق
٦. القراءة	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
٧. القيادة ليلا	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
٨. استخدام الحاسوب او الصراف الالى	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
٩. مشاهدة التلفاز	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
المجموع الفرعي للاجابات من ٦ الي ٩	(ب)					
هل شعرت عيناك بعدم الارتياح فى اى من المواقف التالية خلال الاسبوع الماضى؟	دائما	غالبا	احيانا	نادرا	مطلقا	لا ينطبق
١٠. اجواء عاصفة	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
١١. اماكن جافة (ذات رطوبة منخفضة)	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
١٢. اماكن مكيفة	(٤)	(٣)	(٢)	(١)	(٠)	لا ينطبق
المجموع الفرعي للاجابات من ١٠ الي ١٢	(ت)					
اضف المجاميع الفرعية (أ) و (ب) و (ت) للحصول على (ث) (ث= مجموع الدرجات لجميع الاسئلة التى تمت الاجابة عليها)						(ث)
اجمالى عدد الاسئلة التى تمت الاجابة عليها (لاتقم بتضمين الاسئلة التى لم يتم الاجابة عنها)						(د)
مؤشر امراض سطح العين						

Figure (2): The validated Arabic version (translation) of the OSDI questionnaire.

Assessment of RA disease activity was performed for all patients (DAS-28) which includes a count of 28 tender joints, 28 swollen joints, Erythrocyte sedimentation rate (ESR) and a general health assessment on a visual analog scale [27].

AS-OCT Pachymetry Maps:

Corneal thickness and CET mapping were provided by the by the Fourier-domain optical coherence tomography (FD-OCT) system (Optovue, Fremont, California, USA) with a high-speed camera, with a scan rate of 26,000 axial scans per second, axial resolution of 5 µm, transversal resolution of 15 µm, a wavelength of 830 nm, and an add-on lens of the corneal adaptor module (CAM-L "long" mode: 6.0–2.0 mm). Being a non-contact technique, OCT was performed before the ophthalmologic examination to prevent possible epithelial changes. A "pachymetry wide" scan pattern, with 9-mm scan diameter and eight radial B scans- was chosen to map the cornea. The examiner centered the scan on the corneal vertex by adjusting the joystick until a bright vertical flare line was seen at the center of the real-time OCT image. To confirm thickness measurement reproducibility, two scans were taken for each case by an experienced operator with deviation no more than 3 µm in central corneal thickness (CCT). If deviation was found as >3 µm, the scan was repeated for a third time. The data were valid if the measurement outcomes showed sufficient image signals and good quality images centered at the corneal ver-tex- with complete coverage and free of motion artifacts- were accepted for analysis. Subjects were instructed to blink before the scan began to ensure that the tear film would be spread out evenly. The CT and CET of 25 sectors were generated automatically and divided into four zones:

central (0–2 mm), paracentral (2–5 mm), mid-peripheral (5–7 mm), and peripheral (7–9 mm) [22].

Statistical Analysis

All analyses were done using IBM SPSS v.26.0 statistical software (IBM Corporation, NY). Qualitative data were described using numbers and percentages and were compared using Chi-Square $\chi 2$-test and Fisher's LSD exact test as appropriate. Quantitative data were described using mean ± SD or median IQR (interquartile range) and were compared using independents sample t test (for normally distributed data) and Z Mann Whitney test (for non-parametric variables). For subgroups analysis, one-way analysis of variance (ANOVA) test was used. Pearson's correlation coefficient (r) was used to evaluate the association. TBUT, OSDI and disease duration were used as predictors for CT and CET in a linear regression analysis. The results were considered statistically significant when there was a p value of <0.05.

Results

This study included 35 eyes of 18 patients with RA and 25 eyes of 14 age- and sex-matched healthy controls. The TBUT were significantly lower [*median*=8(7–9) seconds**,** p=0.001], while the OSDI was significantly higher in the RA group [17.9(13.9–31.3), p<0.001] than in the controls. The clinical dry eye diagnosis was significantly higher in the RA group [n=27 (77.1%), (p=0.004)] than in the controls (Table 1).

Regarding the CT of the RA patients, it was found to be significantly thinner in all regions than the controls (p<0.05, $p\leq$0.001) (Table 2, figure 3 and 4).

