Evaluation of disease activity markers in relation to dry eye disease in patients with rheumatoid arthritis

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Purpose
The aim of this study was to correlate the presence of anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) antibodies with rheumatoid disease activity and dry eye disease in patients with rheumatoid arthritis (RA).

Patients and methods
A total of 69 patients were evaluated for the activity of RA using the Disease Activity Score (DAS-28), erythrocyte sedimentation rate, and C-reactive protein. We used the Health Assessment Questionnaire-Disability Index to assess functional disability. Anti-CCP and anti-MCV antibodies were measured using enzyme-linked immunosorbent assay technique. We assessed dry eye symptoms using Ocular Surface Disease Index (OSDI) questionnaire. Clinical tests used for dry eye assessment included Schirmer's test, tear breakup time test, and ocular surface fluorescein staining.

Results
Anti-CCP antibody serum levels significantly correlated with DAS (r=0.46, P=0.036), Schirmer's test (r=0.40, P=0.038), and ocular surface fluorescein staining (r=0.6, P=0.04). Anti-MCV antibody serum levels correlated with DAS (r=0.5, P=0.04), ocular surface fluorescein staining (r=0.9, P=0.007), and OSDI score (r=0.3, P=0.03). DAS showed a nonsignificant correlation with OSDI score and all tests of dry eye. OSDI score significantly correlated with Schirmer's test (P=0.036).

Conclusion
Dry eye is the most common ocular manifestation in our investigated patients with RA. Dry eye disease existence is not correlated with disease activity, hence all patients with RA should be regularly examined for dye eye regardless of disease severity. Rheumatologists could use the OSDI questionnaire for screening dry eye disease in patients with RA. The presence of anti-CCP and anti-MCV antibodies may denote the existence of dry eye disease and correlates with RA disease activity.

Keywords:
anti-cyclic citrullinated peptide, anti-mutated citrullinated vimentin, Disease Activity Score-28, dry eye disease, Ocular Surface Disease Index questionnaire, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a common systemic autoimmune disease. It is mainly characterized by persistent joint inflammation that results in the loss of joint function and morbidity [1,2].

Extra-articular manifestations in patients with RA may involve a multiplicity of organs and are of diverse severity [3,4]. Ocular involvement in patients with RA is variable and may arise independently of other forms of extra-articular diseases [5].The common ocular findings of RA are keratoconjunctivitis sicca, anterior uveitis, episcleritis, necrotizing nodular scleritis, and scleromalacia perforans [6,7].

Anti-cyclic citrullinated peptide (anti-CCP) antibodies can be detected by enzyme-linked immunosorbent assay (ELISA) technique, and detection of these antibodies was found to be a more specific serum test for RA than the rheumatoid factor (RF) titer [8].

Several studies demonstrated that anti-mutated citrullinated vimentin (anti-MCV) antibodies have the same specificity as anti-CCP antibodies, but with better sensitivity [9–11]. Other studies support that detection of anti-MCV is as useful as anti-CCP assay in distinguishing patients with RA from healthy controls [9,12], and it can help in the differential diagnosis of RA from other rheumatic diseases [13–15]. Moreover, a significant correlation has been established between anti-MCV antibody titers and

both the severity of RA and Disease Activity Score (DAS) [16–18].

The aim of our study was to correlate the presence of anti-CCP and anti-MCV antibodies with rheumatoid disease activity and dry eye disease in patients with RA.

Patients and methods

The Ethical Committee of Ain Shams University approved this study, and all patients signed an informed consent before participation.

We recruited 69 patients fulfilling the 2010 American College of Rheumatology and European League against Rheumatism classification criteria for RA [19] from the Physical Medicine, Rheumatology, and Rehabilitation outpatient clinic of Ain Shams University Hospitals.

Exclusion criteria were

Pregnant or nursing patients, smokers, and patients having other connective tissue diseases, autoimmune disorders, malignancy, and chronic infection/inflammation were excluded. We also excluded individuals who had any active eye infection or allergy, lid deformity or abnormal lid movement, or abnormal nasolacrimal drainage. Contact lens wearers, patients using topical steroids and other anti-inflammatory treatment for the last 3 months, patients using artificial tears for at least 8 h before examination, patients who performed any refractive surgery within 1 year of the study visit, and patients having any other systemic disease or on long-term systemic medications known to affect tear production were also excluded.

Clinical assessment

Evaluations of patients with RA included full history taking with recording of disease duration, and thorough physical examination, with particular focus on joint pattern involvement, presence of extra-articular manifestations, and ongoing medications.

