SYSTEMATIC REVIEW

Correlation of Tear Osmolarity With Ocular Symptoms and Ocular Surface Parameters in Dry Eye Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: This systematic review and meta-analysis aimed to assess the correlations of tear osmolarity (TO) with ocular symptoms and ocular surface parameters in dry eye disease (DED). **Materials and methods:** A literature search was conducted in PubMed, ScienceDirect, and Google Scholar databases up to 31 December 2022. Observational studies were included if they reported Pearson's-*r* or Spearman's-ρ of TO with ocular symptoms and/or ocular surface parameter(s) in DED patients without or with other underlying diseases. The *r* or ρ values were extracted and assessed using a random effect of meta-analysis. **Results:** Twelve studies were included in the qualitative synthesis and meta-analysis. Overall weighted summary-*r* values amounted to 0.17, -0.35, and -0.29 for the correlations of TO with ocular symptoms, fluorescein break-up time (FBUT), and Schirmer I, respectively. In the DED subgroup, the weighted summary-*r* values amounted to 0.11, -0.32, and -0.12 for the correlations of TO with ocular symptoms, FBUT, and Schirmer I, respectively. Greater weighted summary-*r* values were found in the autoimmune disease-related DED (AID-DED) subgroup for the correlations of TO with ocular symptoms (weighted summary-*r*, 0.38), FBUT (weighted summary-*r*, -0.39), Schirmer I (weighted summary-*r*, -0.47), and corneal staining (weighted summary-*r*, 0.38). The I^2 values were 36% to 92.4%. **Conclusion:** This systematic review and meta-analysis reveal weak to fair correlations between TO and clinical parameters in DED, with stronger correlations in AID-DED. The findings underscore the need for standardised diagnostic methods and further research to explore the distinct mechanisms of AID-DED. Future studies should focus on longitudinal assessments, advanced diagnostic tools, and patient-centred outcomes to enhance understanding and management of DED, ultimately informing clinical guidelines and improving patient care.
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Keywords: Correlation, Dry eye disease, Ocular symptoms, Ocular surface parameters, Tear osmolarity

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INTRODUCTION

Dry eye disease (DED) is a multifactorial disease of the ocular surface identified by disruption of tear film homeostasis and complemented by ocular symptoms. The established predisposing factors of DED include instability and hyperosmolarity of the tear film, inflammation and damage of the ocular surface, and newly highlighted neurosensory abnormalities (1). DED has been identified as one of the most common ocular surface abnormalities, with a prevalence of 5% to 50% globally (2–4).

DED commonly contributes to suboptimal vision quality, ocular discomfort, and quality of life degradations (1). In routine clinical practice, DED has been evaluated based on patient-reported ocular symptoms and observed clinical signs using commonly measured ocular surface parameters, namely fluorescein break-up time (FBUT), Schirmer test, and ocular surface staining (OSS) assessments (5). However, the lack of consistency between the ocular symptoms and clinical signs results in an accurate diagnosis of DED complicated (5–7). Moreover, most clinical dry eye tests are assessed subjectively based on various grading scales, which leads to high inter-observer variations in diagnosing and classifying DED (8,9).

To date, there is no consensus on any clinical test that served as a gold standard to diagnose DED. In

the recent Tear Film and Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) Definition and Classification Report, the instability and hyperosmolarity of tear film are the main predisposing factors of DED (1). Tear osmolarity (TO) represents tear concentration that could be objectively measured in milliosmoles per litre unit. Hence, the TO results may assist a clinician in diagnosing DED, which has been given attention in current DED research (10–13).

This paper aims to systematically review and meta-analyse the available evidence of the correlation between TO and patient-reported ocular symptoms quantified through established DED questionnaires score (ocular symptoms) as well as ocular surface parameters. To the best of our knowledge and literature search, this is the first systematic review and meta-analysis to assess the strength and trend of the correlations of TO with ocular symptoms and ocular surface parameters. This review would provide a clearer picture of tear hyperosmolarity associated with patient-reported ocular symptoms and observed clinical signs of ocular surface parameters in DED. Consequently, it contributes valuable insights into the understanding and diagnosis of DED.

MATERIALS AND METHODS

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. This systematic review protocol has been registered and accessible on the PROSPERO website (ID: CRD42022358900). This paper aims to answer the question, "Does TO correlate with ocular symptoms and/or ocular surface parameters in DED?" by systematically reviewing and meta-analysing data from all relevant evidence.

Search Strategy

Articles search was conducted through PubMed, ScienceDirect, and Google Scholar databases without language restriction. The search terminologies used were ("dry eye" OR "dry eye syndrome" OR "DES" OR "dry eye disease" OR "DED" OR "keratoconjunctivitis sicca") AND ("tear film osmolarity" OR "tear osmolarity" OR "osmolarity") AND ("tear function test" OR "tear test" OR "dry eye sign" OR "ocular surface parameter") OR ("dry eye symptom" OR "ocular symptom" OR "questionnaire" OR "score" OR "scale") AND ("correlation" OR "relationship" OR "association"). The reference lists of included and/or related (e.g., in the subject area of our review but not eligible for this review) studies and related systematic reviews (e.g., reviews including the population or intervention examined in our review) were screened for studies not identified by the database searches. We reviewed and meta-analysed data from all relevant evidence published from 2000 to December 2022.

Eligibility Criteria for Studies

Studies were selected based on the inclusion criteria following the recommendation of the Cochrane Diagnostic Test Accuracy Description (14).

Type of studies

We included observational studies such as cross-sectional, cohort, or case-control studies that reported Pearson's (r) or Spearman's (ρ) correlation coefficients of TO with ocular symptoms and/or ocular surface parameter(s) in DED patients. Studies were excluded if there were no possibility of retrieving the correlation coefficients from the reported results and the authors did not respond to our email queries about incomplete or ambiguous data. Any studies reported in languages other than English, review articles, case reports or series, editorial letters, and expert opinions were also excluded. Randomised clinical trials were also excluded unless the required correlation coefficients were reported.

Participants

Patients in the studies were older than 18 years without or with other underlying diseases.

Index Test

TO was measured using the electrical impedance or freezing point depression technique. We also accepted other techniques adopted by the authors of individual studies if the authors provided sound justification.

Target Condition

DED was diagnosed based on the TFOS DEWS Definition and Classification Report (1,8).

Comparators

Ocular symptoms and/or ocular surface parameter(s).

Selection of Studies

Two review authors (MMMMS, SDAM) independently reviewed the results of the search and selected the studies for inclusion using the predefined eligibility criteria. The title and abstract were screened, and potentially relevant published and unpublished studies were then retrieved in full-text form and screened for eligibility. Any disagreements between the two reviewers were resolved via discussion, and a third review author (MAMH) was consulted if required. Kappa statistic (κ) value was determined for each screening level (title, abstract, and full text). The selection process was recorded in sufficient detail to complete the PRISMA flow diagram, which is presented in Fig. 1, and the reason for excluding studies at the full-text screening level is shown in Table I.

