

## Study of the Tear Film in Patients with Different Degrees of Rheumatoid Arthritis

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### Abstract

**Background:** Rheumatoid arthritis (RA) is an autoimmune disease that affects mainly joints with extra-articular manifestations (e.g. neurological, pulmonary, cardiac), the most common of which is ocular manifestations which affect quality of life. Mechanism of dry eye in RA patients is not well understood and needs further studies.

**Aim of Study:** The aim of this was to evaluate the tear film parameters in patients with different degrees of rheumatoid arthritis and compare them with healthy control group.

**Patient and Methods:** Our study was a case-control study that was conducted on 64 patients (i.e. 128 eyes), divided into 2 equal groups (each group 32 patients, i.e. 64 eyes).

**Patients Group:** Patients with rheumatoid arthritis.

**Control Group:** Healthy controls. Both groups had no ophthalmological or physical disease causing dry eye.

**Results:** This study found that prevalence of dry eye in RA patients is 46.7% according to schirmer test and 40.6% according to TBUT. Concerning healthy controls, prevalence of dry eye was 21.9% according to schirmer test and 18.8% according to TBUT. Ocular surface symptoms were present in all RA patients and in 50% of healthy controls. MGD (Meibomian gland dysfunction) was present in 53.1 % of RA patients and 9.4% of healthy controls. There was significant relation between RA activity and dry eye symptoms & MGD but no relation between RA activity and TBUT & schirmer test.

**Conclusion:** Patients with RA have a significantly higher prevalence and severity of dry eye when compared to age- and sex-matched healthy controls. There was significant relation between the RA activity and ocular surface symptoms, MGD but no significant relation with TBUT, schirmer test. All RA patients should be always examined for dry eye regardless of disease activity.

**Key Words:** Tear film – Rheumatoid arthritis.

### Introduction

**RHEUMATOID** arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints [1]. The disease can also cause extra-articular inflammation and injury in other organs in the body, including the skin, eyes, lungs, heart and blood vessels [2].

About 17.8-47.5% of patients present the extra-articular manifestations, among which the ocular surface manifestation is the most common, which seriously affects the quality of life [3].

Dry eye syndrome (DES) is the most common ocular manifestation in RA patients. Symptoms include irritation, redness, discharge, and easily fatigued eyes. Blurred vision may also occur. The symptoms can range from mild and occasional to severe and continuous. Scarring of the cornea may occur in some cases without treatment [4].

Ocular sicca usually develops in the setting of long-standing rheumatoid disease, although it may be an early or presenting manifestation of RA [5].

### Patients and Methods

A case-control study that was conducted on 64 patients (i.e. 128 eyes), divided into 2 equal groups (each group 32 patients; i.e. 64 eyes):

Patients group “Patients with rheumatoid arthritis” (recruited from rheumatology outpatient clinic) and Control group “Healthy controls” (recruited from patients seeking glasses).

Patients over 18 years old (both groups) and patients previously diagnosed as RA according to the American College of Rheumatology and European League Against Rheumatism classification

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criteria of RA (group A) were included in the study. Exclusion criteria were patients with any disease affecting tear film e.g. glaucoma, blepharitis, allergic diseases, lacrimal drainage system diseases, autoimmune diseases (group A), history of ocular surgery, ocular trauma and recent use of dry eye medications.

Full history taking was done by an ophthalmologist.

*Subjective questionnaire:* Ocular surface disease index (OSDI) questionnaire [6], which consists of 12 items, divided into 3 sections: The experienced symptoms of dry eye, their effect on visual function and the presence of environmental triggers. Each item is graded on a scale from 0 to 4, where (0) means none of the time, (1) some of the time, (2) half of the time, (3) most of the time, (4) all of the time (Fig. 1).

**Ocular Surface Disease Index<sup>c</sup> (OSDI)<sup>c2</sup>**

Ask your patient 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	
6- Reading?	4	3	2	1	0	N/A
7- Driving at night?	4	3	2	1	0	N/A
8- Working with a copmuter or bank machine (ATM)?	4	3	2	1	0	N/A
9- Watching TV?	4	3	2	1	0	

**Subtotal score for answers 6 to 9 (B)**

Have your eyes fely 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	
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)**

Fig. (1): OSDI questionnaire [6].