We assessed DAS-28 in all patients. The DAS-28 includes a count of 28 tender joints, a count of 28 swollen joints, erythrocyte sedimentation rate, and a general health assessment on a visual analog scale. The 28 tender joint count and 28 swollen joint count both range from 0 to 28. Erythrocyte sedimentation rate (ESR) may range from 0 to 150, and general health ranges from 0 to 100. The range of the DAS-28 is 0–9.4. Mild disease activity was assigned to patients with score of 3.2 or less, moderate was more than 3.2 to less than or equal to 5.1, and high activity was more than 5.1. A DAS-28 less than 2.6 corresponds with being in remission according to the American Rheumatism Association criteria [20].

We used the Health Assessment Questionnaire-Disability Index (HAQ-DI) to quantify functional disability [21]. The HAQ-DI includes items that assess fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both the upper and lower extremities. There are 20 items in eight categories that represent a comprehensive set of functional activities [22].

Scoring of the HAQ-DI is modeled after the American Rheumatism Association/American College of Rheumatology functional classes [23].

Ophthalmological examination

All patients recruited in the study filled the Ocular Surface Disease Index (OSDI) questionnaire forms for measuring the severity of dry eye disease symptoms. OSDI is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease [24].

The 12 items of the OSDI questionnaire 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 dry eye disease as normal, mild, moderate, or severe, using different shades of red in the scale for easier detection [25].

Subsequently, we performed a thorough examination for detection of dry eye disease, including the following tests done in order: Schirmer I-test [26], tear breakup time (TBUT) test, and fluorescein ocular surface staining (with grading of staining following the Oxford schema) [27].

Schirmer I-test was performed using Whitman filter paper placed for 5 min between the eyeball and the most lateral part of the inferior lid (without anesthesia). After 5 min, the strips were removed, and amount of wetting noted. Values of 15 mm wetting or more are considered normal, those of 9–14 mm are mild dry eye, 4–8 mm are moderate, and less than 4 mm are severe dry eye [26].

TBUT was measured by staining the conjunctival sac with 2% fluorescein strips wetted with saline and then

the patient is examined under slit lamp using cobalt blue filter. The patient was asked to blink several times and then to stop blinking. The time taken from the last blink until the appearance of the first dark spot 'which is randomly distributed' on the cornea was noted. We calculated the average of three consecutive breakup times, determined manually using a stopwatch. Values of 10 s or less were considered dry eye.

Corneal and conjunctival fluorescein staining was evaluated approximately 2.5–3.0 min following fluorescein instillation, using cobalt blue illumination. Ocular surface staining was evaluated following the Oxford schema [27].

All patients underwent visual acuity testing, a thorough slit lamp examination, and indirect ophthalmoscopy on both eyes.

Laboratory investigations

We collected a venous blood sample from all patients, which were analyzed for measuring ESR measured by Westergen's method (mm/h) [28], C-reactive protein (CRP), and RF measured by latex immunoassay (Plasmatec Laboratory Products Bangladesh, Dhaka, Bangladesh).

Also, in all blood samples, SSA (anti-RO) and SSB (anti-LA) antibodies had been estimated, using ELISA technique (lot n. VDS4203; Calbiotech Inc., El Cajon, California, USA). The procedure was done according to the manufacturer's instructions as supplied with kit from Calbiotech Inc.

Measurement of serum level of anti-CCP and anti-MCV antibodies

Anti-CCP and anti-MCV antibodies were measured in all patients with RA. All blood samples were allowed to clot, and the serum was separated by centrifugation and stored at −20°C until analysis. Assay of anti-CCP and anti-MCV antibodies was performed by means of ELISA technique using human anti-CCP antibody ELISA Kit (ORGENTEC Diagnostika GmbH Company, Mainz, Germany) and the human anti-MCV antibody ELISA Kit (ORGENTEC Diagnostika GmbH Company). The assay procedures were followed as per the manufacturer's instructions.

All biochemical measures were performed in a single batch, and a comparable number of patient and control samples were always assayed simultaneously in the same ELISA plate. The cutoff value for both anti-CCP IgG and anti-MCV IgG antibodies is 20 U/ml. The results recorded were considered positive if the readings were above cutoff values.

Statistical analysis

Statistical analysis was done on a personal computer using the statistical package for social sciences, version 17.0 (SPSS, v. 17.0; SPSS Inc., Chicago, Illinois, USA). Qualitative data were analyzed with Pearson's χ^2-test and were presented as *n* (%). Quantitative data were presented as mean (SD) or median, and interquartile ratio. Correlation analysis was performed by calculating Pearson's correlation coefficient (*r*). Correlation between DAS and fluorescein test grading was performed using Spearman's rank correlation coefficient. *P* values less than 0.05 were considered statistically significant.

