Dry Eye Diagnosis

Santosh Khanal, Alan Tomlinson, Angus McFadyen, Charles Diaper, and Kannu Ramaesh

PURPOSE. To determine the most effective objective tests, applied singly or in combination in the diagnosis of dry eye disease.

METHODS. Two groups of subjects—41 with dry eye and 32 with no ocular surface disease—had symptoms, tear film quality, evaporation, tear turnover rate (TTR), volume and osmolarity, and meibomian gland dropout score assessed.

RESULTS. The subjects with dry eye had TTR, tear evaporation, and osmolarity significantly different from that of healthy normal subjects. Cutoff values between the groups were determined from distribution curves for each aspect of tear physiology, and the effectiveness of the cutoff was determined from receiver operator characteristic (ROC) curves. Values of 12%/min for TTR, 53 g/cm²/h for evaporation, and 517 mOsmol/L for osmolarity were found to give sensitivities, specificities, and overall accuracies of 80%, 72%, and 77%; 51%, 96%, and 67%; and 78%, 78%, and 79%, respectively, when applied singly as diagnostic criteria in dry eye. In combination, they yielded sensitivities, specificities, and overall accuracy of 100%, 66%, and 86% (in parallel) and 38%, 100%, and 63% (in series), respectively. Discriminant function analysis incorporating these three factors in an equation allowed diagnosis with a sensitivity of 93%, specificity of 88%, and overall accuracy of 89%.

CONCLUSIONS. Tear osmolarity is the best single test for the diagnosis of dry eye, whereas a battery of tests employing a weighted comparison of TTR, evaporation, and osmolarity measurements derived from discriminant function analysis is the most effective. (Invest Ophthalmol Vis Sci. 2008;49:1407–1414) DOI:10.1167/iovs.07-0635

Attempts have been made to define the condition of dry eye,1 but the methods for its diagnosis vary widely, underlining attempts at definition by the use of differing diagnostic criteria and creating difficulties in comparisons of prevalence and efficacy of treatment regimens. Diagnosis of dry eye disease is made difficult by its multifactorial etiology, by the need for a comprehensive definition, and by the use of tests that are limited and variable in their assessment of the tears and the ocular surface.

Some studies have used reports of symptoms as the criterion for the diagnosis of dry eye2–8 (see Table 1). It has been suggested that it is appropriate to diagnose dry eye from symptoms alone, as the condition rarely progresses to the stage of causing ocular discomfort without symptoms.9 However, symptoms alone are inadequate for differential diagnosis of dry eye, because the same symptoms can be experienced with a range of ocular surface conditions and tear film disorders.1,10

The most common objective diagnostic test for dry eye, the Schirmer test, which has been in use for more than 100 years,11 lacks standardization,12 is inaccurate and unrepeatable because of the reflex secretion produced by its invasive nature,13 and measures tear production only,14 so that the evaporative aspects of dry eye are overlooked.12 However, the low cost of strips, their ease of application, and the lack of availability of a more acceptable diagnostic test has led to the Schirmer test’s being the most commonly applied clinical test for lacrimal secretory function in dry eye.15

Tear break-up time (TBUT) measurement with fluorescein is another widely used technique for dry eye diagnosis by clinicians. This test is considered to be more reliable than the Schirmer test, as it is repeatable16 and minimally invasive; however, the instillation of fluorescein can destabilize the tear film.17,18 The measurement of break-up time in the absence of fluorescein (NIBUT) can overcome this problem and give a more accurate assessment of tear stability. But all forms of tear break-up measurement fail to give direct information on tear evaporation.12

Ocular surface staining with vital dyes such as rose bengal, lissamine green, and fluorescein have also been used to diagnose dry eye.19–21 The disadvantage of these tests is that dry eye is measured by the extent of ocular surface damage, and therefore do not necessarily detect early dry eye or differentiate dry eye from other conditions causing ocular surface staining.22

