Evaluation of Corneal Thickness in Rheumatoid Arthritic Patients using pentacam

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Background: Rheumatoid Arthritis is a chronic, inflammatory, autoimmune connective tissue disease that affects several tissues and is frequently linked with ocular symptoms. The cornea is one of the most important components of the eye in rheumatic patients. Measurement of corneal thickness in these individuals is critical for determining the level of ocular involvement.

Aim:Evaluation of corneal thickness in RA patients compared to healthy subjects by using pentacam.

Patients and Methods: A total of 48 patients and 48 control subjects were participated in this study. Ophthalmic examination was performed on each subject. Central corneal thickness and peripheral corneal thickness were evaluated using (pentacam). Additionally, the relative peripheral index was calculated by dividing the peripheral corneal thickness by the central corneal thickness.

Results: The mean corneal thicknesses at the center and the superior, inferior nasal and temporal points were significantly lower in the Rheumatoid Arthritis group.

Conclusion: The central corneal thickness and peripheral corneal thickness were thinner in rheumatoid arthritis patients compared to those in control subjects.

Keywords: Rheumatoid Arthritis (RA), Corneal thickness (CT), Central corneal thickness (CCT), Peripheral cornea Thickness

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, and inflammatory condition
that mostly affects synovial joints. Extraarticular symptoms are often seen, including ocular
involvement.(1)
The prevalence of RA is around 0.8% of the population. Females are affected roughly three
times more commonly than men, and it affects between 0.5 and 1% of adults in the industrialised
world, with 5 to 50 per 100,000 persons newly getting the disorder each year.

(2)Ocular

manifestations generally occur in 25% of the patients.(3)
The most prevalent eye symptom of RA is dry eye disease (DED). Dry eye symptoms affect
up to 45% of RA patients and are clinically diagnosed in 2.2% to 16.3%.
(4)

Aside from DED, RA can cause corneal involvement such as stromal keratitis, sclerosing
keratitis, keratolysis, marginal furrowing or guttering, and peripheral ulcerative keratitis. Corneal

ulcerations are more prevalent in the peripheral cornea; corneal findings in rheumatic illness are
essential because they can give early diagnosis and therapy for the systemic disease, lowering the
risk of consequences such as permanent vision loss. The findings may be connected with the
illness itself or the administration of systemic immunosuppressive medication.

Various rheumatic disorders can cause corneal symptoms such as pain, itching, tearing,
burning, stinging, redness, and vision loss. (6)

The corneal stromal layer, which is mostly made up of regular collagen fibril lamellae, is
critical in acquiring much of the cornea's elasticity and achieving a high refractive power. Stromal
changes that occur naturally, such as with ageing, may show in pathological situations as a
symptom of several connective tissue illnesses.(7) Measuring corneal biomechanical
characteristics in such disorders is critical to understanding the level of ocular involvement.
(8)
Ultrasound pachymetry is the most often used method for determining corneal thickness.
However, a few constraints, such as relatively high interoperator variability, the necessity for
topical anaesthesia, and direct contact of the probe with the cornea, have resulted in a quest for
non-contact approaches.
(9)

Pentacam is a noninvasive objective device that permits thorough study of the corneal structure using a three-dimensional model displaying the thickness, volume, and spatial section
utilising the Scheimpflug imaging approach. (10)

According to previous research, corneal thickness is an important tool in ophthalmic examination in Rheumatoid arthritis patients because it can provide valuable information on
suspected glaucoma cases, calculation of intraocular lens power, keratoconus monitoring, and
investigation of refractive disorders.
So, this study was conducted to improve the ophthalmic outcome in those patients by recognizing the magnitude of the problem and effect of other disease variables.

AIM OF THE WORK

Evaluation of corneal thickness in RA patients compared to healthy subjects by using pentacam.

MATERIAL & METHODS

The study was approved by the Faculty of Medicine Ethics Review Board and in accordance with the Declaration of Helsinki tenets.