The total OSDI score is calculated by the following formula:

$$\text{OSDI} = \frac{\text{Some of scores of total questions answered} \times 100}{\text{Total number of questions answered} \times 4}$$

According to, OSDI scores, patients were classified as having a normal ocular surface (0-12 points) or as having mild (13-22 points), moderate (23-32 points) or severe (33-100 points) ocular surface disease.

#### Objective methods:

- 1- Full anterior segment examination by slit lamp biomicroscopy for signs of dry eye eg. MGD, Punctate epitheliopathy, filamentary keratitis.
- 2- Schirmer test for aqueous tear production (Fig. 2):

*Basic Schirmer Test was done by the following steps [7]:*

- Instillation of topical anesthetic (benoxinate hydrochloride 0.4%).
- Dry the cul-de sac.
- The paper strip is bent and the 5mm end is inserted into the lower fornix of the eye.
- The moistening of the exposed portion of paper strip (The 30mm segment) over a 5 minutes period is a measure of the rate basic tear secretion.
- Interpretation of results:
  - Wetting of more than 15mm is considered normal.
  - 10-15mm: Mild dryness.
  - 5-10mm: Moderate dryness.
  - Less than 5mm: Severe dryness.



Fig. (2): Schirmer test showing severe dryness.

- 3- TBUT for tear film stability (Fig. 3):

#### *Steps of TBUT [8]:*

- Fluorescein was instilled by means of an impregnated paper strip (wetted with a drop of saline).
- The patient was asked to blink 2 or 3 times to distribute the dye then stop and stare straight ahead (with the patient on the slit lamp).

- The cornea was scanned with cobalt blue light looking for an area of tear film rupture manifested by a black island within the green sea of fluorescein. The time between the last blink and the appearance of the first dry spot recorded was calculated by using a stopwatch.
- Interpretation of results: If TBUT is less than 10 seconds this diagnoses dry eye; and if TBUT is more than 10 seconds this is normal.

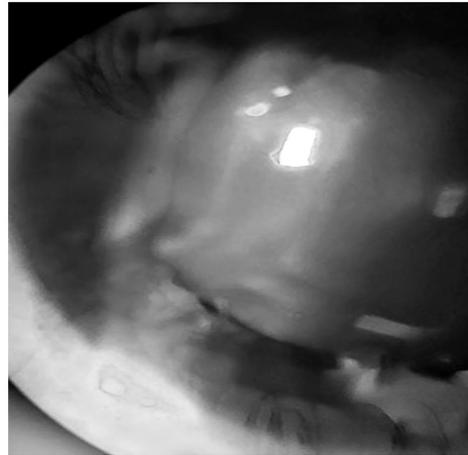


Fig. (3): Tear break up.

**Rheumatoid arthritis grading:** Rheumatoid disease activity was measured in group B using the DAS28-ESR (Disease Activity Score 28 -ESR) [9]. This score is calculated based on swollen joint count (SJC), tender joint count (TJC), ESR, and general health (GH) (patient assessment of disease activity using a 100mm visual analog scale with 0=best and 100=worst). Values more than 5.1 corresponds to high disease activity, between 3.2 and 5.1 corresponds to moderate disease activity, between 2.6 and 3.2 corresponds to a low disease activity, less than 2.6 corresponds to remission.

**Statistical analysis:** Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data with parametric distribution were presented as mean, standard deviations and ranges. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent *t*-test while between more than two independent groups were done by using One Way ANOVA test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-

value of less than 0.05 was considered Significant (S), less than 0.01 considered highly significant (HS).

**Results**

*Demographic data:*

For patients group, mean age was 44.56±9.87, 93.8% were females. For control group, mean age was 40.31±8.69, 78.1% were females. There was no significant difference between both groups regarding age and sex (Table 1 & Fig. 4).

Table (1): Comparison between studied groups as regard demographic data.

