Association of rheumatoid arthritis with aqueous deficient dry eye development

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Research Article

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Abstract

Purpose: to evaluate rheumatoid arthritis (RA) as a potential risk factor for the development of aqueous deficient dry eye (ADDE) compared to evaporative dry eye (EDE).

Study Design: The study design was observational and cross-sectional.

Methods: Two hundred volunteer participants with dry eye disease (DED) were recruited based on the TFOS DEWS II criteria, which included tear film osmolarity, Fluorescein Break-Up Time, and ocular surface damage assessment. To obtain OSDI scores, demographics, and RA diagnosis by their medical doctor, participants were recruited using QR codes linked to designated mobile Forms. Tear meniscus height and lipid layer pattern were measured in all participants to differentiate between ADDE, EDE, or Mixed dry eye in addition to the DED diagnostic criteria.

Results: after the initial recruitment, a total of 113 eligible participants were included in the final analysis. The ADDE group had a higher likelihood of having RA (OR 5.65, 95% CI 1.20-26.55) compared to the EDE group. Additionally, the number of participants with RA in the ADDE group was statistically higher than those in the EDE group (Fisher's exact test, all p = 0.020). Furthermore, a correlation was obtained between RA and an ADDE differential diagnosis (Cramer's V = 0.227, p = 0.026).

Conclusion: the present study supports the hypothesis that RA could be a risk factor for the development of ADDE over EDE type.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes pain, swelling, and stiffness in the joints, primarily affecting the hands, feet, and wrists [1, 2]. This condition has a significant impact on patients' quality of life, as it can result in reduced mobility, fatigue, and disability. Between 2013 and 2015, approximately 58.5 million people in the US were diagnosed with RA, and it is projected that by 2040, the prevalence of the disease will increase to 78.4 million adults aged 18 years and older [3–5]. Unfortunately, there is currently no known cure for RA, but early diagnosis and appropriate treatment can help patients manage the condition and reduce the frequency and severity of flares, enabling them to lead active lives and maintain employment. Recent research has suggested a possible link between RA and dry eye syndrome, a condition that occurs when the eyes fail to produce enough tears to keep them lubricated [6]. The association between these two conditions is believed to be due to the inflammation that occurs in the eyes and joints of patients with RA. However, more research is needed to understand the precise relationship between these two conditions and to develop effective treatments for patients who suffer from both conditions simultaneously.

The Tear Film Ocular Society (TFOS) has redefined dry eye syndrome as dry eye disease (DED) in the Dry Eye Workshop II (DEWS II). According to TFOS, DED is a multifactorial disease characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, with tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities playing etiological roles [7, 8]. TFOS DEWS II etiological classification report has established two predominant and non-mutually exclusive categories of DED: aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) [8–10]. ADDE describes conditions affecting lacrimal gland function such as Sjögren's syndrome (SS), whereas EDE includes both lid-related factors (such as Meibomian gland dysfunction and blink-related issues) and ocular surface-related causes (such as mucin and contact lens-related problems). Additionally, there is a "third" type called mixed DED, which is a combination of the
other two categories and usually originates from a mix of factors that affect the general homeostasis of the whole lacrimal functional unit [8–10]. In a clinical setting, it is crucial to distinguish between ADDE and EDE as they require different management approaches. ADDE is linked to the aqueous component of tears, which is assessed through a total tear evaluation, while EDE is associated with lipid layer abnormalities, which are evaluated by assessing Meibomian Glands function. The aim of this study was to investigate whether rheumatoid arthritis (RA) is a risk factor for the development of ADDE compared to EDE.

**Material And Methods**

**Study design and calculation**

A total of 200 consecutive patients who visited the Optometry Clinic with complaints related to dry eye were recruited for the study. These patients had been referred by their medical doctors or the health service of the institution for an ocular surface examination due to dry eye symptoms. Patients willing to participate were provided with a self-administered electronic questionnaire through a designated mobile form, which took approximately five minutes to complete. The questionnaire gathered information on the patients’ demographics, Ocular Surface Disease Index (OSDI) score [11, 12], and whether they had previously received a diagnosis of rheumatoid arthritis (RA) from their medical doctor. Informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Ethics Committee of the university.