Study design

This was a comparative study that was conducted at Physical Medicine, Rheumatology and Rehabilitation Outpatient Clinic and Ophthalmology Outpatient Clinic, Suez Canal University Hospitals.
This study was conducted on 96 patients that were divided into 2 groups:
- Group A: this group included 48 eyes of 24 patients known to have RA.

- Group B: This group included 48 eyes of 24 healthy subjects.

Patients were recruited based on the following criteria:

Inclusion Criteria:

1. Age: 18 years or more.
2. Both sexes.
3. Previously and newly diagnosed patients with RA fulfilling the 2010American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.(11)

Exclusion Criteria:

1. Patients with corneal scars.
2. Patients with Keratitis or active uveitis
3. Severe dry eye.
4. Patients with glaucoma.
5. Contact lens users.
6. Patients with a history of ocular surgery.
7. Patients with other autoimmune disease other than Rheumatoid Arthritis (sjogren syndrome).

All RA patients were referred from the Physical Medicine, Rheumatology and Rehabilitation outpatients clinics of Suez Canal University hospitals for their routine eye

RESULTS

The 2010 ACR/EULAR classification criteria for rheumatoid arthritis(11)

1. Joint involvement (0 to 5 points max)
– One medium to large joint – 0
– 2–10 medium to large joints – 1
– 1–3 small joints – 2
– 4–10 small joints (with or without large joints) – 3
– > 10 joints (at least one small joint involved) –
2. Serology (0 to 3 points max)
– Negative RF and negative ACPA – 0
– Low positive RF or ACPA (<3× upper limit normal) – 2
– High positive RF or ACPA (>3× upper limit normal) – 3
3. Acute phase reactants (0 to 1 point max)
– Normal CRP and ESR – 0
– Abnormal CRP or ESR – 1
4. Duration of symptoms (0 to 1 point max)
– <6 weeks – 0
– ≥6 weeks – 1

1. Joint involvement defined as swollen or tender joint on examination or synovitis on ultrasound/MRI;
medium/large joints include shoulders, elbows, hips, knees, ankles; small joints include MCPs, PIPs, 2–
5 MTPs, wrists; RF rheumatoid factor, ACPA anti-citrullinated protein antibodies, CRP C-reactive
protein, ESR erythrocyte sedimentation rate
2.
aTotal score ≥ 6/10 meets classification criteria for rheumatoid arthritis

Methods

All participants were subjected to the following:

1- History taking:

Personal history: name, age, sex, occupation, marital status, offspring, special habits, residence.

Present history:

- Onset, Course, Duration of disease.
- Musculoskeletal affection: pain, swelling, muscle weakness.
- Morning stiffness: location, duration in minutes.
- Numbness and tingling in extremities may indicate neuropathy.

Constitutional symptoms: fever, malaise, fatigue, night sweeting, weight loss, anorexia.
Dermatological symptoms: subcutaneous nodules, photosensitivity, rashes, urogenital ulcers, purpura, and Raynaud`s phenomenon.
Respiratory history: cough, dyspnea, expectoration, chest pain, hemoptysis.
Cardiovascular symptoms: palpitation, chest pain, edema lower limbs.
Urological symptoms: dysuria, anuria, oliguria, puffy eyelids, lion pain and generalized edema.
Gynecological and obstetric history: menstrual problems and fetal loss.
Chronic disease: Diabetes mellitus and Hypertension.
Therapeutic history: drugs used types and dosages, duration, side effects of therapy.
Past history: of trauma, surgery, drug sensitivity.
Family history: of similar conditions, other rheumatic disease, DM and hypertension.

2- General examination:

- General appearance and body built.
- Height (m) and weight (kg).
- Complexion, pallor, jaundice and cyanosis.

- Pulse, blood pressure, and temperature.
- Rheumatic nodules.
- Gait: may be affected in sever joint destruction

3- Systemic examination:

- Cardiovascular examination.
- Respiratory examination.
- Abdominal examination.
- Neurological examination.

