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Relative importance of tear homeostatic signs for the diagnosis of dry eye disease

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ABSTRACT

Aim: Disease misdiagnosis is more likely if standardised diagnostic criteria are not used. This study systematically examined the effect on diagnosing dry eye disease (DED), when tests for evaluating tear film homeostasis were included or excluded from a multi-test protocol.

Method: For 1,427 participants across five sites, data for the full suite of diagnostic tests defined in the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Diagnostic Methodology report algorithm were evaluated; diagnostic sensitivity was calculated when individual signs were removed, and when different combinations of signs were required.

Results: Evaluating just one of the three TFOS DEWS II homeostatic signs resulted in between 12.3 % and 36.2 % of patients who met the DED diagnostic criteria not being assigned this diagnosis. While comprehensive ocular surface staining evaluation, comprising of corneal, conjunctival and lid margin staining, in combination with symptoms had the highest sensitivity (87.7 %) of the three markers, the sensitivity dropped to 44.6 % if only corneal staining was evaluated. Omitting either non-invasive tear breakup time or tear osmolarity each dropped the sensitivity by <5 %. The prevalence of DED was substantially reduced if a diagnosis required symptoms and two of the three signs to be present (by 43.7 %–61.2 %) and by 65.9 % if all three signs indicating a loss of tear film homeostasis were required. The outcomes of the analysis did not change significantly across differing severities of DED symptoms.

Conclusions: The TFOS DEWS II diagnostic algorithm of symptoms plus assessing for a tear film (non-invasive tear breakup time or tear osmolarity) and ocular surface sign can be considered a robust and appropriate approach for DED diagnosis.

1. Introduction

For many health conditions, a formal 'diagnosis' is critical for patients to receive acknowledgement that the symptoms that they experience, and any signs that they have observed, are real and are recognised by healthcare practitioners. For practitioners, the use of standardised diagnostic criteria is valuable for providing confidence in diagnostic outcomes and consistency amongst peers. In the context of clinical research, a standardised protocol for diagnosing a disease is also important for clearly defining a study population, including when evaluating the efficacy and safety of therapeutic interventions. Recruitment of a targeted (enriched) participant population may also improve the likelihood of demonstrating clinically significant treatment effects, as necessary to achieve regulatory approvals, and can assist with recruiting the optimal sample size for clinical investigations. In addition, robust epidemiological and economic data to inform appropriate health resource allocation require a consistent diagnosis. Hence, the diagnosis of a disease is ideally made using standardised, universally accepted and

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adopted criteria. For widespread uptake, clinical tests should be readily accessible, ideally inexpensive, and have validated cut-off (threshold) values to stratify 'healthy' from 'diseased' states. It has been reported that anchoring bias (described as "belief in an incorrect initial diagnosis or paying too much attention to one (specific) finding despite subsequent evidence to the contrary") appears to be responsible for a large number of patients being referred with a misdiagnosis of dry eye disease based on a patient report of dryness, even if subsequent objective signs fail to support the diagnosis [1].

One of the most universally accepted definitions of dry eye disease (DED) was developed by the Tear Film and Ocular Surface Society (TFOS), which defines DED as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." [2] It identifies that dry eye symptoms must be present, in association with a loss of the physiological (homeostatic) function of the tear film. DED is recognised not to be monomorphic, however, the characteristics of tear film instability, tear hyperosmolarity, and ocular surface damage are common to all forms of DED and form the basis of an initial diagnosis. Subsequent subclassification testing aids identification of the drivers of this multifactorial disease, which inform clinical management. The current paper focuses on the initial diagnostic element.

Standardised symptom assessment involves use of a validated questionnaire, with either the Ocular Surface Disease Index (OSDI) or 5-item Dry Eye Questionnaire (DEQ-5), which were deemed to fit this remit [3]. A loss of tear film homeostasis is identified by the presence of at least one clinical sign of reduced non-invasive tear breakup time (NIBUT $<$10 s), tear hyperosmolarity ($\geq$308 mOsm/L) or interocular osmolarity difference ($>$8 mOsm/L), or a threshold degree of ocular surface staining (which includes evaluation of the cornea, the bulbar conjunctiva and eyelid margin) [3].