Table (1): Summarizes demographic and clinical data of the studied groups.

	Case group Mean ± SD	**Control group Mean ± SD**	**t**	**p**
Age (years)	50.78 ± 6.9	47.79 ± 12.11	0.826	0.419
	N=18 (%)	**N=14 (%)**	**χ^2**	**p**
Gender:			2.815	0.093
• **Male**	5 (27.8%)	8 (57.1%)		
• **Female**	13 (72.2%)	6 (42.9%)		
	Mean ± SD	**Mean ± SD**	**t**	**p**
BCVA (decimal)	0.72 ± 0.2	0.84 ± 0.18	-3.425	**0.001****
IOP (mmHg)	15.22 ± 1.59	15.21 ± 1.63	0.014	0.989
	Median (IQR)	**Median (IQR)**	**Z**	**p**
TBUT(seconds)	8(7 – 9)	11(8.5 – 13)		
Abnormal eye TBUT < 10 s, n (%)	28 (80%)	10 (40%)		
OSDI	17.9(13.9 – 31.3)	11.4(8.85 – 16.75)	-3.892	**<0.001****
• **Normal**	4 (22.2%)	9 (64.3%)	6.689	**0.01***
• **Mild**	7 (38.9%)	4 (28.6%)		
• **Moderate**	4 (22.2%)	1 (7.1%)		
• **Severe**	3 (16.7%)	0 (0%)		
Dry eye	27 (77.1%)	10 (40%)	8.511	**0.004***
ESR (mm/1st h)	31.5 (21.5 – 53)	N/A	–	**–**
Disease duration (years)	9.5 (3 – 13.5)	N/A	–	**–**
DAS-28	3.75 (2.83 – 5.35)	N/A	–	**–**
Positive anti-CCP	14 (77.8%)	N/A	–	**–**
Positive RF	13 (72.2%)	N/A	–	**–**

t independent sample t test χ^2Chi square test Z Mann Whitney test **p≤0.001 is statistically highly significant

*BCVA: Best corrected visual acuity; *anti-CCP: Anti-cyclic citrullinated peptide antibodies; *RF: Rheumatoid factor;

*N/A: Not applicable.

Table (2): Comparison between the studied groups regarding corneal thickness (pachymetry map):

Corneal	Case group Mean ± SD	Control group Mean ± SD	t	p
Central	510.94 ± 22.26	530.52 ± 32.5	-2.607	**0.013***
Superior				
• **Inner**	545.97 ± 34.05	565.32 ± 34.05	-2.37	**0.021***
• **Middle**	585.8 ± 35.17	614.52 ± 36.94	-3.054	**0.003***
• **Outer**	617.37 ± 44.51	659.96 ± 42.84	-3.711	**<0.001****
Superior nasal				
• **Inner**	546.51 ± 24.42	564.48 ± 36.42	-2.146	**0.038***
• **Middle**	586.37 ± 28.38	607.2 ± 40.09	-2.229	**0.031***
• **Outer**	626.6 ± 30.81	655.92 ± 43.88	-2.874	**0.006***
Superior temporal				
• **Inner**	531.17 ± 30.89	551.92 ± 32.33	-2.516	**0.015***
• **Middle**	563.83 ± 38.06	588.84 ± 33.96	-2.623	**0.011***
• **Outer**	600.0 ± 40.09	634.16 ± 36.81	-3.365	**0.001****
Nasal				
• **Inner**	541.09 ± 22.5	560.64 ± 35.03	-2.453	**0.019***
• **Middle**	576.77 ± 26.05	598.56 ± 37.91	-2.485	**0.017***
• **Outer**	622.4 ± 33.57	654.32 ± 42.27	-2.251	**0.029***
Temporal				
• **Inner**	518.71 ± 26.4	541.32 ± 33.09	-2.941	**0.005***
• **Middle**	542.14 ± 31.25	567.12 ± 35.94	-2.867	**0.006***
• **Outer**	573.66 ± 39.85	599.0 ± 40.05	-2.424	**0.019***
Inferior nasal				
• **Inner**	536.0 ± 21.81	557.44 ± 36.66	-2.613	**0.013***
• **Middle**	571.69 ± 41.6	596.32 ± 41.6	-2.585	**0.014***
• **Outer**	620.38 ± 39.66	646.76 ± 52.05	-2.121	**0.04***
Inferior				
• **Inner**	529.8 ± 21.27	533.0 ± 36.2	-2.87	**0.007***
• **Middle**	562.74 ± 24.59	592.6 ± 42.52	-3.154	**0.003***
• **Outer**	600.2 ± 37.81	636.28 ± 56.77	-2.769	**0.009***
Inferior temporal				
• **Inner**	520.49 ± 23.89	544.0 ± 34.16	-2.693	**0.005***
• **Middle**	545.63 ± 26.4	575.2 ± 38.48	-3.324	**0.002***
• **Outer**	578.71 ± 31.55	612.36 ± 44.98	-3.217	**0.003***