	Control group No. = 32	Patients group No. = 32	Test value	p-value	Sig.
<i>Age:</i>					
Mean ± SD	40.31±8.69	44.56±9.87	-1.829*	0.072	NS
Range	24-54	28-65			
<i>Sex:</i>					
Male	7 (21.9%)	2 (6.2%)	F*	0.147	NS
Female	25 (78.1%)	30 (93.8%)			

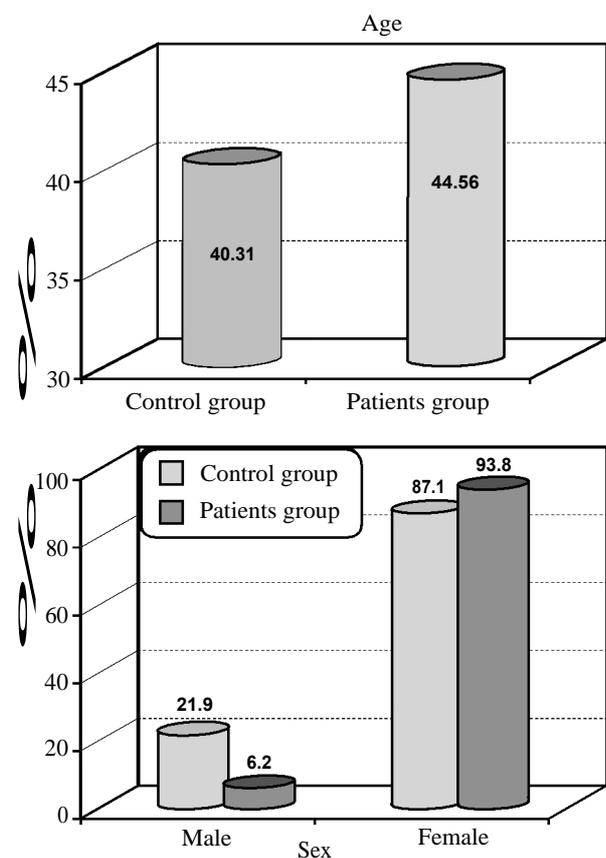


Fig. (4): Comparison between studied groups as regard demographic data.

*Ocular surface disease index questionnaire:* OSDI for patients group showed that 21.9% had mild, 65.6% had moderate and 12.5% had severe ocular surface symptoms. For control group; 50.0% were normal, 31.2% had mild, 18.8% had moderate

and 0.0% had severe ocular surface symptoms. There was statistically significant difference between both groups regarding OSDI with *p*-value 0.000 (Table 2 & Fig. 5).

Table (2): Comparison between studied groups as regard OSDI questionnaire.

	Control group No.=32	Patients group No.=32	Test value	p-value	Sig.
<i>OSDI:</i>					
Normal	16 (50.0%)	0 (0.0%)	F*	0.000	HS
Mild	10 (31.3%)	7 (21.9%)			
Moderate	6 (18.8%)	21 (65.6%)			
Severe	0 (0.0%)	4 (12.5%)			

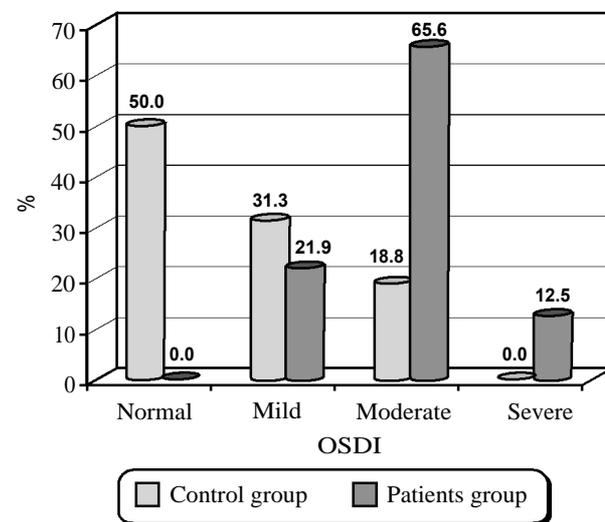


Fig. (5): Comparison between studied groups as regard OSDI questionnaire.

*Anterior segment examination using slit lamp biomicroscopy:* For patients group, 53.1% were abnormal (44 eyes showed MGD and one of them showed also filamentary keratitis) and 46.9% were normal. For control group, 9.4% showed MGD and 90.6% were normal.