Results

We performed a cross-sectional study on 69 patients with RA, with a mean age of 43.4±10.8 years. The recruited patients included 54 females and 15 males. The demographic, clinical, and laboratory characteristics of patients with RA are shown in Table 1.

Regarding ophthalmological examination, none of our patients showed any anterior segment abnormalities, other than the presence of visually insignificant cataract, of grades 1–2, according to LOCS III

Table 1 Demographic, clinical, and laboratory characteristics of patients with rheumatoid arthritis

Characteristics	Patients with RA (*n*=69) [*n* (%)]
Sex	
Female	54 (78.26)
Male	15 (21.73)
Age	
Years (mean±SD)	43.4±10.8
RA characteristics	
Disease duration (mean±SD) (years)	7.47±5.5
DAS-28 (mean±SD)	3.89±1
Laboratory findings	
ESR [median (IQR)] (mm/h)	35 (15–54)
CRP (mg/l)	
Mean±SD	0.87±0.341
Positive anti-Ro antibodies	6 (8.7)
Positive anti-La antibodies	6 (8.7)
Positive RF	60 (87)
Anti-CCP titers (IU/l)	
Median (IQR)	11 (4–20)
Anti-MCV titers (IU/l)	
Median (IQR)	20 (15–35)

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; IQR, interquartile range; MCV, mutated citrullinated vimentin; RA, rheumatoid arthritis; RF, rheumatoid factor.

classification, with a visual acuity range for these patients of 20/40–20/20.

Moreover, no posterior segment abnormalities were detected on fundus examination. The mean best corrected visual acuity in recruited patients was 0.15±0.09 in logMAR (20/30 Snellen acuity).

Patients' dry eye test results are shown in Table 2.

Anti-CCP antibody serum levels showed a statistically significant correlation with DAS, CRP, Schirmer I-test, and ocular surface fluorescein staining (P=0.036, 0.018, 0.038, and 0.04, respectively), whereas anti-MCV antibody serum levels correlated significantly with DAS-28, ocular surface fluorescein staining, and OSDI score (P=0.04, 0.007, and 0.03, respectively) Table 3.

Worthy of mention is that DAS showed a statistically nonsignificant correlation with OSDI score and all clinical tests of dry eye Table 4.

We found OSDI score significantly correlated with Schirmer I-test values (P=0.036).

Table 2 Dry eye tests results

Ophthalmological examinations	*n* (%)
Schirmer's test	
Mild	43 (62.32)
Moderate	12 (17.39)
Severe	14 (20.29)
OSDI score (mean±SD)	19.60±14.73
Fluorescein staining (Oxford schema)	
Grade 0	25 (36.34)
Grade 1	21 (30.43)
Grade 2	15 (21.73)
Grade 3	8 (11.50)

OSDI, Ocular Surface Disease Index.

Discussion

Ocular manifestations of RA can cause serious ocular morbidity. In our study, dry eye disease was the most common ocular manifestation. The correlation between dry eye and RA disease showed controversy in previous studies [5,29,30].

In our study, we evaluated anti-CCP and anti-MCV antibodies titers and correlated them with RA disease activity (DAS-28, HAQ, ESR, and CRP). We also correlated the antibody titers to OSDI scores and clinical tests of dry eye (Schirmer I-test, TBUT, and ocular surface fluorescein staining).

To the best of our knowledge, our study is the first to evaluate the association between anti-MCV antibodies and the symptoms and clinical signs of dry eye in patients with RA.

We found both anti-CCP and anti-MCV antibodies significantly correlated with ocular surface fluorescein staining (P=0.04 and 0.007, respectively). Anti-CCP antibody serum levels also showed a statistically significant correlation with Schirmer I-test, whereas anti-MCV antibodies showed a significant correlation with OSDI scores. This denotes that positive antibodies titers correlate with dry eye disease existence.

In 2015, Vignesh and colleagues found a strong association between the presence of anti-CCP antibodies and dry eye disease in patients with RA, and dry eye was the most common ocular manifestation. This is comparable to our results [31].