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

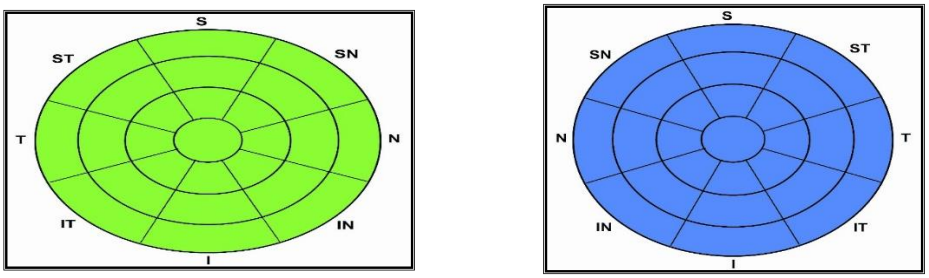
Regarding the CET, it was found to be significantly thinner in the superior and the superonasal sectors (middle and outer region) in RA-DE subgroup compared to control-No DE and RA-No DE subgroups (p<0.001, p=0.031, p=0.001 and p=0.005, respectively). Furthermore, the CET was significantly thinner in the superior middle region in RA-DE subgroup compared to control-DE subgroup (p<0.001). Otherwise, the remaining epithelial zones showed no statistically significant difference between the studied groups (Table 3, figure 3 and 4).

Table (3): Comparison between the studied groups regarding epithelial thickness map:

Epithelial	Case group		Control group	
	No DE	DE	No DE	DE
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Central	53.5 ± 2.33	53.63 ± 3.92	53.53 ± 1.64	53.1 ± 3.14
Superior				
• **Inner**	53.75 ± 2.92	51.74 ± 4.35	53.6 ± 2.59	51.7 ± 4.11
• **Middle**	53.75 ± 3.24	47.96 ± 4.19	52.87 ± 2.75	49.2 ± 4.76
LSD	**P_1 <0.001****	**P_2 <0.001****	**P_3 0.024***	P_4 0.604
• **Outer**	49.64 ± 3.11	45.22 ± 5.75	48.4 ± 2.67	44.5 ± 5.19
LSD	**P_1 0.025***	**P_2 0.043***	P_3 0.05	P_4 0.559
Superior nasal				
• **Inner**	53.63 ± 2.45	52.0 ± 4.13	53.4 ± 2.23	52.0 ± 3.43
• **Middle**	54.13 ± 2.8	49.56 ± 3.88	53.53 ± 1.64	50.7 ± 4.32
LSD	**P_1 0.002***	**P_2 0.001****	**P_3 0.047***	P_4 0.693
• **Outer**	52.63 ± 2.39	47.15 ± 5.9	51.53 ± 2.95	47.7 ± 4.27
LSD	**P_1 0.005***	**P_2 0.005***	P_3 0.842	P_4 0.597
Superior temporal				
• **Inner**	53.75 ± 3.81	51.96 ± 4.28	52.8 ± 2.24	51.7 ± 3.74
• **Middle**	52.75 ± 2.92	49.37 ± 4.85	51.73 ± 1.67	50.2 ± 5.07
• **Outer**	51.38 ± 2.13	46.63 ± 6.43	49.4 ± 2.26	46.5 ± 5.6
Nasal				
• **Inner**	53.75 ± 1.67	52.37 ± 4.09	52.87 ± 1.64	52.6 ± 3.41
• **Middle**	53.75 ± 1.49	51.41 ± 3.78	53.33 ± 1.63	52.1 ± 3.9
• **Outer**	54.25 ± 2.38	53.48 ± 4.13	53.4 ± 1.5	53.4 ± 3.72
Temporal				
• **Inner**	52.38 ± 2	51.89 ± 3.78	52.23 ± 1.76	51.8 ± 3.33
• **Middle**	51.75 ± 2.38	50.37 ± 3.94	52.07 ± 1.87	50.2 ± 3.77
• **Outer**	51.0 ± 2.2	49.81 ± 6.66	52.13 ± 2.13	49.5 ± 3.54
Inferior nasal				
• **Inner**	54.25 ± 2.38	53.48 ± 4.13	53.4 ± 1.5	53.4 ± 3.72
• **Middle**	53.88 ± 2.23	52.26 ± 4.4	54.07 ± 1.71	52.3 ± 4.3
• **Outer**	54.5 ± 3.74	52.78 ± 4.98	55.4 ± 3.42	52.6 ± 4.12
Inferior				
• **Inner**	54.75 ± 2.82	54.44 ± 4.48	53.87 ± 1.36	53.9 ± 3.54
• **Middle**	54.75 ± 3.89	53.59 ± 5.08	54.73 ± 2.02	52.5 ± 4.25
• **Outer**	54.13 ± 2.8	49.56 ± 3.88	53.53 ± 1.64	50.7 ± 4.32
Inferior temporal				
• **Inner**	54.0 ± 2.62	53.41 ± 3.84	53.4 ± 1.6	53.2 ± 3.23
• **Middle**	54.38 ± 2.72	52.44 ± 4.85	53.93 ± 1.67	52.9 ± 3.25
• **Outer**	54.75 ± 3.11	51.93 ± 6.02	53.93 ± 3.44	51.8 ± 3.36

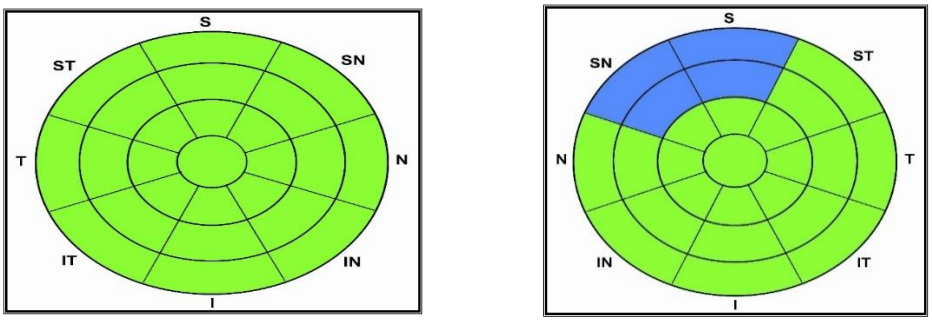
*p<0.05 is statistically significant **p≤0.001 is statistically highly significant F One way ANOVA test LSD Fisher least significant difference p1 difference between RA-DE and RA-No DE subgroups p2 difference between RA-DE and control-No DE p3 difference between control-No DE and control-DE p4 difference between RA-No DE and control-No DE p5 difference between RA-No DE and control-DE p6 difference between RA-DE and control-DE

Pachymetry Map



Control **RA**

Epithelium Map



Control **RA-DE**

Figure (3): Graphical representation for: pachymetry and epithelium thickness maps for the normal subjects (left) and the RA patients (right), showing thinner cornea in RA patients in all corneal regions and thinner epithelium in the superior and superonasal regions (blue sectors).