The sample size was calculated using PS Power and Sample Size Calculations Version 3.1.2 (Copyright© by William D. Dupont and Walton D. Plummer) based on the TFOS DEWS II Diagnostic Methodology report principles [7, 13, 14]. The literature-reported standard deviations (SDs) for symptomatology status (OSDI score), tear film osmolarity, tear film FBUT, and fluorescein corneal staining were assumed to be 6.7, 4.8 mOsm/L, 2.9 s, and 2, respectively [7, 11]. To achieve a power of 80% (Type II error associated) for a significance level of $\alpha = 0.05$ (Type I error associated) and a confidence level of 95% to detect a clinical difference between non-pathological and pathological participants of 7.3, 5 mOsm/L, 5 s, and 1, respectively, a minimum of 20, 18, 12, and 17 subjects in each group were required to achieve a minimum control/experimental ratio of 1:1. These results were in line with the recommendations of the TFOS DEWS II Diagnostic Methodology report [7]. The highest value among these was used as the reference for the sample size per group (20 participants) to ensure a more reliable study. A larger sample size was recruited to increase the impact of the study results.

**Study Design and Diagnostic Criteria**

A battery of clinical procedures was conducted in all participants according to the TFOS DEWS II Diagnostic Methodology report [7, 13, 14]. The tests were always performed in the same order, from the least to the most invasive, while the first eye to be measured was randomly selected [7, 13, 14]. The procedures included tear film osmolarity, lipid layer pattern (LLP), tear meniscus height (TMH), tear film break-up time (FBUT), and fluorescein corneal staining.

To diagnose dry eye disease (DED), the cut-off values used were an OSDI score $\geq 13$, tear osmolarity $\geq 308$ mOsm/L, FBUT $< 10$ s, and corneal staining (Oxford Scheme) $\geq 2$ (Table 1). Only participants who were classified as having DED, with positive symptomatology and positive results on at least one clinical test, were included in the study sample [7, 13, 14]. According to the TFOS DEWS II criteria [7, 8], participants were classified as having
aqueous-deficient DED (ADDE) if they obtained a low tear meniscus height ($\text{TMH} \leq 20\text{mm}$), as having evaporative DED (EDE) if they obtained a thin lipid layer pattern ($\text{LLP} \leq \text{CM}$), or as having mixed DED if both criteria were met [8, 15, 16]. Participants classified as mixed DED were not included in the final analysis to avoid possible interferences (Table 1).

### Table 1

Summary of the battery of clinical procedures performed [7, 13, 14]. OSDI = ocular surface disease index; FBUT = fluorescein break-up time. TMH = tear meniscus height; LLP = lipid layer pattern. CM = closed meshwork. ADDE = aqueous deficient dry eye. EDE = evaporative dry eye.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSDI score $\geq 13$</td>
<td>Only one condition must be filled:</td>
<td></td>
</tr>
<tr>
<td>- Osmolarity in one eye $\geq 308 \text{ mOsm/l}$</td>
<td>TMH $\leq 20\text{mm}$</td>
<td>ADDE</td>
</tr>
<tr>
<td>- FBUT in one eye $&lt; 10$ s</td>
<td>LLP $&lt; \text{CM}$</td>
<td></td>
</tr>
<tr>
<td>- Corneal staining (Oxford Scheme) in one eye $\geq 2$</td>
<td>TMH $&lt; 20\text{mm}$</td>
<td>EDE</td>
</tr>
<tr>
<td></td>
<td>LLP $\leq \text{CM}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMH $\leq 20\text{mm}$</td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>LLP $\leq \text{CM}$</td>
<td></td>
</tr>
</tbody>
</table>

All measurements were performed and recorded by the same examiner who was unaware of the questionnaire results. The measurements were taken in a single session to avoid inter-examiner or intra-session variability. The instruments and materials used, such as the fluorescein strip and TearLab test cards, were kept in a humidity- and temperature-controlled room with a temperature of 20–23°C and humidity of 50–60%, where the study was conducted [17]. Participants were allowed to rest for 5–10 minutes to adapt to the ambient conditions prior to the measurements.

### Evaluation Procedures

#### Symptomatology Assessment

The symptomatology of DED was assessed using a self-administered OSDI questionnaire. Participants scanned a QR code provided prior to the examination and were asked questions related to their symptoms during the previous week using a standardized interview model. The scores obtained were computed by the researchers on a scale of 0 to 100 points according to published guidelines, with higher scores indicating greater disability [18].