Itty *et al.* [32], in their study, found that patients with combined presence of anti-CCP antibodies and RF

Table 3 Correlations between anti-cyclic citrullinated peptide antibody and anti-mutated citrullinated vimentin antibody serum levels in relation to Disease Activity Score, inflammatory markers, and dry eye tests in patients with rheumatoid arthritis

	Correlation Coefficient	DAS	ESR	CRP	Schirmer test	BUT	fluorescein staining	OSDI
Anti-ccp	*r*-value	0.46	–0.2	0.4	0.4	–0.05	0.6	0.2
	P-value	0.036*	0.34	0.018*	0.038*	0.8	0.04	0.23
Anti-mcv	*r*-value	0.5	0.22	0.03	–0.08	0.3	0.9	–0.3
	P-value	0.04*	0.14	0.86	0.56	0.113	0.007	0.03*

Correlation between anti-CCP antibodies, anti-MCV antibodies and HAQ-DI are (Rho = 0.2, P = 0.32 and Rho = 0.12, P = 0.412 respectively).

Table 4 Correlations between Disease Activity Score and clinical tests of dry eye

	Correlation Coefficient	Schirmer test	BUT	OSDI
DAS	*r*-value	0.2	0.3	0.28
	P-value	0.4	0.13	0.24

Correlation between DAS score and Fluorescein test grading (RHO = 0.2, P = 0.43).

had more severe ocular involvement compared with those who were negative for these antibodies.

On the contrary, other studies have found no positive correlation between anti-CCP and anti-MCV antibodies and extra-articular organ involvement [33–35].

It had been reported that anti-MCV antibodies were correlated with disease activity parameters such as DAS-28, ESR, CRP, serum RF levels, and tender joint and swollen joint count [1,17,18,36]. This is in accordance to our results. However, analysis of the correlation between anti-CCP antibody titer and RA disease activity showed conflicting results. Some studies results were in accordance to ours, where they found that in patients with RA, the presence of anti-CCP antibody was associated with increased disease activity [37–39]. On the contrary, some studies found no significant correlation between anti-CCP antibody and disease activity (DAS-28 and HAQ) or inflammatory markers(ESR and CRP) [40,41].

We found that dry eye symptoms and signs were not associated with severity of RA, as a nonsignificant correlation was found between clinical tests and symptoms of dry eye and DAS.

Our results imply that deterioration of the systemic condition of RA does not necessarily lead to aggravation of dry eye symptoms. Conversely, dry eye cannot be excluded, even in patients with only mild RA. These results are in agreement with Zakeri *et al.* [29].On the contrary, Wolfe *et al.* [30] revealed that the symptoms of dry eye are more common in patients with RA who had higher DAS, pain, and disability.

One of the possible explanations for these differences is the use of nonstandard regimes (such as steroids) that can affect the severity of the disease. Furthermore, DAS-28 formula is dependent on subjective individual's tolerance to pain.

We had noticed that only six (8.70%) of our patients were positive for anti-Ro and anti-La antibodies. Those patients had a secondary Sjogren's syndrome (SS). In the study of Fujita and colleagues, dry eye was common in patients with RA including those without SS. Interestingly, all patients with SS were positive for anti-Ro antibodies, and all patients without SS were negative for those antibodies [5]. It seems that the cause of dry eye may be different in patients with RA and SS than in patients with RA but without SS. The cause of dry eye in patients with RA might be the result of local pathology affecting the tear film, conjunctiva, or cornea because anti-Ro and anti-La antibodies had been found not only in the serum but also in the saliva, tear film, and labial salivary glands in patients with SS [42,43].

An important finding in our study was that OSDI scores were significantly correlated with Schirmer I-test (ρ=0.4, P=0.046). This implies the possibility of using OSDI questionnaire by a rheumatologist as a preliminary assessment of dry eye in patients with RA before ophthalmological consultation. This finding is in agreement with Schiffman *et al.* [25], who found a low to moderate statistically significant correlation between OSDI and Schirmer test type I, TBUT, and fluorescein staining.

On the contrary, other studies showed that objective clinical signs often conflict with symptoms of dry eye disease [44,45]. Studies on dry eye disease are still ongoing for reaching a consensus of clinical signs to better capture the disease and not to rely solely on disease symptoms in diagnosis and management.

Conclusion

Dry eye is the most common ocular manifestation in our investigated patients with RA. Dry eye disease existence is not correlated with disease activity, hence all patients with RA should be regularly examined for dye eye regardless of disease severity. Rheumatologists to screen for dry eye disease in patients with RA could use OSDI questionnaire. The presence of anti-CCP and anti-MCV antibodies may denote the existence of dry eye disease and correlates with RA disease activity.

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Conflicts of interest

There are no conflicts of interest.

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