*Schirmer test:* As regard patients group, 53.1% were normal, 31.3% had mild, 10.9% had moderate and 4.7% had severe dryness. As regard control group; 78.1% were normal, 21.9% had mild dryness.

*TBUT:* As regard patients group 59.4% were normal, 40.6% had dryness. As regard control group 81.2% were normal, 18.8% had dryness. There was statistically significant difference between the patients group and control group regarding Schirmer test, TBUT and anterior segment examination with *p*-value 0.001, 0.007 and 0.000 respectively (Table 3 & Fig. 6).

Table (3): Comparison between studied groups as regard schirmer test, TBUT & anterior segment examination.

	Control group		Patients group		Test value	p-value	Sig.
	No.	%	No.	%			
<b>Schirmer test:</b>							
Normal	50	78.1	34	53.1	F*	0.001	HS
Mild	14	21.9	20	31.3			
Moderate	0	0.0	7	10.9			
Severe	0	0.0	3	4.7			
<b>TBUT:</b>							
Normal	52	81.0	38	59.4	7.336*	0.007	HS
Mild	12	18.8	26	40.6			
<b>Ant. Segment exam:</b>							
Normal	58	90.6	30	46.9	14.255	0.000	HS
Abnormal (MGD)	6	9.4	34	53.1			

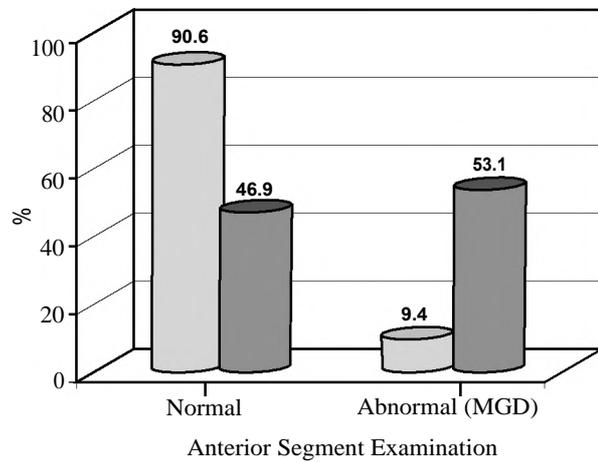
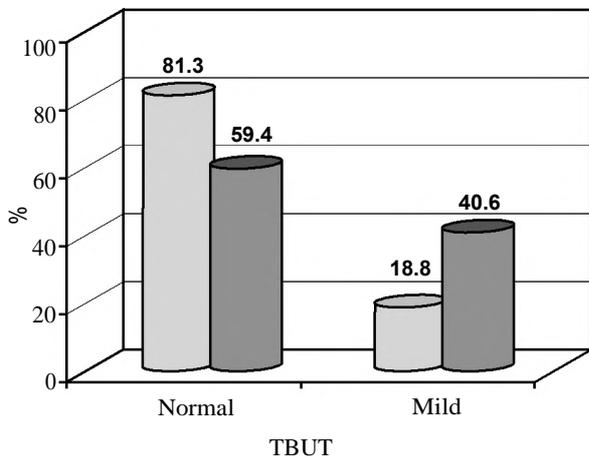
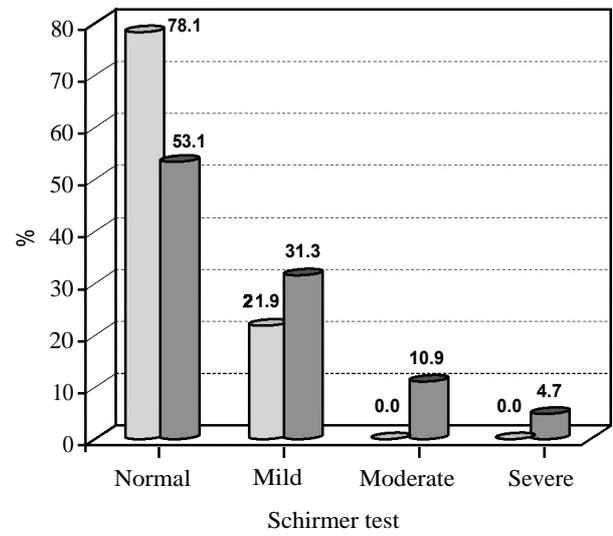


Fig. (6): Comparison between studied groups as regard schirmer test, TBUT & anterior segment examination.