#### Tear Film Osmolarity

The TearLab osmometer (TearLab Corp, San Diego, CA, United States) was used to measure tear film osmolarity [19]. Participants were instructed to sit with their head tilted back and eyes looking up towards the ceiling. The osmometer probe was then placed on the lower tear meniscus until a beep was emitted, indicating that the tear sample had been collected. The osmometer converted the electrical impedance of the sample into osmolarity (mOsm/L), which was displayed on the device screen. To avoid any inter-eye interference, the contralateral eye was measured after a 5–10-minute interval following the same protocol [17]. The system’s correct function was regularly verified using a quality control electronic check card, which confirmed that the reading was $334 \pm 3$ mOsm/L, indicating that the device was working accurately.

#### Fluorescein Break-Up Time
The FBUT measurement was conducted and videorecorded using the fluorescein function of the Keratograph 5M (Oculus Optikgerate GmbH, Wetzlar, Germany)[20]. To avoid inter-patient evaluation interference, a fluorescein strip hydrated with saline solution was applied to the patient's eye in the upper bulbar conjunctival area[21]. After applying the dye, participants were instructed to blink normally to ensure even distribution and then to blink three times while keeping their eyes open until the end of the test [22]. The FBUT was defined as the time interval between the last blink and the appearance of the first black spot on the corneal surface. The procedure was repeated three times for each participant [22]. The FBUT was calculated by a second masked examiner using the recorded videos and the open-source software VisuaIDub64, which improved temporal resolution by converting the video into frames (8 frames = 1s) [22]. The final value was the mean of the two closed measurements [22].

**Corneal Staining**

Immediately following the FBUT assessment, corneal staining was evaluated and recorded by the Keratograph 5M using the fluorescein function while the participants remained seated in the same position [20]. Participants were instructed to focus on a red target at the center of the device, after which they were asked to look in various directions (right, left, up, and down) to assess the paracentral areas; during the "look down" phase, the upper lid was slightly manipulated to examine the upper part of the cornea [23, 24]. A second masked examiner assessed the recorded videos of this test using the Oxford Scheme, which grades the severity of dry eye as mild (stage 0 or 1), moderate (stage 2 or 3), or severe (stage 4 or 5) [23, 24].

**Tear Meniscus Height**

TMH was semi-automatically quantified using a previously established protocol [15, 25]. Participants were seated at a Topcon SL-D4 slit-lamp biomicroscope (Topcon Corporation, Japan) and instructed to maintain primary eye gaze with a natural blink while fixating on a target. A Topcon DC-4 digital camera connected to a computer was used to record video of the tear meniscus. A 3x5 mm light beam with moderate illumination was used to avoid reflex tearing and prevent direct light from shining into the pupil during measurements [15, 25]. The central meniscus was captured at the 6 o'clock position without tilting the illumination column, and images of the tear meniscus were extracted from the recording. The images were then measured by a second experienced observer, who was masked to the study groups, using computer-assisted image analysis software (ImageJ software v1.53i, National Institutes of Health, Bethesda, MD; http://imagej.nih.gov/ij/) [15, 25, 26]. The data were converted from pixels to millimetres.

**Lipid Layer Interference Pattern**

The lipid layer of the tear film was assessed using a Tearscope (Keeler, Windsor, United Kingdom)[27], which was fixed at a constant distance with the chinrest of the Topcon SL-D4 slit-lamp to provide a standardized area. Image acquisition was performed following a previously established protocol [16]. The participant was seated behind a slit-lamp and instructed to look at a target to maintain primary eye gaze, with the lipid layer region of interest centered, while a natural blink was allowed. Throughout the procedure, the illumination was provided by the Tearscope. The tear film was recorded by a digital camera attached to the slit-lamp and stored on a connected computer. Care was taken to ensure that the videos met minimum quality requirements, including being free of blur, the lipid layer being well spread after a complete blink, and being well centered. It is important to note that correct centering and focusing on the LLP videos requires prior training [16]. Images were acquired from recorded videos by a second experienced masked observer [16]. When the LLP evolution was stable with minimal variations, the clearest image was extracted (approximately 1-1.5 seconds after blinking). As the appearance of
the lipid layer is not static between blinks, the images were categorized following Guillon's Clinical scheme as open meshwork (OM), closed meshwork (CM), wave (W), amorphous (AM), and color (COL) [16, 28]. Since LLPs do not follow a discrete classification, but rather a continuous evolution of the lipid tear film thickness, when the pictures fell between two grades, the observers classified them as the pattern that was closer, following the Guillon scheme and their own experience.