4- Locomotor system examination:

Clinical examination of the joints:

- Inspection: diffuse and local swelling, bruising, dislocation, muscle wasting and deformities.
- Palpation: localized or diffuse changes in temperature, tenderness.
- Movement: passive range of motion, active range of motion, limitation or loss of movement, and fixed deformities.
- Muscle examination: muscle power.

The examination includes the following joints: Both elbows, Both wrists, MCP joints, PIP joints, Both hips, Both sacroiliac joints, Both knees, Both ankles, Metatarsophalangeal joints Shoulders, Cervical, dorsal, lumbar spines, Temporomandibular joints.

Assessment of disease activity:

Assessment of disease activity was formed using the disease activity score (DAS28):(12) includes a 28_ swollen joint count, 28_tender joint count, ESR, and general health assessment on VAS.

"28" describes the number of different joints including in the measurement:

- Proximal interphalangeal joints (10 joints)
- Metacarpophalangeal joints (10)
- Wrists (2)
- Elbows (2)
- Shoulders (2)
- Knees (2)

When looking at these joints, both the number of joints with tenderness upon touching and swelling are counted.

With the above-mentioned parameters, DAS28 is calculated as:

DAS 28 =0.56 + 0.28 + 0.70Ln (ESR) + 0.14 (G H).

- TEN28: number of joints with tenderness upon touching
- SW28: number of swollen joints
- ESR: measured erythrocyte sedimentation rate (ESR)
- GH: general health on a visual analog (VAS) scale between 0 and 100 ("0": no activity, "100": highest activity possible)
- The DAS28 provides an absolute indication of RA disease activity on a scale of 0.49 to 9.07
- A DAS28 value >5.1 corresponds to a high disease activity
- A DAS28 value between 3.2 and 5.1 corresponds to a moderate disease activity.
- A DAS28 value between 2.6 and 3.2 corresponds to a low disease activity
- A DAS28 value < 2.6 corresponds to remission

5- Laboratory investigations:

- Complete Blood Picture (Hb% with Coulter S+ counter) (CBC).
- Erythrocyte Sedimentation Rate.
- Serum C-reactive Protein (CRP).
- Serum Rheumatoid Factor (RF).
- Laboratory tests to detect other organ affection e.g., serum creatinine and liver function tests.

Ophthalmic examination

All enrolled patients will be evaluated by meticulous ophthalmic evaluation.

- History taking about any previous ocular trauma, family history of significant ocular disorder.
- Examination of lids, orbit, lacrimal system, ocular motility, conjunctiva, cornea, sclera, anterior chamber, iris, pupil, lens and vitreous humour.
- Assessment of the visual acuity (VA) [Unaided visual acuity and Best corrected visual acuity]were done using Landolt's VA chart and then transformed for statistical analysis to logarithm of minimal angle of resolution units (Log MAR).
- Patient's refractive error using AutorefractometerUsing Topcon RM-800 autorefractometer.
- Slit lamp nidek (Sl-450) made in Japan.
- Measurement of intraocular pressure (IOP): Intraocular pressure was measured using Goldmann Applanation Tonometer (SL-TM B-45) (Japan.)
- Fundus examination by indirect ophthalmoscope neitz (Q05) made in Jaban and by volk double aspheric 20D (USA.)

- Corneal assessment:
  - Corneal parameters were performed using a high-resolution rotating Scheimpflug imaging system (Homa IR pentacamRotating Schimflug camera & topography system) (Pentacam® HR, Ref 70900, Germany).

- Cornea thickness at the apex point (regarded as the CCT), the superior, inferior, nasal, and temporal (at 9 mm from the apex) points (regarded as PCT) and the thinnest locations were evaluated automatically.
- In addition, the relative peripheral index (RPI) was calculated by dividing the peripheral corneal thickness (PCT) by the central corneal thickness (CCT). This index represents the rate of thickening of the cornea from the center to the periphery.

Statistics

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were

1- Chi-square test: For categorical variables, to compare between different groups.