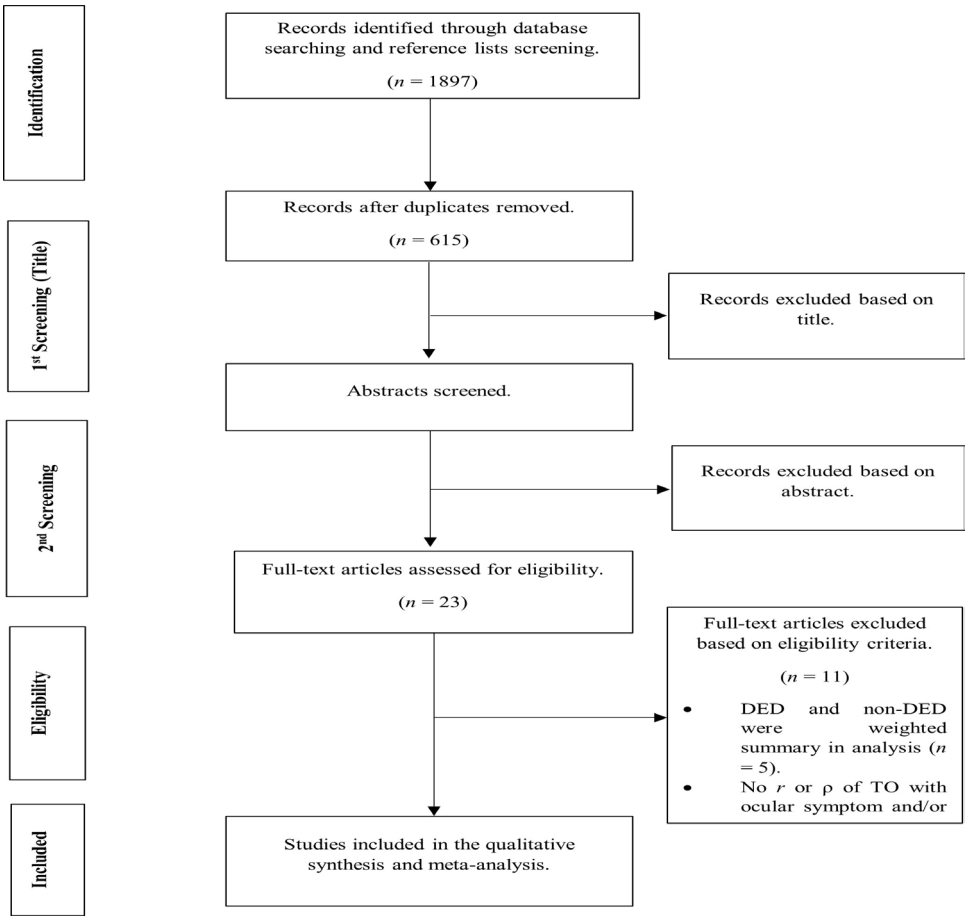


Figure 1: PRISMA Flow Diagram of the Systematic Review Search Process

Table I: Reason for Exclusion of the Studies

First Author, Year	Reason
Amparo, 2014 (15)	No correlation coefficient of TO with ocular symptoms and/or ocular surface parameter(s) was reported.
Bunya, 2013 (16)	Both DED and non-DED patients were pooled for correlation analysis.
Garcia-Resьa, 2014 (17)	Both DED and non-DED patients were pooled for correlation analysis.
Hajar-Maidin, 2018 (18)	Both DED and non-DED patients were pooled for correlation analysis.
Mathews, 2017 (19)	No correlation coefficient of TO with ocular symptoms and/or ocular surface parameter(s) was reported.
Najafi, 2015 (20)	Both DED and non-DED patients were pooled for correlation analysis.
Park, 2021 (21)	Both DED and non-DED patients were pooled for correlation analysis.
Rentka, 2017 (22)	No correlation coefficient of TO with ocular symptoms and/or ocular surface parameter(s) was reported.
Schargus, 2015(23)	No correlation coefficient of TO with ocular symptoms and/or ocular surface parameter(s) was reported.
Schmidl, 2015 (24)	No correlation coefficient of TO with ocular symptoms and/or ocular surface parameter(s) was reported.
Sullivan, 2014 (7)	No correlation coefficient of TO with ocular symptoms and/or ocular surface parameter(s) was reported.

DED = dry eye disease; TO = tear osmolarity

Data Extraction

Two review authors (MMMMS, SDAM) independently extracted the data from each selected study. After the extraction, the data were cross-checked by each other. Any discrepancy was resolved through discussion leading to consensus. The characteristics of the data extracted from each selected study were: 1. General information: first author of the study, year of publication, declaration of conflict of interest, and source of funding; 2. Study design and setting: design of the study, location, and country; 3. Sample of population: number of patients (number of eyes), age, and gender; 4. Index test: TO measurement; 5. Comparator(s): ocular symptoms and/or ocular surface parameter(s); 6. Outcome measures: *r* or ρ correlation coefficient, *p*-value, and confidence interval (CI) if available. Only data extracted from each study and not from interim analyses were included.

Quality Assessment

Two review authors (MMMMS, SDAM) independently assessed the quality of the selected studies using the Appraisal Tool for Cross-Sectional Studies (AXIS) (25). There were 20 questions: seven questions on the quality of study reporting (No.1, 4, 10, 11, 12, 16, and 18), seven questions on the quality of study design (No. 2, 3, 5, 8, 17, 19, and 20), and six questions on the risk of study bias (No. 6, 7, 9, 13, 14, and 15). Each question was rated 'Yes', 'No', 'Do Not Know', or any other relevant comments. Any disagreement between MMMMS and SDAM was resolved by discussion, and a third review author (MAMH) was contacted as an arbiter

to reach a consensus. κ-value was calculated to evaluate the agreement level between MMMMS and SDAM.

Data Analysis

We performed the statistical analyses using MedCalc Statistical Software version 20.217 (MedCalc Software, Ostend, Belgium). The correlation coefficients and CIs of the studies were weighted summaries using random-effects models in view of the variability in the population and methodologies adopted by individual studies. Hedges-Olkin method using a Fisher Z transformation of the correlation coefficients was used to calculate the weighted summary correlation coefficient (weighted summary-*r*). Studies that reported *r* or ρ correlation coefficients were treated equally if the sample size was more than nine (26). The correlation coefficients of < 0.3, 0.3 to 0.59, 0.6 to 0.8, and > 0.8 were considered poor, fair, moderately strong, and very strong correlation, respectively (27). We assessed the heterogeneity of results across all the included studies using the I^2 statistic. I^2 values between 0 to 40%, 30 to 60%, and 50 to 90% suggest small, moderate, and substantial heterogeneity, respectively (28). In the presence of high heterogeneity, sensitivity analyses were conducted to weigh up the relative influence of individual studies on the magnitude and direction of the weighted summary effect size.