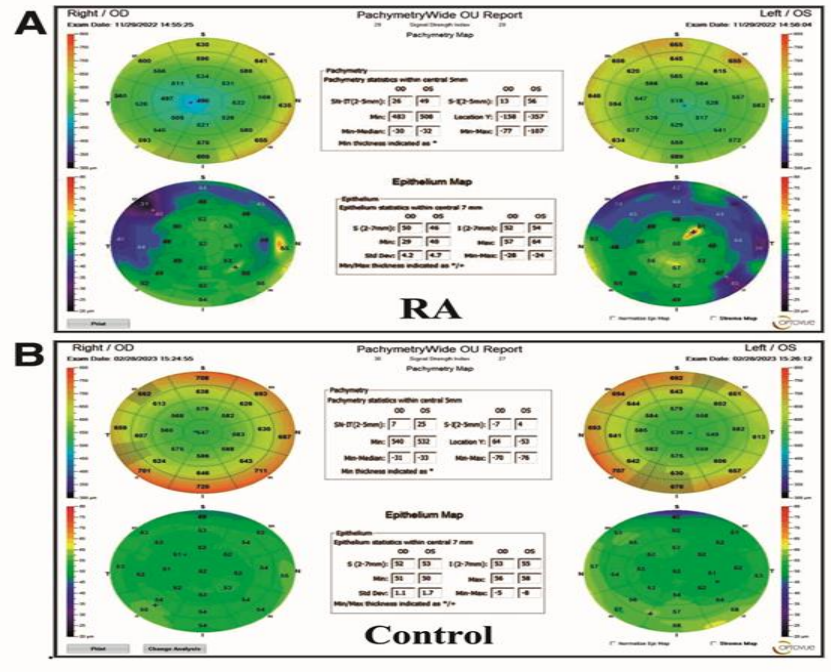


Figure (4): AS-OCT, showing thinning in the corneal and epithelial thickness maps in RA (4-A) compared to the control (4-B).

As regard CET, RA group had significantly lower minimum thickness (p=0.003), more negative Min–Max value (p<0.001), and greater standard deviation (p<0.001) than controls. Moreover, the minimum CT was significantly lower (p=0.004) in RA group than that in controls (Table 4).

Regarding correlation coefficient, there was statistically significant positive correlation between "mean (CT, CET)" and TBUT (r=0.352, p=0.006 and r=0.493, p<0.001, respectively). There was statistically significant negative correlation between mean CET and (OSDI, disease duration, DAS, ESR) (r=0.493, p<0.001, r=-0.603, p<0.001, r=-0.468, p<0.005, r=-0.57, p=0.001 and r=-0.547, p<0.001, respectively), while no statistically significant correlation was observed between mean CT and these parameters (Table 5, figure 5).

Regarding linear regression analysis, TBUT was significantly associated with mean CT (unstandardized β=4.804, p=0.006). ocular surface disease index and disease duration were significantly associated with mean CET (unstandardized β=-0.225, p<0.001) and (unstandardized β=-0.199, p=0.005) (Table 6).

Table (4): Comparison between the studied groups regarding (min, max, min-max, SD) and (CET, CT map):

Epithelial	Case group Mean ± SD	Control group Mean ± SD	t	p
Min	43.14 ± 6.06	47.32 ± 3.97	-3.223	**0.003***
Max	59.74 ± 5.03	57.88 ± 3.44	1.602	0.115
Min-max	-17.71 ± 9.01	-10.56 ± 2.92	-4.389	**<0.001****
SD	3.06 ± 1.17	2.03 ± 0.4	4.813	**<0.001****
Corneal				
Min	500.2 ± 25.75	523.96 ± 32.36	-3.047	**0.004***
Min-max	-74.2 ± 21.81	-67.68 ± 12.8	-1.453	0.152

t independent sample t test *SD: standard deviation; *Min: minimum; *Max: maximum

Table (5): Correlation between "mean (CT, CET)" and (TBUT, OSDI, disease duration, DAS, ESR) among studied participants:

	CT		CET	
	r	p	r	p
TBUT	0.352	**0.006***	0.493	**<0.001****
OSDI	-0.208	0.111	-0.603	**<0.001****
Disease duration	0.143	0.411	-0.468	**0.005***
DAS	-0.235	0.175	-0.57	**<0.001****
ESR	-0.199	0.251	-0.547	**<0.001****

r Pearson correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (6): Linear stepwise regression analysis of factors associated with means (CT, CET):