The Asian Dry Eye Society [4,5], supported by the Japanese Dry Eye Society [6], proposed that DED should be diagnosed based on the presence of both ocular symptoms (with four possible questionnaires options) and an unstable tear film (defined as a fluorescein tear breakup time $<$5 s). This approach is similar to that described in the TFOS DEWS II Diagnostic Methodology report, but it is possible that greater practitioner-choice in symptom questionnaire selection, combined with the use of fluorescein to assess tear break-up time (which inherently affects the volume and chemical composition of the tear film) [7,8], albeit with a lower cut-off threshold, could impact consistency in diagnosis.

It has been proposed that diagnostic certainty in DED, measured using sensitivity and specificity, is increased when 'the maximum' number of tests are positive, with the simultaneous presence of corneal and conjunctival staining was suggested as key diagnostic attributes [9] as this was reported to more closely match a Bayesian informed global prevalence of DED [10]. However, a caveat to this interpretation is that existing estimates of the global disease burden of DED will be inherently reliant on studies that have adopted heterogeneous diagnostic criteria. Appropriate interpretation of a test's 'diagnostic accuracy' necessitates a consideration of factors that can introduce bias in a diagnostic test accuracy study, and thus impact the valid derivation of quantitative measures, such as sensitivity and specificity. As discussed in the TFOS DEWS II report in the context of DED [3], and well established in the field of diagnostic research [11], key study design considerations that can induce biased estimates of diagnostic accuracy include patient selection, and the choice of reference standard.

It is likely that there will be an increased chance of misdiagnosing a disease if standardised diagnostic criteria are not, or are only partially, used. Factors that may contribute to a reduced number of tests being performed include equipment availability, testing cost and/or the duration constraints of clinical appointments. This study sought to systematically examine the impact of omitting specific homeostatic clinical markers that form part of the TFOS DEWS II multi-test protocol, on deriving a DED diagnosis. The impact of a proposal that multiple signs need to be present to increase the sensitivity of a diagnosis of DED was also assessed.

2. Methods

De-identified data reporting Ocular Surface Disease Index (OSDI) questionnaire results, NIBUT, tear osmolarity and ocular surface staining, completed at the same visit, were drawn from consenting individuals attending primary eye care clinics / patient registries in the United Kingdom (Aston University Eye Clinic), Canada (Centre for Ocular Research & Education, University of Waterloo), Australia (University of New South Wales Optometry Clinic; University of Melbourne - Anterior Eye, Clinical Trials and Research Translation Unit) and New Zealand (University of Auckland Ocular Surface Registry). The use of all data sets was approved by the local institutional ethics committees.

In all cases, the OSDI was self-completed after explanation on paper / electronically to avoid score inflation from supported completion [12]. The OSDI was used predominantly across all sites, in preference to the DEQ-5, and was the instrument of choice in this evaluation on the basis of its more robust characteristics [13]. DED signs of NIBUT (Oculus Keratograph 5M (K5M, Oculus Optikgeräte GmbH, Wetzlar, Germany)), tear osmolarity (TearLab Osmolarity System, TearLab Corporation, California, USA) and comprehensive ocular surface staining (Keratograph 5M or slit lamp biomicroscope) were assessed. All DED signs were analysed for the worse eye for that sign, except for tear osmolarity, where the difference between the eyes was also included in the evaluation. NIBUT was measured three times per eye, with the mean recorded and used for analysis. Ocular surface staining comprised corneal fluorescein staining, conjunctival lissamine green (where available) or fluorescein staining, and upper and lower lid wiper epitheliopathy (LWE) lissamine green (where available) or fluorescein staining. Both fluorescein and lissamine green were applied via saline-wetted paper strips to the temporal eyelid canthus [3]. The former was instilled once (with the excess saline flicked off), whereas a whole drop of the lissamine green (remaining on the strip for 5 s to increase in concentration) was instilled twice, 5 min apart [3]. Ocular surface staining was quantified by counting corneal (with blue light observed through a yellow filter) and conjunctival (with white light illumination) spots. The length and the relative width of the lower and upper lid margin staining were graded subjectively at the slit lamp biomicroscope [3,14].