**RA grading:** According to DAS28-ESR grading score of patients group, 6.3% had mild, 31.3% had moderate and 62.5% had high disease activity (Table 4 & Fig. 7).

Table (4): RA grading of patients group.

	Patients group	
	No.	%
<b>RAgrading:</b>		
Remission	0	0.0
Mild	2	6.3
Moderate	10	31.3
High	20	62.5

There was no statistically significant relation between RA grading and Schirmer test & TBUT with *p*-value 0.077 and 0.346 respectively, while there was high statistically significant difference

between RA grading and OSDI & Anterior Segment examination with *p*-value 0.000 and 0.000 (Table 5 & Fig. 8).

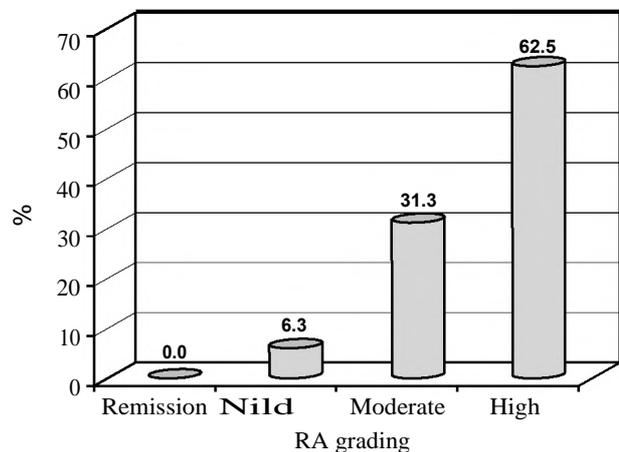


Fig. (7): RA grading of patients group.

Table (5): Relation between RA grading & schirmer test, TBUT, anterior segment examination, OSDI in patients group.

	RA grading						Test value	P-value	Sig.
	Mild (2)		Moderate (10)		High (20)				
	No.	%	No.	%	No.	%			
<i>Schirmer test:</i>									
Normal	1	25.0	15	75.0	18	45.0	F*	0.077	NS
Mild	3	75.0	5	25.0	12	30.0			
Moderate	0	0.0	0	0.0	7	17.5			
Severe	0	0.0	0	0.0	3	7.5%			
<i>TBUT:</i>									
Normal	3	75.0	14	70.0	21	52.5	2.125*	0.346	NS
Mild	1	25.0	6	30.0	19	47.5			
<i>Ant. Segment exam:</i>									
Normal	4	100.0	18	90.0	8	20.0	F*	0.000	HS
Abnormal	0	0.0	2	10.0	32	80.0			
<i>TBUT:</i>									
Mild	1	50.0	6	60.0	0	0.0	F*	0.000	HS
Moderate	1	50.0	4	40.0	16	80.0			
Severe	0	0.0	0	0.0	4	20.0			