Sensitivity Analysis

We performed sensitivity analyses under several conditions: when the I^2 value was greater than 50%, when there were differences in the techniques used to assess ocular symptoms and/or ocular surface parameters, when there were differences in the unit of analysis used, and when the studies were of low quality based on the AXIS assessment.

Unit of Analysis Issues

One eye per patient (either right or left eye) was the unit of analysis for this review. However, we also included studies that used both the eyes and the mean of the two eyes measurement as their unit of analysis if no information was available to allow only one eye to be analysed. We performed sensitivity analysis by excluding studies that used other than one eye per patient to assess the impact of including these studies on the direction and magnitude of the weighted summary estimates.

Summary of Findings and Assessment of The Certainty of The Evidence

We adapted the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, as outlined in the GRADE Handbook (29). Two review authors (MMMMS, MAMH) independently assessed the certainty of the evidence for each of the analyses. We downgraded the evidence by one level for serious (or two levels for very serious) limitations based upon the following: quality of the studies (based on the AXIS assessment), consistency across studies, and precision of estimates. We created a 'Summary of Findings with the Certainty of Evidence Assessment' table to report the certainty of evidence (Table II).

Table II: Summary of Findings with the Certainty of Evidence Assessment

Analysis	Weighted Summary-*r* (95% CI)	Heterogeneity, I^2 (%)	No. of Patients/Eyes (No. of Studies)	Certainty of Evidence
TO-Ocular Symptoms				
DED	0.114 (-0.067 to 0.288)	74.3	566 (5)	Very low [a,b]
AID-DED	0.375 (0.258 to 0.481)	0.0	241 (5)	Moderate[c]
Overall	0.168 (0.099 to 0.235)	73.6	807 (9)	Low[b,d]
TO-FBUT				
DED	-0.316 (-0.609 to 0.052)	92.4[a]	398 (3)	Very low [a,b]
AID-DED	-0.378 (-0.634 to -0.0474)	85.4	241 (5)	Low[b]
Overall	-0.349 (-0.540 to -0.124)	88.1	639 (7)	Low[b]
TO-Schirmer I				
DED	-0.116 (-0.314 to 0.091)	78.9	441 (5)	Low [b]
AID-DED	-0.469 (-0.602 to -0.310)	44.0	231 (5)	Moderate[c]
Overall	-0.292 (-0.459 to -0.105)	81.7	672 (9)	Low [b]
TO-OSS				
AID-DED (corneal staining)	0.383 (0.182 to 0.553)	36.0	146 (3)	Moderate[c]

AID-DED = autoimmune disease-related dry eye disease; CI = confidence interval; DED = dry eye disease; No. = number; OSS = ocular surface staining; TO = tear osmolarity; FBUT = fluorescein break-up time

Footnotes

[a] Majority of the included studies were of low quality based on the AXIS tool. Certainty of evidence was downgraded by one level for serious limitation.

[b] The heterogeneity was substantial with I^2 more than 70%. The heterogeneity remained high even after the performance of sensitivity analysis by removing potential problematic studies. Certainty of evidence was downgraded by one level for inconsistency.

[c] The weighted summary estimate has a wide confidence interval that includes the possibility of a small or no effect. Certainty of evidence was downgraded by one level for imprecision.

[d] Despite the meta-analysis included large number of participants, the weighted summary estimate has a wide confidence interval that includes the possibility of a small or no effect. Certainty of evidence was downgraded by one level for imprecision

The certainty of the evidence was graded into one of four categories following the GRADE approach (29); "High" if we are very confident that the true effect lies close to that of the effect estimate, "Moderate" if we are moderately confident in the effect estimate where the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different, "Low" if our confidence in the effect estimate is limited or the true effect may be substantially different from the estimate of the effect, and "Very low" if we

have very little confidence in the effect estimate or when the true effect is likely to differ substantially from the estimate of effect.

RESULTS

Characteristics of the Included Studies

Database searches identified 1895 records, and an additional two records were identified from the reference lists screening. After removing 1282 duplicates and excluding 592 records based on the title/abstract screening, 23 full-text articles were assessed, and 11 were excluded based on the eligibility criteria. Finally, 12 studies were included in the qualitative synthesis and meta-analysis. κ-values of > 0.90 were recorded between the two review authors (MMMMS, SDAM) at all three levels of study selection. The full search strategy is presented in Fig. 1.

The characteristics of the included studies are shown in Table III. Of 12 articles, five studies (5/12) were conducted in Asia (30–34), five studies (5/12) were conducted in Europe (35–39), and two studies (2/12) were performed in America (40,41). All studies (12/12) were conducted within the last decade, with the latest in 2022. Eight studies (8/12), two studies (2/12), and one study (1/12) included one eye (30,32–36,40,41), both eyes (37,38), and one and/or both eyes [39] of each patient for TO and other ocular surface parameters analysis, respectively. One study (1/12) measured both eyes and analysed the mean value (34).

Table III: Characteristics of the Included Studies

First Author, Year (Location, Country)	No. of Patients (Eyes), N; Age, Mean ± SD/ Range; Sex, % Female	Tear Osmolarity Measurement	Ocular Surface Parameters & Ocular Symptom: Test Method	Correlation Coefficient (95% CI)
		DED		
Caffery, 2014 (40) (Ontario, Canada)	N = 249 (249); 18-80 years; 43.8%	Electrical impedance, TearLab Osmolarity System	Symptom: DEQ-5	*r* = -0.020 (-0.105,0.144)
Kang, 2022 (34) (Bucheon, Korea)	N = 24 (24)[#]; 48.33 ± 14.80 years 70.8%	Electrical impedance, I-PEN® Osmolarity System	NIBUT: K5M Schirmer I: Non-anesthetised OSS[$]: Corneal staining; FL; Oxford	*r* = 0.026 (-0.381, 0.425) *r* = 0.115 (-0.302, 0.495) *r* = 0.299 (-0.119, 0.627)
Kim, 2017 (31) (Seoul, Korea)	N = 116 (116)[#]; 20 - above 60 years; 95.7%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI FBUT: Non-anaesthetised Schirmer I: Non-anaesthetised OSS[‡]: Corneal + conjunctival stainings; FL; SICCA	ρ = 0.101 (-0.083, 0.278) ρ = 0.133 (-0.051, 0.308) ρ = 0.119 (-0.065, 0.295) ρ = 0.145 (-0.038, 0.319)
Lee, 2020 (33) (Seoul, Korea)	N = 45 (45); 51.5 ± 14.4 years; 80%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI	*r* = 0.034 (-0.262, 0.324)
Ozulken, 2020 (36) (Ankara, Turkey)	N = 170 (170); 37.85 ± 8.86 years; 77.6%	Electrical impedance, TearLab Osmolarity System	FBUT: Anaesthetised NIBUT: Sirius Schirmer I: Anaesthetised	ρ = -0.554 (-0.650, -0.440) ρ = -0.528 (-0.629, -0.410) ρ = 0.030 (-0.121, 0.180)
Suzuki, 2010 (41) (New York, US)	N = 19 (19); 52.1 ± 16.4 years; 89.5%	Freezing point depression, Tear Osmometer Model 3100	Schirmer I: Anaesthetised	*r* = -0.520 (-0.788, -0.086)
Tukenmez-Dikmen, 2016 (37) (Istanbul, Turkey)	N = 22 (44); 54.3 ± 12.5 years[a,b], 51.3 ± 12.5 years[c]; NR	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI	*r* = -0.236 (-0.598, 0.206)