Model		Unstandardized Coefficients		Standardized Coefficients	t	p	95.0% Confidence Interval	
		â	Std. Error	Beta			Lower Bound	Upper Bound
CT	(Constant)	531.833	16.167		32.896	**<0.001****	499.471	564.195
	TBUT	4.804	1.676	0.352	2.866	**0.006***	1.449	8.160
CET	(Constant)	58.317	1.007		57.902	**<0.001****	56.265	60.368
	OSDI	-.225	.039	-.642	-5.729	**<0.001****	-.305	-.145
	Disease duration	-.199	.065	-.341	-3.043	**0.005***	-.332	-.066

*p<0.05 is statistically significant **p0.001 is statistically highly significant

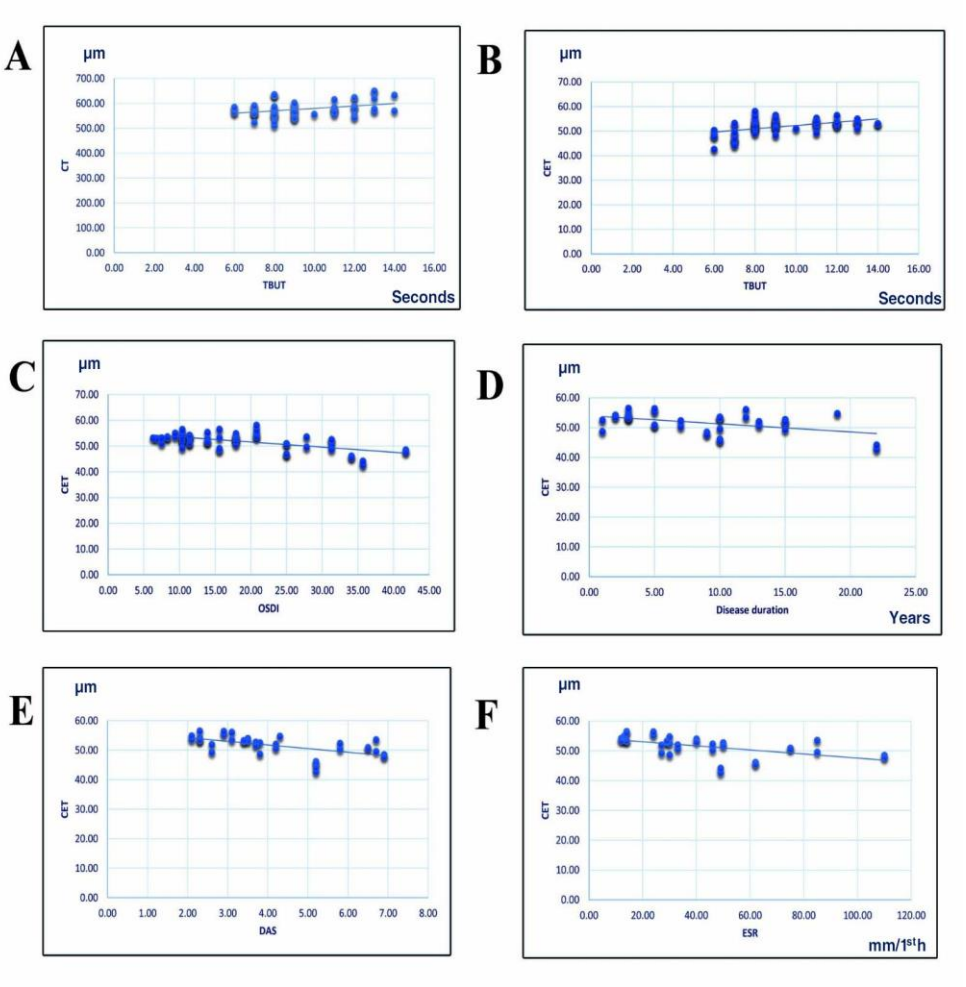


Figure (5): Scatter plot, (A, B) show significant positive correlation between (CT, CET) and TBUT and (C, D, E, F) show significant negative correlation between CET and (OSDI, disease duration, DAS and ESR, respectively).

Discussion

In our study, we reported that RA patients had significantly thinner corneas (in all regions) than the control group, and thinner corneal epithelium (in the superior region) in RA-DE subgroup. The generalized corneal thinning was found to be associating with the reduction of TBUT, but not associating with the increase in; OSDI, disease duration, DAS28 or ESR. In addition, we reported that the corneal epithelial thinning was strongly associating with all parameters (TBUT, OSDI, disease duration, DAS28, ESR).