**Statistical Analysis**

Data analysis was performed using SPSS statistical software version 25.0 for Windows (SPSS Inc., Chicago, IL, United States). Significance was set at $p \leq 0.05$ for all analyses. Prior to analysis, the normal distribution of the data was checked using the Shapiro-Wilk test [29]. Tear osmolarity, FBUT and TMH showed a normal distribution (Shapiro-Wilk, all $p > 0.05$), while OSDI, corneal staining, and LLP were not normally distributed (Shapiro-Wilk, all $p < 0.05$). Descriptive statistics were calculated as mean with SD for parametric variables, median and interquartile range (IQR) for non-parametric variables, and minimum and maximum values were reported in all cases. Differences in parameter values between groups or subgroups were analyzed using unpaired t-tests for parametric variables and Mann-Whitney U tests for non-parametric variables.

Odds ratios (OR) along with 95% confidence intervals (CI) were estimated to assess the magnitude of the association between RA and the established DED category [29]. Due to the categorical nature of the data, a chi-squared test was used to compare the outcomes of the risk factor studied across different DED categories. Fisher's exact tests and Cramer's V were performed to evaluate the associations and correlations between categorical data [29].

**Results**

A total of 113 eligible participants were included in the analysis from an initial sample of 200 patients. Descriptive statistics for all measurements on each subgroup are provided in Table 2. No statistical differences were found in age, OSDI, osmolarity, corneal staining, or FBUT distribution between the groups (all $p \geq 0.173$), whereas significant statistical differences were found in TMH and LLP (all $p \leq 0.001$).
Table 2
Descriptive statistics of the ADDE and EDE groups. SD = standard deviation. IQR = interquartile range. OSDI = ocular surface disease index. FBUT = fluorescein break-up time. TMH = tear meniscus height. LLP = lipid layer pattern. OM = open meshwork. CM = closed meshwork. W = wave. AM = amorphous. COL = color. *Mean and SD displayed on parametric parameters. **Median and IQR displayed on non-parametric parameters. ‡Unpaired t-test. †Mann-Whitney U test.

<table>
<thead>
<tr>
<th></th>
<th>Age (Years)*</th>
<th>OSDI (Score)**</th>
<th>Osmolality (mOsm/l)*</th>
<th>Corneal Staining (Oxford Scheme)**</th>
<th>FBUT (s)*</th>
<th>TMH (mm)*</th>
<th>LLP (Guillon Scheme)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADDE (n = 63)</strong></td>
<td>Mean/Median</td>
<td>48.46</td>
<td>25.00</td>
<td>318.70</td>
<td>1.00</td>
<td>9.28</td>
<td>0.137</td>
</tr>
<tr>
<td></td>
<td>SD/IRQ</td>
<td>14.68</td>
<td>20.83</td>
<td>16.45</td>
<td>1.50</td>
<td>8.78</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>18.00</td>
<td>10.42</td>
<td>286.00</td>
<td>0.00</td>
<td>1.06</td>
<td>0.060</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>71.00</td>
<td>78.13</td>
<td>389.00</td>
<td>4.00</td>
<td>41.60</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>EDE (n = 50)</strong></td>
<td>Mean/Media</td>
<td>44.20</td>
<td>23.96</td>
<td>316.13</td>
<td>1.00</td>
<td>7.84</td>
<td>0.259</td>
</tr>
<tr>
<td></td>
<td>SD/IRQ</td>
<td>18.23</td>
<td>16.65</td>
<td>16.71</td>
<td>1.00</td>
<td>4.95</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>18.00</td>
<td>13.64</td>
<td>279.00</td>
<td>0.00</td>
<td>1.40</td>
<td>0.208</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>71.00</td>
<td>77.27</td>
<td>362.00</td>
<td>4.00</td>
<td>27.31</td>
<td>0.570</td>
</tr>
<tr>
<td>p</td>
<td>0.173‡</td>
<td>0.475†</td>
<td>0.415‡</td>
<td>0.303†</td>
<td>0.305‡</td>
<td>&lt; 0.001‡</td>
<td>&lt; 0.001†</td>
</tr>
</tbody>
</table>

Table 3 shows the distribution of ADDE and EDE participants based on the presence or absence of RA. The ADDE group had a higher likelihood of having RA (OR 5.65, 95% CI 1.20-26.55) than the EDE group. Furthermore, the number of participants with RA in the ADDE group was significantly higher than in the EDE group (Fisher’s exact test, all p = 0.020; Table 3). Additionally, a correlation was observed between RA and a differential diagnosis of ADDE (Cramer’s V = 0.227, p = 0.026; Table 3).