CONTINUE

Table III: Characteristics of the Included Studies. (CONT.)

First Author, Year (Location, Country)	No. of Patients (Eyes), N; Age, Mean ± SD/ Range; Sex, % Female	Tear Osmolarity Measurement	Ocular Surface Parameters & Ocular Symptom: Test Method	Correlation Coefficient (95% CI)
		DED		
Versura, 2010 (39) (Bologna, Italy)	Total N = 105 (141); 54.8 ± 15.0; 56.74%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI	Mild DED: *r* = 0.313 (0.052, 0.534) Moderate DED: *r* = 0.462 (0.229, 0.645)
	Mild DED: N = NR (55); NR; NR		FBUT: Non-anaesthetised	Mild DED: *r* = -0.408 (-0.608, -0.160) Moderate DED: *r* = -0.372 (-0.577, -0.123)
	Moderate DED: N = NR (57); NR; NR		Schirmer I: Non-anaesthetised	Mild DED: *r* = -0.110 (-0.365, 0.160) Moderate DED: *r* = -0.440 (-0.629, -0.203)
	Severe DED*: N = NR (29); NR; NR		OSS[Φ]: Conjunctival staining; LG; grading scale used was not reported.	Mild DED: *r* = 0.668 (0.489, 0.793) Moderate DED: *r* = 0.846 (0.751, 0.907)
		AID-DED		
		SS		
Kim, 2017 (31) (Seoul, Korea)	N = 39 (39)[#]; 52.5 ± 11.9 years/ 20-above 60 years; 94.9%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI FBUT: Non-anaesthetised Schirmer I: Non-anaesthetised OSS[‡]: Corneal + conjunctival stainings; FL; SICCA	ρ = 0.405 (0.103, 0.639) ρ = 0.110 (-0.213, 0.411) ρ = -0.625 (-0.786, -0.385) ρ = 0.592 (0.340, 0.765)
Kook, 2020 (32) (Gwangju, Korea)	N = 63 (63); 54.2 ± 13.9 years; 96.8%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI FBUT: Non-anaesthetised Schirmer I: Non-anaesthetised OSS[‡]: Corneal (FL) + conjunctival (LG) stainings; SICCA OSS[§]: Corneal staining; FL; SICCA OSS[Φ]: Conjunctival staining; LG; SICCA	*r* = 0.310 (0.067, 0.518) *r* = -0.180 (-0.410, 0.071) *r* = -0.220 (-0.444, 0.029) *r* = 0.120 (-0.132, 0.357) *r* = 0.220 (-0.029, 0.444) *r* = 0.230 (-0.019,0.452)
Utine, 2011 (38) (Istanbul, Turkey)	N = 10 (20); 31.0 ± 6.4 years; 90%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI FBUT: Non-anaesthetised Schirmer I: Anaesthetised OSS[§]: Corneal staining; FL; NEI OSS[Φ]: T conjunctival staining; LG; Oxford	*r* = 0.550 (-0.122, 0.876) *r* = -0.500 (-0.859, 0.189) *r* = -0.620 (-0.899, 0.016) *r* = 0.510 (-0.176, 0.863) *r* = 0.580 (-0.078, 0.886)
		GVHD		
Berchicci, 2014 (35) (Milan, Italy)	N = 56 (56); 47.2 ± 15.9 years; 41.1%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI FBUT: Non-anaesthetised Schirmer I: Non-anaesthetised	ρ = 0.455 (0.218, 0.641) ρ = -0.728 (-0.832, -0.575) ρ = -0.476 (-0.657, -0.244)
Na, 2015 (30) (Seoul, Korea)	N = 63 (63); 41 years ± NR; 42.9%	Electrical impedance, TearLab Osmolarity System	Symptom: OSDI FBUT: Non-anaesthetised Schirmer I: Non-anaesthetised OSS[§]: Corneal staining; FL; NEI	ρ = 0.289 (0.044, 0.501) ρ = -0.422 (-0.606, -0.195) ρ = -0.511 (-0.673, -0.301) ρ = 0.475 (0.258, 0.647)

AID-DED = autoimmune disease-related dry eye disease; CI =confidence interval; DED = dry eye disease; DEQ-5 = 5-item Dry Eye Questionnaire; FBUT = fluorescein break-up time; FL = fluorescein; GVHD = graft-versus-host disease; K5M = Keratograph 5M (Oculus, Wetzlar, Germany); LG = lissamine green; MMP-9 = tear film matrix metalloproteinase-9 was measured by the InflammaDry test kit (Rapid Pathogen Screening Inc., Sarasota, Florida, United States); N = number of patients/eyes; NEI = National Eye Institute scale; NIBUT = non-invasive break-up time; NR = not reported; OSDI = Ocular Surface Disease Index questionnaire; OSS = ocular surface staining; Oxford = Oxford scale; SD = standard deviation; SICCA = Sjögren's International Collaborative Clinical Alliance ocular staining score scale; Sirius = Sirius topography (Costruzione Strumenti Ophthalmici, Florence, Italy); SS = Sjögren's syndrome; SS-I = Primary Sjögren's syndrome; SS-II = Secondary Sjögren's syndrome; Symptom = ocular symptoms; T = temporal; US = United States; *r* = Pearson's correlation coefficient; ρ = Spearman's correlation coefficient; + = plus; % = percentage.

