

The prevalence and the associated factors of dry eye in rheumatoid arthritis

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Short Report

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Abstract

Objective:

Dry eye disease (DED) is a prevalent condition in both the general population and in individuals with rheumatoid arthritis (RA), significantly affecting quality of life. Multiple factors, including systemic inflammation, contribute to the development of DED, making it crucial to understand its prevalence and associated factors for effective treatment and prevention strategies. The present study aims to fill the gaps in previous studies by providing comprehensive data on the prevalence of DED in RA patients from different clinical settings.

Results:

A total of 288 RA patients (77% female) with a mean age of 55.7 ± 10 years and a mean disease duration of 11 ± 6.3 years were included in the study. DED was detected in 23 patients (7.98%). DED was more common in older patients and women (OR = 1.98, P = 0.28). The prevalence of DED was higher in RF-positive patients (12.5% vs. 3.4%, OR = 3.6, P = 0.0136) and CCP-positive patients (14.6% vs. 2.5%, OR = 5.77, P = 0.0018) compared to seronegative patients. Additionally, DED was more prevalent in patients with moderate disease activity compared to those with mild disease activity (30% vs. 0.8%, OR = 33.75, P = 0.0001).

Introduction

Dry eye disease (DED) is a prevalent ocular condition characterized by insufficient tear production or poor tear quality, leading to discomfort, visual disturbances, and potential damage to the ocular surface (1). DED is associated with significant reductions in both physical and mental health-related quality of life, impacting daily activities, visual function, and workplace productivity (2, 3 and 4).

The prevalence of DED is notably higher in individuals with rheumatoid arthritis (RA), an autoimmune disorder that primarily affects the joints but also involves extra-articular systems, including the eyes (5, 6). This association between RA and DED significantly impacts patients' quality of life and exacerbates the overall disease burden. Inflammatory processes inherent to RA contribute to lacrimal gland dysfunction, reduced tear production, and tear film instability (7). Systemic inflammation and autoimmune dysregulation play critical roles in the pathogenesis of DED, with medications like disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) potentially affecting tear production and quality (8).

Multiple studies have documented the heightened incidence of DED in RA patients. For instance, a nationwide cohort study using Taiwan's National Health Insurance research database reported an incidence of DED at 23.14 per 1,000 person-years in RA patients, compared to 10.25 per 1,000 person-years in those without RA. After adjusting for covariates, RA was significantly associated with DED (aHR:

2.03, 95% CI: 1.93–2.13, $p < 0.0001$) (9). Other studies, such as those by Moutsopoulos et al. and Schaumberg et al., have consistently shown a robust link between RA and increased DED prevalence (10).

Despite these findings, the prevalence rates of DED in RA patients vary, highlighting the need for further research. For example, Wong Yumori et al. found that 96.15% of RA patients in a prospective, observational study had DED of severity greater than Level 1, yet other studies report differing prevalence rates (11). A systematic review of 35 studies estimated the prevalence of ocular involvement in RA at 18% (12).

Given the significant impact of DED on the quality of life of RA patients, there is an urgent need for updated and detailed epidemiological data. Understanding the prevalence and implications of DED in RA is crucial for developing comprehensive management strategies to improve patient outcomes. Despite the high prevalence of DED in RA patients, gaps remain in understanding the specific mechanisms underlying this association. Additionally, the impact of DED on RA disease activity and overall well-being is an area of active investigation. Addressing DED early in the disease course can improve patient comfort, prevent ocular complications, and enhance adherence to RA treatment regimens.

This study aims to fill existing gaps in the literature by providing comprehensive prevalence data of DED in RA patients from diverse clinical settings. Recognizing and managing DED promptly through collaborative efforts between non-eye care professionals and eye care specialists is essential for optimizing patient outcomes and enhancing the overall well-being of individuals living with RA.

Patients and Methods

The population for this study was prospectively selected from RA patients attending the rheumatology clinic at Rouhani Hospital for follow-up examinations. All patients who consented to undergo ophthalmologic examination were consecutively enrolled in the study. Patients with a history of ophthalmologic diseases or surgeries, other connective tissue diseases such as lupus erythematosus, Sjögren's syndrome, or psoriatic arthritis, as well as patients taking anticholinergic drugs, were excluded.

All RA patients had been previously diagnosed based on the 2010 ACR/EULAR criteria, and the severity of RA was assessed using the DAS-28-ESR score (13). The diagnosis of dry eye was confirmed using the tear breakup time (TBUT) test, with a TBUT of less than 10 seconds considered abnormal (14). Data were collected regarding patients' demographic features and RA characteristics.