2- Student t-test: For normally distributed quantitative variables, to compare between two studied groups.

3- Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups.

4- Pearson coefficient: To correlate between two normally distributed quantitative variables.

5- Spearman coefficient: To correlate between two distributed abnormally quantitative variables.

Table (1): Comparison between the two studied groups according to demographic data

	Patients diagnosed with RA (n = 24)		**Control (n = 24)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Sex Male	7	29.2	6	25.0	χ^2= 0.105	0.745
Female	17	70.8	18	75.0		
Age (years) Min. – Max.	20.0 – 50.0		20.0 – 40.0		t= 1.910	0.063
Mean ± SD.	33.38 ± 8.68		29.25 ± 6.05			
Median (IQR)	34.0 (25.50 – 40.0)		29.0 (24.50 – 33.0)			

IQR: Inter quartile range
SD: Standard deviation

χ^2: Chi square test

t: Student t-test

p: p value for comparing between the two studied groups

Table (2): Comparison between the two studied groups according to PCT

PCT	Patients diagnosed with RA (n = 48)	Control (n = 48)	t	p
Superior	502.0 – 751.0	560.0 – 680.0	1.944	0.055
Min. – Max.	645.6 ± 58.39	626.29 ± 36.42		
Mean ± SD.	654.5 (611.5 – 687.5)	627.0 (598.0 – 660.5)		
Median (IQR)				
Inferior	523.0 – 758.0	522.0 – 719.0	0.356	0.723
Min. – Max.	612.9 ± 47.29	609.3 ± 53.46		
Mean ± SD.	625.5 (580.5 – 643.5)	614.5 (564.0 – 647.5)		
Median (IQR)				
Nasal	541.0 – 768.0	560.0 – 724.0	1.558	0.123
Min. – Max.	644.7 ± 51.85	630.2 ± 38.33		
Mean ± SD.	639.0 (605.5 – 675.0)	631.5 (596.5 – 656.5)		
Median (IQR)				
Temporal	553.0 – 710.0	540.0 – 722.0	2.218*	0.029*
Min. – Max.	619.4 ± 41.16	601.2 ± 39.36		
Mean ± SD.	612.0 (586.5 – 641.0)	598.5 (580.0 – 622.5)		
Median (IQR)				
Average	532.0 – 732.0	553.0 – 678.0	1.886	0.062
Min. – Max.	630.8 ± 38.51	616.8 ± 33.87		
Mean ± SD.	628.5 (605.5 – 650.0)	622.0 (588.5 – 646.0)		
Median (IQR)				

IQR: Inter quartile range SD: Standard deviation t: Student t-test p: p value for comparing between the two studied groups

*: Statistically significant at $p \leq 0.05$

16

Table (3): Comparison between the two studied groups according to CCT

	Patients diagnosed with RA (n = 48)	Control (n = 48)	t	p
CCT	464.0 – 691.0	461.0 – 561.0	1.945	0.055
Min. – Max.	523.7 ± 37.47	510.25 ± 30.01		
Mean ± SD.	517.0(503.0 – 535.0)	502.0(487.0 – 543.0)		
Median (IQR)				

IQR: Inter quartile range SD: Standard deviation t: Student t-test
p: p value for comparing between the two studied groups
*: Statistically significant at $p \leq 0.05$

Table (4): Comparison between the two studied groups according to Thinnest corneal location

	Patients diagnosed with RA (n = 48)	Control (n = 48)	t	p
Thinnest corneal location	461.0 – 584.0	461.0 – 548.0	1.701	0.092
Min. – Max.	512.58 ± 27.77	502.83 ± 28.40		
Mean ± SD.	507.0 (496.5 – 527.5)	498.5 (479.0 – 533.0)		
Median (IQR)				

IQR: Inter quartile range SD: Standard deviation t: Student t-test
p: p value for comparing between the two studied groups