[#]Mean of both eyes has been used for analysis; *In the severe DED group, it was a combination of severity grade 3 (26 eyes) and grade 4 (3 eyes) based on DEWS I classification, and four of the patients were SS-I or SS-II (Versura et al. 2010) (39); Thus, because of the DED and AID-DED patients were weighted summary, this subgroup was not included in our analysis.

[‡]total ocular surface staining, which was total staining of cornea and conjunctival; [§]corneal staining; [Φ]conjunctival staining; [a]mild DED; [b]moderate DED; [c]severe DED

Eight studies (8/12) evaluated the correlation of TO with ocular symptoms and/or ocular surface parameter(s) in DED patients without other underlying diseases (31,33,34,36,37,39–41). Whereas five studies (5/12) assessed the correlation of TO with ocular symptoms and/or ocular surface parameter(s) in autoimmune disease-related DED (AID-DED) patients (30–32,35,38). Of the five studies, three studies (3/5) involved Sjogren's syndrome (SS) patients (31,32,38), and the other two studies (2/5) included graft-versus-host disease (GVHD)

patients (30,35).

The majority of the studies (9/12) reported correlations between TO and ocular symptoms (31–33,35,37–40). All studies utilised the Ocular Surface Disease Index (OSDI) questionnaire as a tool to quantify patient-reported ocular symptoms, except for Berchicci et al. (2014) study (35), which used the 5-Item Dry Eye Questionnaire (DEQ-5). Nine studies (9/12) reported correlations between TO and Schirmer I, either anaesthetised-Schirmer I (36,38,41) or non-anaesthetised-Schirmer I (30–32,34,35,39). Seven studies (7/12) reported correlations between TO and FBUT, either with (36) or without anaesthesia (30–32,35,38,39).

Six studies (6/12) reported correlations between TO and OSS (corneal and/or conjunctival staining) (30–32,34,38,39). For OSS assessment, all studies (5/5) evaluating corneal staining used fluorescein (30–32,34,38), whereas most of the studies (3/4) evaluating conjunctival staining used lissamine green (32,38,39). Regarding the OSS grading scale, two studies (2/5) used the Sjugren's International Collaborative Clinical Alliance (SICCA) ocular staining score (31,32), two studies (2/5) graded by the National Eye Institute (NEI) scale (30,38), and one study (1/5) evaluated by the Oxford scale (34) for corneal staining assessment, while for conjunctival staining assessment, two studies (2/4) utilised the SICCA ocular staining score (31,32), one study (1/4) used the Oxford scale (38), and one study (1/4) did not specify the grading scale (39). Only four studies (4/12) reported correlations between TO and other ocular surface parameters, namely non-invasive break-up time (NIBUT) (34,36), tear meniscus (37), tear film matrix metalloproteinase-9 (34), tear clearance, tear ferning, corneal aesthesiometry, and conjunctival cytology (39). Due to insufficient data, a comparison and meta-analysis of correlations between TO and other ocular surface parameters were therefore not performed.

This review revealed homogeneity in the methods used for TO measurement. All studies, except for Suzuki et al. (2010) (41) utilised the electrical impedance technique with the TearLab Osmolarity System (TearLab Corporation, California, United States). In contrast, Suzuki et al. (2010) employed the freezing point depression technique with the Tear Osmometer Model 3100 (Advanced Instruments, Inc. Norwood, Massachusetts, United States) (41). Tear sample collection steps were carried out consistently per the instruction of each osmometer model or system.

Quality of the Included Studies

The two review authors (MMMMS, SDAM) achieved high interrater agreement (κ of 0.979) in assessing the quality of the selected studies. All included studies met the above average for all quality assessment criteria, except for the risk of study bias. For the quality of study reporting criteria, all studies met seven out of seven criteria except for Versura et al. (2010) (39), which did not include the grading scale used for OSS evaluation and the limitations of their study. Of the seven criteria for evaluating the quality of study design, all studies met ≥ five criteria, with none reporting on sample size determination. In addition, Berchicci et al. (2014)(35), Kang et al. (2022)(34), and Utine et al. (2011) (38) did not provide a conflict of interest statement, made conclusions not fully supported by the results (Utine and colleagues (38) concluded that TO and corneal staining might correlate, despite a poor and insignificant correlation [$r = 0.299$; $p = 0.16$]), and did not include ethical approval and consent information, respectively. Regarding the criteria for assessing the risk of study bias, three studies did not achieve an average score (meeting only two out of six criteria), as they included both eyes of each patient in the analysis, took no measures to treat non-responders, and the response rate raised concerns about non-response bias (37–39). Only three studies addressed non-responders (32,35,40). One study (32) had a quality issue with the internal consistency of the results reported, specifically a discrepancy in the number of patients reported in the Abstract and Results sections. The details of the quality assessment are shown in Table IV.

Table IV: Quality Assessment of the Included Studies

Questions*/Studies	Berchicci, 2014	Caffery, 2014	Kang, 2022	Kim, 2017	Kook, 2020	Lee, 2020	Na, 2015	Ozulken, 2020	Suzuki, 2010	Tukenmez-Dikmen,2016	Utine, 2011	Versura, 2010
Introduction												
1[a] Study Aim	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods												
2[b] Study Design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3[b] Sample Size	No	No	No	No	No	No	No	No	No	No	No	No
4[a] Target Population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5[b] Sampling Frame	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6[c] Sample Selection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
7[c] Non-Responder	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No

CONTINUE

Table IV: Quality Assessment of the Included Studies. (CONT.)

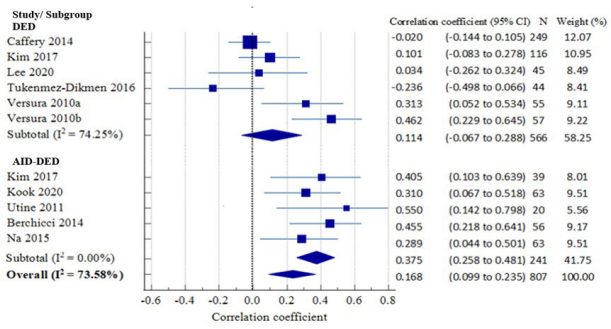
Questions*/Studies	Berchicci, 2014	Caffery, 2014	Kang, 2022	Kim, 2017	Kook, 2020	Lee, 2020	Na, 2015	Ozulken, 2020	Suzuki, 2010	Tukenmez-Dikmen,2016	Utine, 2011	Versura, 2010
Methods												
8[b] Variables	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9[c] Validity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10[a] Statistics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11[a] Overall Methods	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Results												
12[a] Basic Data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13[c] Response Rate	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14[c] Non-Responder	Yes	Yes	No	No	No	No	No	No	No	No	No	No
15[c] Consistency	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16[a] Result-Method	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discussion												
17[b] Justified	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18[a] Limitation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Other												
19[b] Conflicts of Interest	DNK	No	No	No	No	No	No	No	No	No	No	No
20[b] Ethical/Consent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

[a]questions on the quality of study reporting; [b]questions on the quality of study design; [c]questions on the risk of study bias; DNK = do not know
*Full questions described in the Appraisal Tool for Cros-Sectional Studies (AXIS) (25)

Correlation between Tear Osmolarity and Ocular Symptoms

Nine studies with a total of 807 patients/eyes were analysed using a random-effects meta-analysis to assess the correlation between TO and ocular symptoms in all types of DED (31–33,35,37–40). Of the nine studies, one study included patients from both subgroups of DED and AID-DED (34), and one study recruited patients with different severity of DED (mild DED and moderate DED) (39). The overall weighted summary-*r* was 0.168; 95% CI, -0.099 to 0.235, and overall I^2 was 73.6%. Subgroup analyses were then performed using a random-effects meta-analysis, separating the DED and AID-DED.