Our results came in agreement with the results of the study which found that RA patients had significantly thinner corneas (in all regions except inferiorly), and thinner epithelium (in the superior region) than the controls. The corneal thinning in the central and superior regions did not correlate with the disease duration, or disease activity parameters using FD-OCT Optovue "RTVue RT-100" in 43 RA compared with 40 controls over a 6 mm diameter scan area [(28)].

Our current findings were also supported by the results of the *in vivo* confocal microscopic study which found that corneas of RA patients were significantly thinner than those of normal subjects. The disease duration, and the DAS were not found to correlate with any of the corneal measurements [(29)].

Another study was consistent with our results, using the Pentacam technology; they found the corneal pachymetry to be significantly thinner in RA patients than those of controls. However, the disease duration correlates negatively with CT. Nevertheless, this study did not include any disease activity parameter other than disease duration [(30)].

The corneal thinning in patients with RA could be attributed to the chronic degradation of the type IV collagen by activated corneal Langhans cells (LCs), rather than tear film insufficiency [(30,31)]. These cells activate matrix metalloproteinase (MMP) enzymes found in corneal epithelium and stroma, mainly type 9. The MMPs were found to be activated in DE and are thought to be activated by pro-inflammatory cytokines, resulting in an increase in tear film osmolarity which causes ocular surface damage, resulting in dehydration of the cornea, and the cornea becomes thinner [(32,33)].

On DE subgroup analysis, the CT and CET were found to be more affected in the RA-DE group, which suggests that the decrease in the tear volume in RA adds to its effect on the CT and CET. A research that explored the diurnal variation of CT and CET measured using OCT, suggested that increased evaporation of the tear film in the morning reverses overnight swelling of the corneal epithelium, which could be due to secondary increase in the tear film tonicity [(34)].

We also found that the superior quadrants of the corneal epithelium were affected more than the inferior quadrants with gravity as the main factor drawing the tear towards the inferior cornea and the lower tear meniscus. This finding suggests that tear dynamics and flow is an important factor in corneal health [(35)].

Our current findings were supported by a previous study that measured the thickness of the human precorneal tear film and reported that the flow of the tear film with subsequent pooling in the inferior meridian may cause a falsely thick reading. Therefore, it is possible that the OCT may overestimate the inferior meridian due to the tear film, however, this effect is not solely due to this phenomenon [(36)]. It is also proposed that the superior meridian is thinner due to the contact time of the tear film being shorter at this location, so the lubrication and nourishing effects are less pronounced causing a faster desquamation of the epithelium and subsequent thinning over time [(37)].

In addition to that tear dynamics, there are other theories for vertical asymmetry in CET. In a study done previously and pioneered the analysis of the corneal epithelium by mapping over the entire corneal surface in 56 normal patients using a very high-frequency ultrasound. It was found that CET was not uniformly distributed over the cornea, suggesting that friction due to blinking abrades the epithelium of the cornea with a larger force applied on the superior meridian [(38)].

Also, as suggested by some authors, using ultrahigh resolution OCT (UHR-OCT), the constant pressure applied by the upper eyelid on the superior meridian causes long-term thinning. The upper eyelid covers a greater of the superior corneal surface and also applies a greater force on the cornea due to gravity [(39)].

On subgroup analysis for the CT, no significant difference was found between the RA-DE and RA-No DE groups. Our result is supported by two studies [(28,29)]. In contrast with these two studies, we found that the RA-DE groups had significantly thinner epithelium (in the superior region) than the RA-No DE groups. However, this is contradictory to another study which found that the RA subgroup with DE had significantly thinner pachymetric measurements (CT, CET) than the RA subgroup, without DE [(30)].

There was a significant difference between both study groups regarding the distribution of DE diagnosis, TBUT, and OSDI results. Most patients with RA are reported to have some degree of DE. It is thought that the reduced tear secretion results from lymphocytic infiltration of the lacrimal gland [(6)]. We also found a significant positive correlation between (CT, CET) and TBUT, while the CET was negatively correlated with the OSDI scores.