Table (5): Comparison between the two studied groups according to C/P ratio

	Patients diagnosed with RA (n = 48)	Control (n = 48)	t	p
C/P ratio	0.78 – 1.18	0.76 – 0.94	2.969*	0.004*
Min. – Max.	0.87 ± 0.07	0.84 ± 0.04		
Mean ± SD.	0.87 (0.83 – 0.90)	0.84 (0.80 – 0.87)		
Median (IQR)				

IQR: Inter quartile range SD: Standard deviation t: Student t-test p: p value for comparing between the two studied groups
*: Statistically significant at $p \leq 0.05$

Table (6): Correlation between CCT and PCT in each other group

PCT	CCT			
	Patients diagnosed with RA (n = 48)		Control (n = 48)	
	r	p	r	p
Superior	0.555*	<0.001*	0.405*	0.004*
Inferior	0.383*	0.007*	0.670*	<0.001*
Nasal	0.599*	<0.001*	0.554*	<0.001*
Temporal	0.629*	<0.001*	0.611*	<0.001*
Average	0.700*	<0.001*	0.706*	<0.001*

r: Pearson coefficient *: Statistically significant at $p \leq 0.05$

18

Table (7): Correlation between disease activity using DAS and CCT, PCT and thinnest corneal location in the studied group (n = 48)

	DAS	
	r	**p**
CCT	-0.363*	0.011*
PCT	-0.381*	0.008*
Superior	0.004	0.978
Inferior	-0.424*	0.003*
Nasal	-0.244	0.095
Temporal	-0.351*	0.014*
Average		
Thinnest corneal location	-0.377*	0.008*

r: Pearson coefficient

DISCUSSION

The assessment of the CCTs and PCTs is also important for analyzing the corneal biomechanical properties.(13)

In normal eyes, the cornea thickens from the center to the periphery due to an increase in the thickness of Bowman's layer and the stroma when reaching the periphery of the cornea.(14,15)
In the current study, the mean CCT showed a statistically significant decrease as compared to the healthy control (510.25 ± 30.01 µm and 523.7 ± 37.47 µm) (P= 0.050). This agreed with Kamel et al. (16)who showed that the mean central thickness of RA patients was 520.4 ± 23.7 micron and the mean central thickness of control patients was 548.5 ± 25.4 micron with high statistically significant difference (p-value < 0.001).(16)
Also, the results came in accordance with El-Fayoumi et al. (17) who showed that as for the corneal thickness (CT); the central corneal thickness (CCT) was thinner in the RA group as compared to the control group.(17)

The current results also partially agreed with ***Taş et al. (18)*** who showed that the mean CCT in the RA cases was 537.2 ± 27.6 µm as compared to 541.6 ± 15.6 µm in the control group, with no statistically significant difference (p= 0.339).[18]

Corneal thinning mechanism is accused of various factors. Activation of Langerhans cells, a form of dendritic cell, increases cytokine production, which leads to a disproportion among matrix metalloproteinases (MMPs) and tissue inhibitors, mainly tissue inhibitor of metalloproteinases-1 (TIMP-1), and consequently keratolysis as a result of collagenase accumulation in the tissue.[19] According to another hypothesis, corneal defective epithelial barrier function in RA leads to corneal dehydration and secondary to thinning.[20]

All the previous studies including the current study showed reduction in the CCT in the RA cases compared to the healthy control, but the difference was in the level of significance.

In the current study, there was no statistically significant difference between the cases and the control group regarding the PCT in the following regions; superior region (p= 0.055), inferior region (p= 0.723), nasal region (p= 0.123) and average region (p= 0.062). However, there was a statistically significant decrease in the PCT in the temporal region in the RA group compared to the control group (p= 0.024).