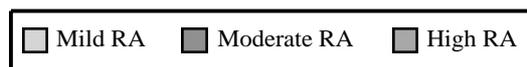
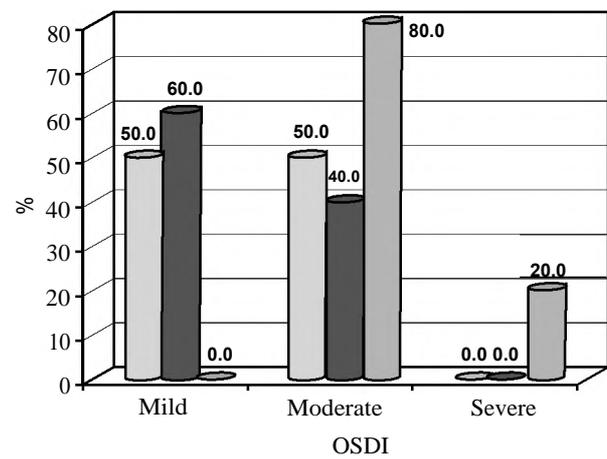
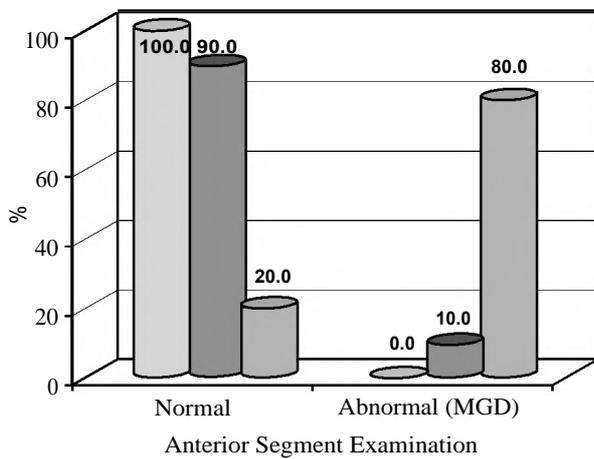
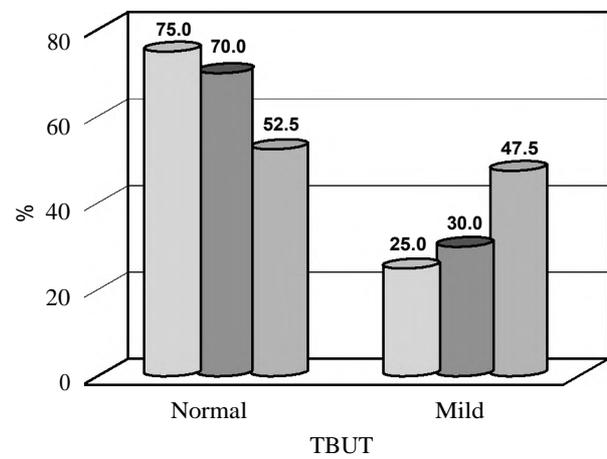
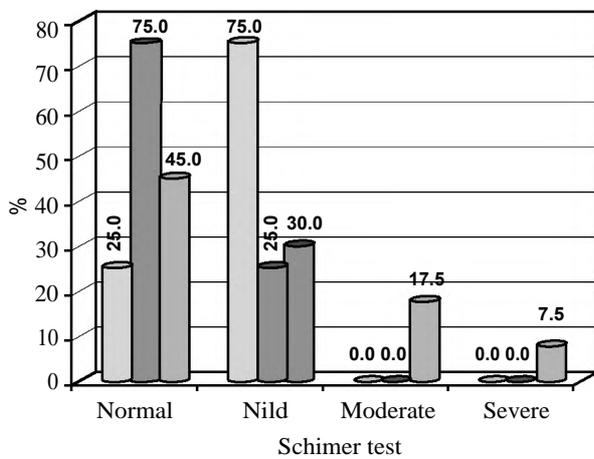


Fig. (8): Relation between RA grading & schirmer test, TBUT, anterior segment examination, OSDI in patients group.

## Discussion

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily affects the peripheral joints in a symmetric pattern with predominant female involvement [10]. RA is mainly considered as a joint disease, but it has the capacity to inflict multiple organs because of the abnormal systemic immune response. About 17.8-47.5% of patients present the extra-articular manifestations, among which the ocular surface manifestation is the most common, which seriously affects the quality of life [2]. There are a variety of ocular manifestations of RA. The most common is keratoconjunctivitis sicca (KCS) or secondary Sjogren syndrome (SS), which is clinically evident in 15-25% of RA patients [11]. Ocular sicca usually develops in the setting of long-standing rheumatoid disease, although it may be an early or presenting manifestation of RA [5]. It has been reported that the incidence of dry eye in the general population is about 5-17%, while in the patients with RA, it is as high as 19-31%. Recent studies show that the pathogenesis of dry eyes is similar to the other extra-articular complications of RA, which may be a mucosal autoimmune disease. It is speculated that the degree of dry eye may also change with the systemic conditions, due to the influence of systemic immune response [2].