The frequency of DED was determined according to the TFOS DEWS II diagnostic criteria [3]. These criteria define the disease by an OSDI score of $\geq$13 and the presence at least one of the following abnormal findings for tear homeostatic markers:

- NIBUT of $<$10s;
- Tear hyperosmolarity, defined as a value of $\geq$308 mOsm/l in either eye, or an interocular osmolarity difference of $>$8 mOsm/l;
- Ocular surface staining, defined as $>$5 corneal fluorescein staining spots, $>$9 conjunctival staining spots, and / or LWE staining of $\geq$2 mm length and $\geq$25 % width [14].

Applying a minimum estimated DED prevalence of 35 % [15–18], the required sample size was 972 for the margin of error or absolute precision of $\pm$3 % in estimating the prevalence with 95 % confidence (Scalex SP calculator) [19].

2.1. Statistical analysis

Data are presented as raw participant numbers and/or the percentage of the data sample that they represent. Effects on diagnostic sensitivity from systematically manipulating the TFOS DEWS II DED diagnostic protocol, to include/exclude individual tear film homeostatic signs, were calculated in Microsoft Excel software. As the TFOS DEWS II

DED diagnosis involves symptoms and any one of the signs, the specificity of removing any option will always be 100 %, justifying comparison of only the sensitivities.

3. Results

The 1,427 participants were aged 36.3 ± 19.3 (mean ± standard deviation (SD)) years, and 53.4 % were female. Of this cohort, 851 (60.5 %) had clinically significant dry eye symptoms (OSDI score: 22.8 ± 19.9) and 1357 (95.1 %) had at least one sign indicative of a loss of tear homeostasis. Only 42 (2.9 %) had neither clinically significant signs or symptoms of DED. The TFOS DEWS II diagnostic criteria for DED were met in 823 participants (57.7 %). DED symptoms occurred without such signs in 28 (2.0 %), and 534 (37.4 %) had ocular surface disease signs, but no clinically significant DED symptoms (i.e., OSDI score <13; Table 1).

On average, NIBUT was 10.8 ± 8.1 (mean ± SD) seconds, with 577 (40.4 %) of participants having a value <10 s. Average tear osmolarity was 306.3 ± 16.6 mOm/L, with 378 (26.7 %) having a measurement ≥308 mOsm/L in both eyes, 319 (22.5 %) with ≥308 mOsm/L in one eye, and 579 (40.6 %) with an interocular difference >8 mOsm/L. Ocular surface staining meeting the TFOS DEWS II diagnostic criteria was present in 569 participants (39.9 %) for the cornea, 582 participants (40.8 %) for the conjunctiva, and 864 (60.5 %) for LWE.

The sensitivity of the current TFOS DEWS II DED diagnostic protocol for various combinations of signs, together with the symptoms, is presented in Table 2. This table includes data from all participants with an OSDI ≥13 and at least one sign (n = 823), who were then further subgrouped by symptom severity level into mild (OSDI 13–22; n = 282), moderate (OSDI 23–32; n = 226) and severe (OSDI ≥33; n = 364) [20]. If only corneal fluorescein staining was assessed, rather than the three-component ocular surface staining elements, the sensitivity when combined with symptoms was only 44.6 % compared to that with the full TFOS DEWS II diagnosis. Severity of disease, based on OSDI scores, did not affect the sensitivity of the various tested algorithms.

Within the study population with DED, the derived occurrence of DED decreased if a diagnosis demanded symptoms and two signs to be present, or if all three signs along with symptoms were required (Table 3).

4. Discussion

This study sought to systematically examine the effect on deriving a diagnosis of DED, if different clinical tests evaluating the homeostasis of the tear film (as defined in the TFOS DEWS II Diagnostic Methodology report) [3] were omitted as part of the multi-test protocol or a more rigid requirement was introduced. In this present study, the presence of at least one abnormal ocular surface sign was common, affecting 95.1 % of the study cohort. This high frequency is not unexpected given that participants were recruited from primary eye care clinics or research centres with established interests in ocular surface disease. A diagnosis of DED, based on the presence of threshold symptoms and an abnormal result for at least one tear homeostatic marker, as per the TFOS DEWS II diagnostic criteria, was recorded for 57.7 % of participants. Only a small proportion exhibited symptoms without signs, which could potentially indicate a pre-clinical state or neuropathically-driven ocular surface symptoms [2].