In the subgroup analysis of DED, five studies with a total of 566 patients/eyes were analysed (31,33,37,39,40), where Versura et al. (2010) study separated DED into mild DED and moderate DED groups (39). There was a weighted summary-*r*, 0.114; 95% CI, -0.067 to 0.288, and an I^2, 74.3%. Whereas the subgroup analysis of AID-DED (five studies with 241 patients/eyes) yielded a weighted summary-*r*, 0.375; 95% CI, 0.258 to 0.481, with an I^2, 0.0% (30–32,35,38). The overall forest plot is presented in Fig. 2.



AID-DED = autoimmune disease-related dry eye disease; CI = confidence interval; DED = dry eye disease; N = number of patients/eyes; % = percentage; a = Only included mild DED patients; b = Only included moderate DED patients.

Fig. 2: Forest plot for the Correlations between Tear Osmolarity and Ocular Symptoms in the DED and AID-DED Patients.

Subsequently, we performed a sensitivity analysis by removing Caffery et al. (2014) (40), which was the only study that used the DEQ-5 for the assessment of ocular symptoms. There were marginal improvements in the overall I^2 to 63.9% (from original overall I^2, 73.6%) and overall weighted summary-*r* to 0.267; 95% CI, 0.127 to 0.397 (from original overall weighted summary-*r*, 0.168). Similarly, the I^2, 73.8%, and weighted summary-*r*, 0.149; 95% CI, -0.078 to 0.360 showed no significant improvement in the DED subgroup (original I^2, 74.3%;

original weighted summary-*r*, 0.114).

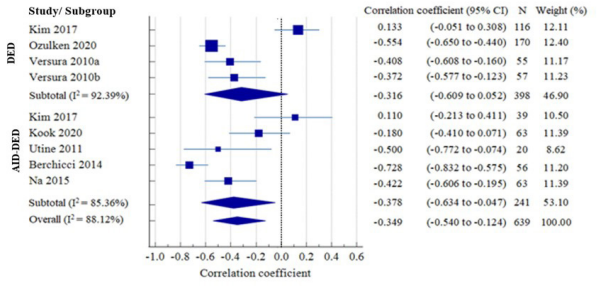
Next, we performed sensitivity analyses by excluding Kim et al. (2017) (31), which used mean measurements of both eyes as the unit of analysis. The removal of the study (31) did not significantly improve the I^2 and weighted summary-*r* either in the DED subgroup (I^2, 77.1%; weighted summary-*r*, 0.237; 95% CI, 0.064 to 0.397), AID-DED subgroup (I^2, 79.3%; weighted summary-*r*, 0.118; 95% CI, -0.117 to 0.341), or overall (overall I^2, 0.0%; overall weighted summary-*r*, 0.369; 95% CI, 0.240 to 0.485). It indicates that the heterogeneity and strength of the correlation between TO and ocular symptoms remained with the exclusion of the study that used different units of analysis.

Lastly, sensitivity analyses were employed by omitting studies with a high risk of bias in both the DED (37,39) and AID-DED (38) subgroups. In the DED subgroup, the I^2 was drastically reduced to 0.0% (from original I^2, 74.3%), but the weighted summary-*r*, 0.2; 95% CI, -0.078 to 0.117 did not significantly improve (compared to original weighted summary-*r*, 0.114). In the AID-DED subgroup, the heterogeneity remains unchanged, with an I^2 ,0.0% (same as original I^2) and a weighted summary-*r*, 0.359; 95% CI, 0.236 to 0.471 (compared to original weighted summary-*r*, 0.375). The overall I^2, 69.9% (compared to original overall I^2, 73.6%) and overall weighted summary-*r*, 0.213; 95% CI, 0.059 to 0.357 (compared to original overall weighted summary-*r*, 0168) also had no significant improvement.

Correlation between Tear Osmolarity and Fluorescein Break-up Time

Seven studies with a total of 639 patients/eyes were analysed using a random-effects meta-analysis to assess the correlation between TO and FBUT in all types of DED (30–32,35,36,38,39). Of the seven studies, one study included patients from both subgroups of DED and AID-DED (31), and one study recruited patients with different severity of DED (mild DED and moderate DED) (39). The overall weighted mean-r was -0.349 with a 95% CI, -0.540 to -0.124. The overall I^2 was 88.1%. Subgroup analyses were then performed using a random-effects meta-analysis, separating the DED and AID-DED.

The DED subgroup analysis included three studies with a total of 398 patients/eyes (31,36,39), where Versura et al. (2010) study (39) categorised DED into mild and moderate groups. The analysis yielded the weighted summary-*r*, -0.316; 95% CI, -0.609 to 0.052 and I^2, 92.4%. The AID-DED subgroup analysis comprised five studies with 241 patients/eyes (30–32,35,38). The weighted summary-*r*, -0.378; 95% CI, -0.634 to -0.047; and I^2, 85.4%. The overall forest plot is illustrated in Fig. 3.



AID-DED = autoimmune disease-related dry eye disease; CI = confidence interval; DED = dry eye disease; N = number of patients/eyes; % = percentage; a = Only included mild DED patients; b = Only included moderate DED patients.

Fig. 3: Forest plot for the Correlations between Tear Osmolarity and Fluorescein Break-Up Time in the DED and AID-DED Patients.

Sensitivity analysis was then employed by removing a study in the DED subgroup that conducted anaesthesia-assisted FBUT (36). The removal of Ozulken et al. (2020) (36) in DED subgroup did not significantly improve the I^2, 87.7% and weighted summary-*r*, -0.216; 95% CI, -0.547 to 0.173 (compared with original I^2, 92.4% and original weighted summary-*r*, -0.316) as well as the overall I^2, 86.6% and overall weighted summary-*r*, -0.317; 95% CI, -0.529 to -0.067 (compared with original overall I^2, 88.1% and original overall weighted summary-*r*, -0.349).