Table 3
Distribution of the healthy and Pre-clinical DED participants by the presence or absence of the RA, regresion and association calculation. ADDE = aqueous deficient dry eye. EDE = evaporative dry eye. RA = rheumatoid arthritis. OR = odds ratio. CI = confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>ADDE</th>
<th>EDE</th>
<th>β</th>
<th>OR (95% CI)</th>
<th>Fisher’s Exacta test</th>
<th>Cramer’s V</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RA</strong></td>
<td>Yes</td>
<td>12</td>
<td>2</td>
<td>1.731</td>
<td>5.65</td>
<td>0.020</td>
<td>0.227</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>51</td>
<td>48</td>
<td>(1.20, 26.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion
RA is a rising prevalence autoimmune disease that highly affects the quality of life who suffers [2–5]. To avoid comorbidities that could affect the quality of life of the patients, the association of this condition with other diseases such as dry eye should require continuous research [6]. In the present study, the association between the presence of RA and the predisposition to a specific type of DED development, the ADDE type, was assessed.
Active autoimmune conditions such can influence dry eye study outcomes and can be problematic if their effect is not stable or changes over time, such as the RA or the SS. RA is defined as a chronic autoimmune-inflammatory disease with extraarticular involvement. The eyes are particularly one of the most common sites of involvement in RA [30]. The present study found that RA could be a risk factor to develop the ADDE dry type over EDE. In addition, an association was obtained between RA with an ADDE differential diagnosis. Previous studies have reported differences in the ocular surface inflammation indicators and clinical data in two samples of RA patients with or without secondary SS [31–33]; RA patients with SS showed worsen results than those without the condition. In the present study, one of the inclusion criteria was “not been diagnosed by a medical doctor of SS,” such it was just assumed as a risk factor for ADDE development [34]. Recent previous studies have also proposed that severe DED presence in RA patients does not necessitate the presence of a secondary SS even accompanied by dry eye manifestations [30].

It is important to note that in those studies [31–33], the Schirmer test value was under the cut-off established for a differential diagnosis of ADDE in both patients with or without secondary SS [34], data which agree with lower tear volume present findings based on TMH measurement [7, 8]. Additionally, previous reports have identified a correlation between the Schirmer test and RA presence [30]. Those reported results are reinforced by those found on a mice model which reproduces an autoimmune-mediated ADDE condition that resembles a human autoimmune dry eye, such as the one caused by SS; experimental procedures on the animals showed inflammatory and clinical findings on rapid progress similar to those found in severe human dry eye [35]. All those findings could be useful for an early and specific dry eye treatment targeting this subtype of the disease in RA patients who initiate to show symptomatology associated with DED. An early diagnosis of the DED and effective local therapy may prevent severe ocular surface complications difficult to be treated once established. Therefore, similar to SS [36], it could be proposed that the RA patient’s quality of life may be benefitted from regular multidisciplinary management of different practice areas (rheumatology and vision specialists).

The main strength of the present study was the large initial sample recruited (a total of 200 participants initially included) where all participants were subjects previously diagnosed with DED. On the other hand, the limitations of this study include that, despite the fact to be a larger sample, the initial sample size studied concluded in a low number of participants with a previous RA diagnostic by their medical doctor only 14 of the total final sample analysed of 113 patients (12,3% of the sample). In future studies, a higher sample with a higher number of previously RA diagnose participants enables the possibility of comparing the clinical test data between both categories of DED studied, ADDE and EDE, which here be not possible with only 2 participants in the EDE subgroup that will not allow a reliable statistical analysis.

In summary, the present study reinforces by a clinical finding the hypothesis that RA has a close relationship with the ADDE over EDE type in DED subjects, which could be considered as a risk factor for the development of this condition.

**Declarations**

The authors declare that they have no conflict of interest in the present study and that they received no specific funding for this study.

**COMPETING INTERESTS:**
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. The authors received no specific funding for this work. The authors declare that they have no conflict of interest in the present work and received no specific funding for this work.

**DATA AVAILABILITY**

The datasets generated and analyzed during the current study are not publicly available due to private clinical history from volunteer patients associated with them and the ongoing research project associated but are available from the corresponding author on reasonable request.

**References**


94-101.