Our study aimed to evaluate the ocular surface and tear film parameters in patients with different degrees of rheumatoid arthritis.

**OSDI questionnaire:** In this study, OSDI revealed prevalence of ocular surface disease symptoms in all RA patients, most of them (65.6%) had moderate symptoms, 21.9% had mild and 12.5% had severe symptoms. Meanwhile in healthy controls, 50.0% had ocular surface symptoms graded as 31.2% mild, 18.8% moderate. There was statistically significant difference between RA patients and healthy controls regarding OSDI. Kosrirukvongs et al., [12] reported that according to OSDI of 61 RA patients, 10 patients (16.4%) had dry eye from interpreted score, graded mild 8 (13.1 %) and moderate 2 (3.3%). Ma et al., [2] showed that of 30 RA patients, according to OSDI, 22 patients had ocular surface disease symptoms and 8 patients had no ocular surface disease symptoms.

**Tear film parameters:** In our study, schirmer test showed 46.7% prevalence of dry eye in RA patients. As regard healthy controls, schirmer test showed that 21.9% had dryness. Similarly, Kosrirukvongs et al., [12] found that according to schirm-

er test, 56 out of 120 eyes in 60 RA patients (46.7%) were diagnosed as dry eye. Punjabi et al., [13] found that as regard schirmer test of 84 RA patients, 61 (72.61%) patients had wetting of more than 5mm and 23 (27.39%) had wetting of less than 5mm (mean wetting of 14mm (SD=7.93mm), While as regard 84 healthy controls, 88.09% (74 patients) had wetting of more than 5mm and 11.90% (10 patients) had wetting of less than 5mm (mean wetting of 29mm (SD=10.8mm). There was high statistically difference in mean wetting between RA patients and normal controls with  $p$ -value 0.003. Usuba et al., [14] reported that as regard schirmer test of 16 RA patients, 6 (37.6%) showed wetting of less than 10mm.

As regard TBUT, we found that 40.6% of RA patients had TBUT of less than 10 seconds while in healthy controls 18.8% had TBUT of less than 10 seconds. Kosrirukvongs et al., [12] found that according to TBUT, 100 of 122 eyes of RA patients (81.9%) had TBUT of less than 10 seconds [6]. Usuba et al., [14] reported that as regard TBUT of 16 RA patients, 11 (68.8%) had TBUT less than 10 sec. Punjabi et al., [13] found that 65 (77.38%) of 84 RA patients had normal TBUT (> 10 seconds), and 19 (22.62%) had abnormal TBUT (<10 seconds). While as regard 84 healthy controls, 76 (90.48%) had normal TBUT, and 8 (9.52%) had abnormal TBUT. The mean value of TBUT in the 84 patients with RA was 10.4 seconds (SD=4.41 seconds). The mean value of TBUT in the 84 healthy controls was 18.9 seconds on mean (SD=4.98 seconds). Between the two groups, there was a statistically significant difference in mean TBUT ( $p$  0.001).

**Anterior segment examination:** Of our 64 RA patients, 34 (53.1%) had MGD, While in control group, 6 cases (9.4%) only had MGD. There was high statistically significant difference between RA patients and health controls regarding MGD. Usuba et al., [14] reported that as regard MGD, of 16 RA patients, 8(50%) had MGD, while of 24 healthy controls, 2 (8.3%) had MGD. According to Usuba, there was high statistically significant difference between RA group and control group regarding MGD with  $p$ -value 0.007. Dry eye parameters revealed a higher overall frequency of DED ( $p$ <0.001) [7].

In brief, our study showed that prevalence of dry eye in RA patients is 46.7% according to schirmer test, 40.6% according to TBUT, while as ocular surface symptoms present in all our RA patients and MGD in 53.1% of them.

Accordingly, we can assume that MGD is a main mechanism for dry eye in RA patients. This is supported by a study done by Ma et al., [2]. Ma et al., reported that there are many causes of MGD in RA, which may be due to the attack of the immune system on one of the target organs, as in the case of Sjogren's syndrome. Tong et al., [15] studied the immune factors that lead to dry eye and correlated them with systemic disease which could lead to potential treatment targets in the future showing the importance of conducting further studies on the ocular surface in RA patients. All this suggests that more research is needed on the markers of ocular surface in RA.