Next, we performed a sensitivity analysis by excluding studies that used mean measurements of both eyes (31) or both eyes of each patient (38,39) as the unit of analysis in both the DED and AID-DED subgroups. We found that the overall weighted summary-*r* slightly increased to -0.497; 95% CI, -0.672 to -0.269 (from original overall weighted summary-*r*, -0.349), but the overall I^2, 82.4% was not significantly reduced (compared to original overall I^2, 88.1%). The sensitivity analysis in the AID-DED subgroup, which excluded Kim et al. (2017) (31) and Utine et al. (2011) (38), also showed a minimal improvement in the weighted summary-*r*, -0.475; 95% CI, -0.733 to -0.0976 (from original weighted summary-*r*, -0.378), but the I^2, 87.3% remained identical (compared to original I^2, 85.4%). In the DED subgroup, a sensitivity analysis excluding studies with differences in the unit of analysis was not performed due to the limited number of studies.

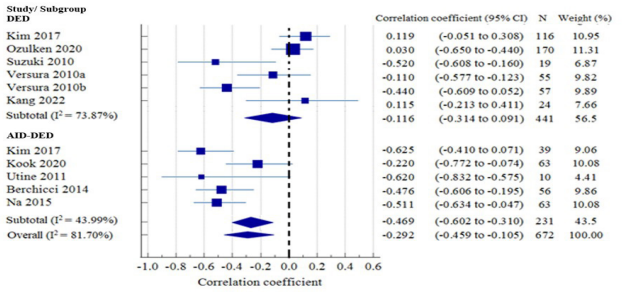
Lastly, we assessed the impact of omitting studies with a high risk of bias (38,39), regardless of the DED and AID-DED. There were no significant changes in overall I^2, 92.5% (compared to original overall I^2, 88.1%) and overall weighted summary-*r*, -0.314; 95% CI, -0.579 to -0.010 (compared to original overall weighted summary-*r*, -0.349). The sensitivity analysis in the AID-DED subgroup, which Utine et al. (2011) (38) omitted, also showed no significant changes in I^2, 88.9% (compared to original I^2, 85.4%) and weighted summary-*r*, -0.351; 95% CI, -0.651 to 0.042 (compared to original weighted summary-*r*, -0.378). Due to the

limited number of studies in the DED subgroup, no sensitivity analysis was conducted to exclude studies with a high risk of bias.

Correlation between Tear Osmolarity and Schirmer I

Nine studies with a total of 672 patients/eyes were analysed using a random-effects meta-analysis to assess the correlation between TO and Schirmer I in all types of DED (30–32,34–36,38,39,41). Of the nine studies, one study included patients from both subgroups of DED and AID-DED (31) and one study recruited patients with different severity of DED (mild DED and moderate DED) (39). The overall weighted summary-*r* was -0.292; 95% CI, -0.459 to -0.105, and the overall I^2 was 81.7%. Subgroup analyses were then performed using a random-effects meta-analysis, separating the DED and AID-DED.

In the subgroup analysis of the DED, five studies with a total of 441 subjects/eyes were included (31,34,36,39,41), where Versura et al. (2010) (39) categorised DED into mild and moderate groups. There was weighted summary-*r*, -0.116; 95% CI, -0.314 to -0.091 with I^2, 73.9%. Subgroup analysis of the AID-DED consisted of five studies with 231 patients/eyes (30–32,35,38). The analysis revealed a weighted summary-*r*, -0.469; 95% CI, -0.602 to -0.310) with I^2, 44%. The forest plot is shown in Fig. 4.



AID-DED = autoimmune disease-related dry eye disease; CI = confidence interval; DED = dry eye disease; N = number of patients/eyes; % = percentage; a = Only included mild DED patients; b = Only included moderate DED patients.

Fig. 4: Forest Plot for the Correlations between Tear Osmolarity and Schirmer I in the DED and AID-DED Patients.

Sensitivity analysis was then conducted by excluding studies that performed anaesthetised-Schirmer I in both the DED (36,39,41) and AID-DED (38) subgroups. The exclusion of the studies (36,38,39,41) did not improve the I^2 and weighted summary-*r* either in the DED subgroup (I^2, 77.9% versus original I^2, 73.9%; weighted summary-*r*, -0.093 versus original weighted summary-*r*, -0.116; 95% CI, -0.365 to 0.193 versus original 95% CI, -0.314 to -0.091), in AID-DED subgroup (I^2, 55.5% versus original I^2, 44%; weighted summary-*r*, -0.46 versus original weighted summary-*r*, -0.469; 95% CI,-0.605 to -0.284 versus original 95% CI, -0.602 to -0.310), or overall (overall I^2, 83.5% versus original overall I^2, 81.7%; overall weighted summary-*r*, -0.292 versus original overall weighted summary-*r*, -0.292; 95% CI, -0.483 to -0.073 versus original 95% CI, -0.459 to -0.105).

Next, a sensitivity analysis was conducted by excluding studies in both subgroups of DED and AID-DED that used mean measurements of both eyes (31) or both eyes of each patient (34,38,39) as the unit of analysis. No significant changes in the overall weighted summary-*r*, -0.333; 95% CI, -0.672 to -0.269 (compared to original overall weighted summary-*r*, -0.292) and in the overall I^2, 83.5% (compared to original overall I^2, 81.7%). Similarly in the sensitivity analysis of the AID-DED subgroup, which excluded studies by Kim et al. (2017) (31) and Utine et al. (2011) (38), we found that the weighted summary-*r*, -0.408, and I^2, 50.5% did not significantly change (compared to original weighted summary-*r*, -0.469, and original I^2, 44%). In the DED subgroup, a sensitivity analysis excluding studies with differences in the unit of analysis was not performed due to the limited number of studies.

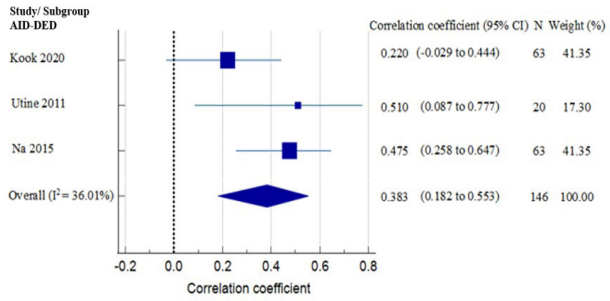
Lastly, a sensitivity analysis was conducted by omitting studies in both the DED and AID-DED subgroups with a high risk of bias (38,39). There were no significant changes in overall weighted summary-*r*, -0.273; 95% CI, -0.477 to -0.041 (compared to original overall weighted summary-*r*, -0.292; 95% CI, -0.459 to -0.105) and overall I^2 of 85.4% (compared to original overall I^2, 81.7%), respectively. In the sensitivity analysis of the DED subgroup, in which Versura et al. (2010) (39) study was excluded, the I^2 significantly improved to 56.7% (from original I^2, 73.9%). However, the weighted summary-*r* was reduced to -0.001; 95% CI, -0.198 to 0.195 (from original weighted summary-*r*, -0.116; 95% CI, -0.314 to -0.091). The sensitivity analysis in the AID-DED subgroup, which Utine et al. (2011) (38) was omitted, also showed no significant changes both in I^2, 55.5% (compared to original I^2, 44%) and weighted summary-*r*, -0.46; 95% CI, -0.605 to -0.284 (compared to original weighted summary-*r*, -0.469; 95% CI, -0.602 to -0.310).