For statistical analysis, Student's t-test and chi-square test were used for comparisons of means and proportions, respectively, utilizing SPSS version 22.

Results

A total of 288 RA patients (77% female) with a mean age of 55.7 ± 10 years and a mean disease duration of 11 ± 6.3 years were included in the study. Patient characteristics are presented in Table 1. Serum rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody positivity were observed in 50% and 45.1% of patients, respectively. Nearly all patients were receiving low-dose methotrexate and prednisolone. Based on DAS-28-ESR scores, 78% of patients had mild disease activity, while 21% had moderate disease activity.

Dry Eye Disease (DED) was detected in 23 patients (7.98%). Patients with DED were significantly older than those without DED (63.4 ± 9.4 years vs. 55.7 ± 8.9 years, $p = 0.0004$). Although DED was more prevalent in women than in men (9% vs. 4.5%), this difference was not statistically significant. The prevalence of DED was significantly higher in RF-positive RA patients compared to RF-negative patients (12.5% vs. 3.4%, OR = 3.6, $p = 0.0136$). Similarly, DED prevalence was significantly higher in CCP-positive RA patients compared to CCP-negative patients (14.6% vs. 2.5%, OR = 5.77, $p = 0.0018$).

A significant association was found between disease activity and DED. DED was detected in 18 out of 60 patients (30%) with moderate disease activity (DAS-28-ESR > 3.2 and ≤ 5.1), compared to 2 out of 225 patients (0.8%) with mild disease activity (DAS-28-ESR < 3.2) (OR = 33.75, $p = 0.0001$). No significant differences were observed regarding disease duration or types of medications between patients with and without DED (Table 1).

Table 1
Demographic and disease characteristics in rheumatoid arthritis patients with and without dry eye disease (DED).

Patients characteristics	Total, no(%) no = 288	DED present no = 23	DED absent no = 265	P value ^a
Gender, no(%)	222 (77)	20(9)	202(91)	0.001 ^b
Women	66 (23)	3(4.5)	63(95.4)	
Men				
Age, year (mean $\pm$ SD)	56 $\pm$ 9.5	63.5 $\pm$ 9.5	55.7 $\pm$ 10	0.0004
Disease activity status ^d , no (%)	225 (78)	2(8.7)	223(84.1)	0.0001
Mild	60 (21)	18(87)	42(15.8)	0.0001
Moderate	3 (1)	1(4.3)	2(7.5)	0.57
Remission				
Disease duration, year, mean $\pm$ SD	11 $\pm$ 7.2	12.5 $\pm$ 9	11 $\pm$ 6.3	0.29
Methotrexate, no(%)	284 (98.6)	23(100)	261(91)	0.20
Hydroxychloroquine, no(%)	23 (8)	0(0)	23(100)	-
Low dose prednisolone, no(%)	286 (99.3)	23 (7.98)	263()	0.67
leflunomide, no(%)	36 (12.5)	2(8.7)	34(12.8)	0.56
Sulfasalazine, no(%)	244(84.7)	20(87)	224(84.5)	0.75
Rheumatoid factor positivity, no(%)	144(50)	18(78)	126(47.5)	0.0048
Cyclic citrullinated peptide antibody positivity, no(%)	130(45.1)	19(82.6)	111(41.8)	0.0002
^a Comparison between patients with and without DED				
^b Comparison between female and male				
^d Disease activity was assessed by DAS-28 -ESR.				

Discussion

This study assessed the prevalence and associated factors of dry eye disease (DED) in rheumatoid arthritis (RA) patients, revealing that 7.98% of RA patients had DED. Significant associations were found between DED and increasing age, rheumatoid factor (RF) positivity, cyclic citrullinated peptide (CCP)

antibody positivity, and disease activity (15).. No correlation was observed between DED and disease duration, sex, or medications.

DED is a common ocular condition, affecting millions worldwide. It is characterized by the loss of tear film homeostasis, leading to ocular surface damage and associated symptoms. The incidence of dry eye has risen due to increased digital screen use, air pollution, and an aging population. Global prevalence varies between 5% and 50%, depending on the region (16). A systematic review and meta-analysis involving 13 studies with 9,808,758 participants estimated a prevalence of 8.1% (95% CI, 4.9%-13.1%). Dry eye prevalence was 3.5% in individuals aged 18 and older, and 7.8% in those aged 68 and older (17).

Predisposing factors for dry eye include environmental conditions, excessive use of electronic devices, systemic diseases, ocular surface disorders, eye surgeries, and the use of eye drops and ointments. Systemic diseases, especially autoimmune rheumatic diseases, are closely linked to dry eye (15, 18). A study of 400 outpatients at a tertiary care hospital with a mean age of 58.6 years found an overall dry eye prevalence of 54.3%, with associations to outdoor work, air-conditioned indoor work, housewifery, diabetes, previous ocular surgery, and meibomian gland dysfunction (19).