Our study demonstrated that there was no statistically significant relation between RA grading and Schirmer test & TBUT with  $p$ -value 0.077 and 0.346 respectively. Whereas, there was high statistically significant relation between RA grading and OSDI & MGD with  $p$ -value 0.000 and 0.000 respectively.

Abd-Allah et al., [16] found that there is no relation between severity of dry eye and RA activity.

Ma et al., [2] found that regardless of the duration, RA activity has no correlation with dry eye severity. Zakeri et al., [17] reported that RA activity (using DAS28-ESR score) has no correlation with severity of dry eye. Wolfe and Michaud [18] reported that the symptoms of dry eye were more common in RA patients who had higher disease activity score, pain and disability. Schargus et al., [19] reported that patients with RA with a high DAS28-ESR score show higher prevalence of tear film hyperosmolarity. According to McGavin et al., [20], the ocular manifestations were more common with prolonged duration of the disease. The severity was also worse with longer duration of the disease.

Among the main limitations of our study beside the small sample size is the ignorance of different modalities of RA treatment and their effect on tear film.

#### Conclusion:

Patients with RA have a significantly higher prevalence and severity of dry eye when compared to age- and sex-matched healthy controls. There was significant relation between the RA activity and ocular surface symptoms, MGD but no significant relation with TBUT, schirmer test. All RA patients should be always examined for dry eye regardless of disease activity.

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## دراسة فيلم الدموع في المرضى الذين يعانون من درجات مختلفة من التهاب المفاصل الروماتويدي

يعد التهاب المفاصل الروماتويدي من أمراض المناعة الذاتية المزمنة ومتعددة الأجهزة والتي تتسبب فيها العوامل البيئية والوراثية. النساء أكثر عرضة ثلاث مرات للإصابة بالمرض من الرجال. يصيب المرض بشكل أساسي المفاصل وعادةً ما يكون مصحوباً بواحد أو أكثر من مشاكل بعيدة عن المفصل. العين هي هدف مهم لهذا المرض وتعد سطح العين، على وجه الخصوص، واحدة من أكثر المناطق تضرراً. تشمل الأعراض العينية لالتهاب المفاصل الروماتويدي مرض جفاف العين والتهاب الصلبة والتهاب القرنية والتهاب القرنية. مرض جفاف العين هو الأكثر شيوعاً من مظاهر العين للمرضى الذين يعانون من التهاب المفاصل الروماتويدي. الهدف من هذه الدراسة هو تقييم سطح العين ومعلومات فيلم المسيل للدموع في المرضى الذين يعانون من درجات مختلفة من التهاب المفاصل الروماتويدي. تم أخذ تاريخ مرضي كامل من المرضى. تم عمل فحص عام للمرضى لتحديد درجة نشاط مرض التهاب المفاصل الروماتويدي واستبعاد الحالات التي تعاني من أي أمراض تسبب جفاف العين. تم قياس حدة الأبصار وإجراء استبيان مؤشر مرض سطح العين وعمل فحص كامل للعينين بواسطة المصباح الشقي وإجراء اختبار شيرمر وحساب وقت تفكك دموع وصبغ القرنية بالفلوريسين. بالإشارة إلى البيانات الديموغرافية للمرضى الخاضعين للدراسة وجدنا أنه لا يوجد فرق كبير بين المجموعات المدروسة فيما يتعلق بالعمر والجنس. بالإشارة إلى اختبار شيرمر ووقت تفكك الدموع واستبيان مؤشر مرض سطح العين وجدنا زيادة مهمة في نسبة جفاف العينين بمرضى التهاب المفاصل الروماتويدي. وجدنا أيضاً أنه لا توجد علاقة بين درجة نشاط المرض واختبار شيرمر ووقت تفكك الدموع بينما توجد علاقة بين درجة نشاط المرض واستبيان مؤشر مرض سطح العين. ننصح بالفحص الدوري لمرضى الروماتويد بواسطة طبيب الرمد بغض النظر عن درجة نشاط المرض.