Correlation between Tear Osmolarity and Ocular Surface Staining

Six studies assessed the correlation between TO and OSS in all types of DED (30–32,34,38,39). Of the six studies, one study included patients from both subgroups of DED and AID-DED (31) and one study recruited patients with different severity of DED (mild DED and moderate DED) (39). As described in the Characteristics of the Included Studies section, each study reported the OSS area differently, either as isolated corneal staining (30,32,34,38), isolated conjunctival staining (32,38,39), or total corneal and conjunctival staining (31,32) using various grading scales (SICCA, NEI, or Oxford).

Due to the inconsistency of OSS reporting and the limited number of studies for each OSS area, the meta-analysis can only be conducted for the correlation between TO and corneal staining as OSS in the AID-DED subgroup. Therefore, three studies with a total of 146 patients/eyes were analysed using a random-effects

meta-analysis to assess the correlation between TO and OSS (isolated corneal staining) in the subgroup of the AID-DED (30,32,38). The weighted summary-*r* was 0.383; 95% CI, 0.182 to 0.55. The heterogeneity was small (I^2, 36%). The forest plot is shown in Fig. 5.



AID-DED = autoimmune disease-related dry eye disease; CI = confidence interval; DED = dry eye disease; N = number of

Fig. 5: Forest plot for the Correlations between Tear Osmolarity and Corneal Staining in the AID-DED patient.

DISCUSSION

Tear hyperosmolarity evaluation has emerged as a valuable biomarker for assessing DED severity and monitoring treatment response due to its sensitivity to changes in tear film composition (42,43). Our systematic review revealed a global interest in investigating the association between TO and ocular surface parameters across different geographical locations, with a notable concentration in Asia (30–34) and Europe (35–39), followed by a smaller representation from America (40,41). Interestingly, all studies included in our analysis were conducted within the last decade (30–41), indicating a recent surge in research activity in this field, possibly driven by advancements in diagnostic techniques and a growing recognition of the clinical significance of TO in ocular surface health.

Furthermore, this systematic review found correlations of TO with various clinical parameters commonly used in the assessment of DED, including ocular symptoms, FBUT, Schirmer I, and OSS. Therefore, we assessed the strength and trend of these correlations by using a random effect meta-analysis.

The overall weighted summary-*r* between TO and ocular symptoms across all types of DED was found to be a poor direct correlation, indicating that as TO increases, ocular symptoms may tend to increase, albeit weakly. Subgroup analysis revealed a similar poor correlation within the DED subgroup, with substantial heterogeneity observed across studies. In contrast, the correlation was fair in the AID-DED subgroup, and the finding was homogeneous (I^2 = 0.0%) at a moderate level of certainty of evidence. This suggests that the underlying mechanisms contributing to ocular symptoms may differ between these subgroups. AID-DED is often associated with systemic inflammatory processes, which may lead to more pronounced symptomatology related to tear film instability and ocular surface damage (44,45).

Similarly, low strength of correlation was shown in the weighted summary-*r* of the DED subgroup and overall weighted summary-*r* between TO and Schirmer I, with substantial heterogeneity. Notably, the AID-DED subgroup demonstrated a fair correlation (weighted summary-*r* = -0.47; 95 CI, -0.6 to -0.31) with a moderate certainty of evidence, indicating an acceptable level of confidence in the observed correlation. It implies a potentially distinct pathophysiological mechanism underlying tear production regulation in autoimmune-related DED compared to non-autoimmune forms (46). Therefore, considering disease aetiology is essential when evaluating tear volume in all DED subtypes.

In contrast, the meta-analysis revealed fair inverse correlations between TO and FBUT, a marker of tear film stability, in both DED and AID-DED subgroups. The findings suggest that tear hyperosmolarity may be indicative of tear film instability, which is a hallmark feature of DED. However, the substantial heterogeneity observed across studies, rated as very low to low certainty of evidence, warrants a cautious interpretation of the findings and underscores the need for standardised methodologies in further studies.

Regarding staining assessment, the meta-analysis could only be conducted for the correlation between TO and corneal staining in the AID-DED subgroup due to the variability in OSS reporting and limited available data. The analysis revealed a fair correlation between TO and corneal staining with small heterogeneity, suggesting that elevated tear hyperosmolarity may contribute to greater epithelial damage and vulnerability of the cornea to staining(47), particularly in AID-DED conditions. Again, inconsistencies in reporting OSS and the low number of studies available highlight the need for standardised assessment methods in future research to elucidate the relationship between TO and overall ocular surface integrity.

Several sensitivity analyses were conducted to assess the robustness of the meta-analysis results. The removal of studies with a high risk of bias, differences in the unit of analysis, or clinical assessment did not significantly alter the overall heterogeneity. Hence, the substantial heterogeneity warrants a cautious interpretation of this meta-analysis's weighted summary-*r* findings.

The inclusion criteria for the studies present a limitation. By focusing on observational studies that reported specific correlation coefficients in adult DED patients, the review may have excluded relevant research that could provide additional insights into the TO-DED relationship. For example, studies involving paediatric populations or different types of research designs might offer complementary perspectives but were not considered in this analysis.

CONCLUSION

In conclusion, this systematic review and meta-analysis highlight the complex interplay between tear hyperosmolarity and various clinical parameters in DED. The trend of the correlations showed that tear hyperosmolarity may tend to exacerbate the ocular symptoms, decrease the tear volume and tear film stability, and increase ocular surface damage. While correlations between TO and ocular symptoms, Schirmer I, FBUT, and OSS were observed, the strength of these correlations varied across studies and DED subgroups. Specifically, autoimmune disease-related DED exhibited fair correlations compared to poor correlations in non-autoimmune forms, suggesting differing pathophysiological mechanisms. However, the substantial heterogeneity observed underscores the need for standardised methodologies and further research to validate and elucidate these findings, ensuring their applicability and reliability in practice.

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