This agreed with Kamel et al. (16) who showed that the mean peripheral thickness of RA patients was 668.6 ± 32.1 micron and the mean peripheral thickness of control patients was 681.2 ± 12.8 micron, with no statistically significant difference between the two groups (p-value = 0.420).[16]

On the contrary, the current results disagreed with ***El-Fayoumi et al*. (17)**who showed that the superior, the nasal, the temporal, the superonasal, and the superotemporal para- central thickness (2–5 mm from the center) were also found to be thinner in the RA group. The pericentral area (5–6 mm from the center) was found to be thinner in the superior and nasal sectors in the RA group than in the controls (Figure 2;

p < 0.05). The inferior and inferotemporal paracentral and pericentral areas were not statistically different in either group (p > 0.05). The corneal epithelium of the RA patients was found to be thinner than in controls in the superior and the superotemporal sectors (paracentral and pericentral region) (p < 0.05).[17]

In the current study, there was a statistically significant increase in the C/P ratio in the RA group compared to the control group (0.87 ± 0.07 and 0.84 ± 0.04 respectively) (p= 0.004).

However, this disagreed with Kamel et al. (16) who showed that the mean C/P ratio of RA patients was 0.78 ± 0.03 and the mean ratio of control patients was 0.8 ± 0.03 with no statistically significant difference between the two groups (p-value = 0.29).[16]

In the current study, in the RA group,there was non-statistically significant correlation between disease duration with CCT, PCT in superior region, inferior region, nasal region, temporal region, average region and Thinnest corneal location.This agreed with ***El-Fayoumi et al***. (17) who showed that disease duration were not found to correlate with any of the corneal measurements (central corneal thickness and peripheral corneal thickness) in the RA group patients (p > 0.05).[17]However, this disagreed with Cingü et al. (21) who found that the disease duration correlates negatively with corneal thickness measurements in the RA group.[21]

Also, in the study conducted by Gurlevik et al. (22), the correlation between the duration of disease and mean corneal curvature values (3/5/7 mm region) and central corneal thickness values was found to be positive correlation between the duration of disease and all values of RA.[22]

In the current study, there was a statistically significant decrease in the CCT (p=0.021) in the cases with high activity compared to cases with moderate activity.However, this disagreed with Nossair et al. (23) who showed that there was no statistically significant difference in the CCT between the cases with active RA and inactive RA respectively (CCT = 517.0±22 µm and 509.5±19.6 µm in the active and the inactive groups respectively).[23]

According to the researcher point of view, the difference could be explained due to association of more disease duration with more disease severity in the studies with statistically significant correlation.

In the current study, in the RA group, there was a statistically significant negative correlation between DAS with CCT, PCT in superior region, nasal region, average region and Thinnest corneal location.

This disagreed with El-Fayoumi et al. (17) who showed that the DAS28 were not found to correlate with any of the corneal measurements (central corneal thickness and peripheral corneal thickness) in the RA group patients (p > 0.05).[17]

Although early recognition and advanced treatment have led to a reduction in severe ocular complications, ocular involvement in RA is still cause significant morbidity.[24]Like the joints,

the sclera and cornea contain proteoglycans and collagen. This histologic similarity likely accounts for many of the ocular manifestations of RA. The majority of the theories of the pathogenesis of the ocular conditions associated with RA support the immunology based mechanism. Immune complex deposition, secretion of collagenases by macrophages and neutrophils, cytokine production, complement activation, and formation of autoantibodies play a role in the process.[25]

The main limitations of the current study are the small sample size included, being a single center study and the cross sectional nature of the study.

conclusion

Our study found thatRheumatoid arthritis was associated with thinning of the CCT and PCTs as compared to the healthy control. Also, the degree of corneal thinning was associated with increased rheumatoid arthritis disease severity.

Therefore, we recommend the evaluation of dry eye tests and corneal parameters is crucial in ophthalmologic examinations, and should be included in rheumatoid arthritis ophthalmic routine follow up. Also, the finding of peripheral corneal thinning in patients with RA may be useful in the early diagnosis and identification of patients at high risk of developing RA associated corneal melting, also could be important when assessing individuals for refractive surgery procedures or when matching donor corneas to recipients. Moreover, we recommend conduction of further prospective researches using larger sample size of rheumatoid arthritis patients.

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