The average tear film stability measurement (assessed using non-invasive tear breakup time) was slightly longer than the cut-off for DED (<10s) in the TFOS DEWS II criteria [3], with just over two-fifths of the cohort recording values below this level. Similar observations were evident for tear osmolarity. On average, tear osmolarity readings were marginally lower than the cut-off for DED (≥308 mOsm/L) [3], with about 40 % of participants meeting the criteria of an interocular difference >8 mOm/L, but only about one-quarter exhibiting tear hyperosmolarity in one eye (one of the two osmolarity based diagnostic criteria) [3] and a similar proportion (only a 4 % difference) in both eyes, suggesting asymmetry in the osmolarity within the tear meniscus between the eyes of those with DED is common. Ocular surface staining meeting the TFOS DEWS II diagnostic criteria [3] was also present in about two-fifths of the cohort for the cornea and conjunctiva, whereas staining of the lid margin occurred in two-thirds of the cohort; this could reflect that LWE occurs earlier in the natural history of DED progression than corneal or conjunctival staining [21]. LWE occurrence in a broader range of disease severities is in keeping with the observation that it was accompanied by an unstable tear film (NIBUT <10s) in 61.0 % of cases, by tear hyperosmolarity (≥308 mOsm/L) or similarly an interocular osmolarity difference (>8 mOsm/L) in 61.2 % of cases, and in 85.4 % of cases with either one or the other of these tear film abnormalities; this finding aligns with the concept that lid wiper epitheliopathy is highly associated with stress on the ocular surface from the eyelid blink motion [22].

Sensitivity analysis of the current TFOS DEWS II diagnostic criteria for DED based on different combinations of tear homeostatic signs, together with the symptom criteria, identified that testing only a single sign would leave 12.3 %–36.2 % of DED patients without a diagnosis. Using symptoms and only a single sign, the complete ocular surface staining approach (i.e., cornea, bulbar conjunctiva and lid margin), in combination with clinically significant symptoms, had the highest sensitivity relative to the full diagnostic protocol, likely because of the known later-stage occurrence of ocular surface staining [23]. However, if corneal fluorescein staining was evaluated as the only clinical sign, the diagnostic sensitivity dropped to half this value (44.6 %), emphasising the importance of simultaneously examining staining of the bulbar conjunctiva and eyelid margin, ideally with lissamine green dye [3].

Omitting testing of tear osmolarity and / or NIBUT had a lesser impact on the diagnostic outcome; not using either of these approaches each reduced sensitivity by only <5 %. If ocular surface staining was the only diagnostic sign omitted, sensitivity dropped by just over 10 %. Taken together, these findings suggest that the quantification of dry eye symptoms, combined with comprehensive ocular surface staining assessment and performance of at least one test out of NIBUT or tear osmolarity, is likely sufficient for making a DED diagnosis, yielding a sensitivity of >95 % relative to the full TFOS DEWS II diagnostic protocol if the questionnaire and either one of the two signs of loss of homeostasis meet the threshold cut-off. Sensitivity analysis for a single homeostatic sign relative to the severity of dry eye symptoms showed little effect, suggesting the diagnostic algorithm is robust regardless of disease severity in terms of the presenting symptomology.

Within the study population, the number of individuals diagnosed with DED reduced substantially if the diagnosis required a threshold

Table 1
Occurrence of the homeostatic signs defined in the TFOS DEWS II diagnostic algorithm for DED, grouped by dry eye symptom severity (based on the OSDI). NIBUT = non-invasive tear breakup time; OSDI = Ocular Surface Disease Index.

		Below OSDI threshold	Symptom score (OSDI) (stratified by severity)		
		<13	13–22	23–32	≥33
NIBUT	<10s	53.3 %	56.0 %	64.7 %	65.7 %
Tear Osmolarity	≥308 mOsm/L in either eye	46.7 %	47.9 %	50.9 %	52.8 %
	Interocular difference >8 mOsm/l	38.0 %	41.3 %	38.5 %	46.2 %
Ocular Surface Staining	Cornea >5 punctate spots	27.7 %	43.1 %	48.9 %	52.6 %
	Conjunctiva >9 punctate spots	31.2 %	42.9 %	48.1 %	58.5 %
	Lid margin ≥2 mm length and ≥25 % width	62.3 %	64.7 %	68.6 %	64.3 %

Table 2
Sensitivity of the TFOS DEWS II diagnostic algorithm for DED, when combining a positive symptom score (OSDI ≥13) with single or variously combined signs of a loss of tear homeostasis. NIBUT = non-invasive tear breakup time; OSDI = Ocular Surface Disease Index.