It has been reported that OCT mapping of 9 mm CET, especially the mean upper mid-peripheral thickness using Optovue "RTVue XR 100 Avanti" in 120 patients (60 in each group)- could constitute a strong and reliable criterion for diagnosing DE since it was statistically thinner in the DE group than in the control group. Also, the average peripheral CET was highly correlated with TBUT; the worse the tear film was, the thinner the peripheral epithelium [(40)].

Furthermore, a study showed an average decrease in superior CET in patients with DE, which correlates with the severity of the disease and not correlates with TBUT using FD-OCT in 100 DE patients compared with 35 healthy volunteers. Notably, the thinner tendency was larger and extended centrally in the more severe dry eyes. Thus, it was suggested that superior CET is the first location to be stricken in DE. It has also been proven that the alteration of CET caused by DE affects- more profoundly- the peripheral corneal epithelium rather than that in the central region [(41)].

Additionally, some authors [(42)] observed a significant decrease in the peripheral CET and non-significant difference in the central CET in the DE group compared with the control group using FD-OCT in 54 patients with DE and 32 controls. They also found a correlation between (OSDI, TBUT) and CET, consistent with the work conducted by two researches [(43,44)]. It might be attributed to the benefiting from immune and angiogenic privilege, central cornea appears less sensitive to inflammation than the periphery (away from limbus), and the moderate severity of DE.

Moreover, a study found that CET was thinner in 26 patients with severe DE than in 10 healthy people using in vivo confocal, further hypothesizing that the chronic and progressive destruction of limbal stem cells should lead to such a DE-related thinning [(45)].

In our study, we reported a higher standard of deviation in the CET in the RA group that could be reflecting the irregularity of the corneal epithelium in DE or represent a tomographic visualization of punctate epithelial erosions. Supporting our results,

a recent study using ultrahigh-resolution OCT on 52 DE patients and 19 controls to assess CET in DE, reported that patients with DE had a highly irregular corneal epithelial surface, compared with the controls. Furthermore, there was a decrease in CET standard of deviation after DE therapy, suggesting that a greater CET standard of deviation may reflect a damaging effect of DE on the ocular surface and the CET standard of deviation could be used to differentiate the severity of DE [(46)].

In addition, a more recent study reported that the peripheral CET standard of deviation was higher in the severe DE, suggesting that the peripheral ocular surface is more damaged. It was also found a positive correlation between the CET standard of deviation in the 9 mm zone and the OSDI. There were also negative correlations between the standards of deviation of the 7 mm and 9 mm zones using FD-OCT Zeiss Cirrus 500 on 92 dry eyes [(47)].

In contrast, a study comparing a group of 35 DE patients with 35 healthy controls reported an overall thickening of the corneal epithelium as measured by FD-OCT RTVue-100. These conflicting findings may be due to the lack of a unified objective measure to determine the diagnosis of DE, the difference in stages and causes of dryness, the heterogeneity of the studied population and in the OCT mapping that differed from that used in our study. The data recorded by this study included maps of CET up to the 6 mm diameter cornea, whereas in our study, the region of interest was extended to 9 mm. Thus, by moving away from the centre of the cornea towards the peripheral zone, the corneal epithelium is thinner [(48)].

Our study has some limitations, first, the relatively small sample size of the subject groups, second, the inability of OCT to discriminate the precorneal tear film from the corneal epithelium, third, the problem of definite dry eye assessment is confused by many parameters and several aspects may make a safe diagnosis challenging particularly in the early or mild stages, finally, the TBUT tests lack proper standardization because they are affected by variations in dye concentration and light levels during surface-staining operations, a lack of grading uniformity, poor reproducibility and a significant operator dependence.

Finally, we recommend AS-OCT as a useful and patient-friendly tool to document and examine the corneal parameters in RA patients. This may be useful in the early diagnosis and identification of patients at high risk of developing RA-associated corneal melting.

Conclusion

Rheumatoid arthritis patients had diffusely thinner CT than controls regardless of DE diagnosis, which associated with reduced TBUT and focally thinner CET in RA-DE subgroup which associated with all parameters (reduced TBUT, increased OSDI, increased disease duration, increased DAS and increased ESR).

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