Autoimmune rheumatic diseases (ARDs) are significant causes of dry eye, with prevalence rates ranging from 10% to 95% across different conditions. Sjögren's syndrome (SS) shows the highest prevalence of dry eye among ARDs, with females being nine times more susceptible to ARD-related dry eye than males (15). Dry eye is a frequent extra-articular complication in RA patients. Even without secondary SS, RA patients commonly experience dry eye (20).

Our study found a 7.98% prevalence of DED in RA, compared to another study of 286 RA patients that reported a 44% prevalence with a clinical diagnosis of DED. This higher prevalence in the latter study may be due to increased baseline risk factors for DED in RA patients, independent of RA disease activity (11). A systematic review and meta-analysis of 65 studies indicated an 18% prevalence of eye involvement in RA patients (12). Our findings, showing significant associations between DED and RA activity, RF positivity, and CCP antibody positivity, are consistent with several studies (21, 22, 23). The association between DED and RF positivity suggests that systemic inflammation and autoimmune responses contribute to dry eye pathology. The higher prevalence of DED among CCP-positive patients highlights the role of autoantibodies in ocular surface disease development (22, 23). Elevated CCP antibodies often indicate more severe RA, potentially exacerbating ocular symptoms due to increased inflammation and immune dysregulation (21). In a study of 117 patients with autoimmune diseases, serum RF levels were an independent factor for DED (21). For patients with inflammatory arthritis, anti-CCP antibodies and RF are valuable for ophthalmologists to identify those at high risk for inflammatory ocular disease (24).

In a different study of 70 RA patients, 48.5% had DED. Unlike our study, this prevalence was not associated with disease activity or RF positivity but was associated with age and disease duration (25). Other studies have also shown no association between DED and RA activity or disease duration (26, 27). Despite women showing a higher prevalence of DED in our cohort, the difference was not statistically

significant, aligning with other studies suggesting gender differences in DED prevalence in RA populations are not always significant (12).

Interestingly, we observed no significant differences in disease duration or medication types between patients with and without DED. This suggests that while disease activity and serological markers are linked to DED, disease duration or specific medications might not directly influence the development of dry eye symptoms. However, long-term use of certain medications like DMARDs and NSAIDs can impact tear production, though our study did not find significant differences in medication use between the groups (8).

Limitation

This study has limitations, including its cross-sectional design, which restricts the ability to establish causation between RA and DED. The sample may not fully represent all RA patients, and the impact of various disease-modifying treatments on DED was not extensively explored. Additionally, there was a lack of data on several factors associated with dry eye syndrome (23).

The lower prevalence of DED in our RA study compared to others (11, 15, 28, 29) aligns with the variability in DED prevalence observed in studies of both RA and non-RA populations (16, 19, 17). This discrepancy may be attributed to variations in demographic characteristics, such as age and sex, as well as differences in the distribution of associated factors across various populations. Since several factors contributing to DED in non-RA patients can also influence DED in RA patients, the variability observed in RA prevalence reflects broader trends seen in the general population.

A meta-analysis of 48 studies with 493,630 individuals identified several associated factors for dry eye syndrome, including disease conditions, demographics, geographic area, race, sex, and educational levels. In this meta-analysis, the odds ratios for arthritis and systemic disease in relation to DED were 1.76 and 1.45, respectively (30). Differences in treatment quality and follow-up in RA patients may affect DED outcomes and prevalence across studies. Future longitudinal studies could provide more comprehensive insights into how RA treatments and disease progression impact dry eye development.

Declarations

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Hemmat Gholinia]. The first draft of the manuscript was written by

[Mansour Babaei] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

DATA AVAILABILITY STATEMENT

All relevant data are within the paper however, any question or other file data is required you can contact us using the email address, upon reasonable request. (rohanresearch88@gmail.com)

FUNDING

Not funding supported the study.

Ethics approval

All methods were carried out in accordance with the recommendations of the Declaration of Helsinki, as revised in 1989, and applicable local regulations. The protocol of this study was approved by the Ethics Committee of Babol University of Medical Sciences under the code" IR.MUBABOL.HRI.REC.1401.183". Patient confidentiality was strictly maintained by removing all personal identifiers prior to data analysis. All extracted data were securely stored and accessed only by the research team.

Consent to participate

Informed consent was obtained from all participants involved in the original studies. The patients privacy and confidentiality have been strictly maintained throughout this report.

Consent for publication

Not applicable.

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