Symptoms (OSDI ≥13) +	NIBUT	Tear Osmolarity	Ocular Surface Staining	NIBUT or Tear Osmolarity	NIBUT or Ocular Surface Staining	Tear Osmolarity or Ocular Surface Staining
All	64.3 %	63.8 %	87.7 %	89.3 %	95.7 %	96.6 %
Mild	59.2 %	61.8 %	89.5 %	88.8 %	96.3 %	96.3 %
Moderate	66.5 %	62.9 %	84.2 %	89.6 %	93.2 %	95.5 %
Severe	66.9 %	66.0 %	88.7 %	89.6 %	97.0 %	97.6 %

Table 3
Sensitivity of the TFOS DEWS II diagnostic algorithm for DED when a requirement to combine a positive symptom score (OSDI ≥13) with combinations of multiple signs of a loss of tear homeostasis is imposed. NIBUT = non-invasive tear breakup time; OSDI = Ocular Surface Disease Index.

Symptoms (OSDI ≥13) +	NIBUT & Ocular surface staining	Tear Osmolarity & Ocular Surface Staining	NIBUT & Tear Osmolarity	NIBUT & Tear Osmolarity & Ocular Surface Staining
All	56.3 %	54.9 %	38.8 %	34.1 %
Mild	52.4 %	55.1 %	32.2 %	29.2 %
Moderate	47.5 %	51.6 %	39.8 %	35.3 %
Severe	68.5 %	57.0 %	43.3 %	37.3 %

level of symptoms and two signs to be present (to between 38.8 % and 54.9 %) and to about one-third (34.1 %) if all three signs of a loss of homeostasis were required. Again, symptom severity grouping did not change this outcome significantly. This would leave many patients who report dry eye symptoms (as assessed by the OSDI) without a diagnosis, which would seem inappropriate unless an alternative condition, requiring differing treatment from DED, can be identified in these individuals.

The limitations of this study include basing 'ground truth' on the TFOS DEWS II algorithm and assessing symptomology based only on the OSDI rather than with the DEQ-5 as an alternative. Populations with dry eye may vary across different clinical settings, and future study is warranted to fully explore population heterogeneity (to include a broader range of ages, ethnicities and geographies), nevertheless, the data appear robust, at least in terms of reported range of symptom severity. This study used the recommended non-invasive method of assessing tear film stability, with three measurements averaged to mitigate the inherent variability of this parameter. While a significant proportion of eye care practitioners continue to rely on fluorescein to assess tear breakup time it was outside the scope of this study to explore the impact of this on appropriate diagnosis.

In conclusion, this study that focuses specifically on the initial diagnosis of DED, prior to subclassification, has shown that the impact of omitting the assessment of various clinical measures from the TFOS DEWS II recommended dry eye diagnostic algorithm on dry eye diagnosis sensitivity is highly influenced by the nature of the test and number of tests omitted. Data from this study show that at minimum two clinical signs should be assessed, with a combination of a tear film marker assessment (non-invasive breakup time or osmolarity) and ocular surface staining assessment (cornea, bulbar conjunctiva and lid margin) resulting in the highest sensitivity (>95 %) of an accurate DED diagnosis.

CRediT authorship contribution statement

James S. Wolffsohn: Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sònia Travé-Huarte:** Writing – review & editing, Resources, Data curation. **Fiona Stapleton:** Writing – review & editing, Resources, Data curation. **Laura E. Downie:** Writing – review & editing, Resources, Data curation. **Marc-Matthias Schulze:** Writing – review & editing, Resources, Data curation. **Sarah Guthrie:** Writing – review & editing, Resources, Data curation. **Ulrike Stahl:** Writing – review & editing, Resources, Data curation. **Michael T.M. Wang:** Writing – review & editing, Resources, Data curation. **Jennifer P. Craig:** Writing – review & editing, Resources, Methodology, Data curation.

Data sharing

The participants did not give consent for their data to be shared.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: James Wolffsohn and Jennifer Craig reports a relationship with Tear Film and Ocular Surface Society that includes: board membership and travel reimbursement. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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