Tear physiology tests can also be used to diagnose dry eye. Normal tear film dynamics require adequate production, retention on the ocular surface, and balanced elimination.23 The quantitative aspects of tear dynamics include distribution, turnover (and drainage), evaporation, and absorption of the tears. An imbalance in any of these components would disrupt the normal tear physiology and lead to dry eye. The proportion of ocular surface absorption of a dye in eyes with normal corneas has been shown to be minimal at only 0.24% ± 0.13%.24 Therefore, the contribution of tear absorption to the overall tear elimination can be said to be negligible. Tear osmolarity represents the end product of changes in tear dynamics25 and is thought to be an attractive index for dry eye diagnosis.26 Direct measurements of tear production, stability, evaporation and osmolarity have the potential to be accurate and sensitive tests for dry eye, and these are the tests assessed in this study.

It has been shown that there is poor correlation between symptoms and signs of dry eye. Only 57% of the symptomatic patients have been shown to have objective signs of dry eye.9,10,27–29 This finding has been attributed to the symptoms preceding the signs, or the differing etiology and pathophysiology of dry eye.30 Also, a single objective test for dry eye is of limited value without a report of symptoms.5

A large number of tests have been used singly, or in combination, to diagnose the condition with variable success,13,17,23,31–45 (Table 1), because of the inherent variability...
of most tests and their inability to measure specifically the change in tear physiology in the multifactorial condition of dry eye.10

The purpose of this study was to assess as directly as possible tear physiology and meibomian gland function in a range of dry eye conditions in an attempt to optimize the possible tear physiology and meibomian gland function in a

<table>
<thead>
<tr>
<th>Test</th>
<th>Author, Reference</th>
<th>Cutoff</th>
<th>Sens %</th>
<th>Spec %</th>
<th>False–ves %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>OA %</th>
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<tr>
<td>Single Tests</td>
<td>Symptoms</td>
<td>McMonnies52</td>
<td>Any</td>
<td>98</td>
<td>97</td>
<td>2</td>
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<td>Symptoms score</td>
<td>Narayanan et al.31</td>
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<td>100</td>
<td>25</td>
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<td></td>
<td>TERTC-DEQ</td>
<td>Patel et al.53</td>
<td>≤10 mm</td>
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<td>83</td>
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<tr>
<td></td>
<td>Phenol red thread</td>
<td>Goren and Goren54</td>
<td>Any</td>
<td>25</td>
<td>90</td>
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<td></td>
<td>Rose bengal</td>
<td>Lucca et al.13</td>
<td>&lt;5 mm/5 min</td>
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<td>Schirmer I</td>
<td>van Bijsterveld56</td>
<td>&lt;5.5 mm/5 min</td>
<td>85</td>
<td>83</td>
<td>15</td>
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<td>Schirmer I</td>
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<td>83</td>
<td>68</td>
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<tr>
<td></td>
<td>F BUT</td>
<td>Vitali et al.56</td>
<td>≤10 s</td>
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<td>62</td>
<td>28</td>
<td>25</td>
<td>93</td>
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<td></td>
<td>N I BUT</td>
<td>Mengher et al.17</td>
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<td>17</td>
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<td>Goto et al.57</td>
<td>≤5 s</td>
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<td>63</td>
<td>2</td>
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<td>Meniscus height</td>
<td>Mainstone et al.58</td>
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<td>Meniscus radius</td>
<td>Yokoi and Kumoro59</td>
<td>≤0.25 mm</td>
<td>89</td>
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<td>Tear film index</td>
<td>Xu and Tsaiota60</td>
<td>≤95</td>
<td>67</td>
<td>60</td>
<td>33</td>
<td>23</td>
<td>91</td>
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<tr>
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<td>Osmolarity</td>
<td>Gilbard et al.60</td>
<td>&gt;312 mOsmol/L</td>
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<td>94</td>
<td>55</td>
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<tr>
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<td>Tomlinson et al.61</td>
<td>&gt;316 mOsmol/L</td>
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<td>92</td>
<td>31</td>
<td>60</td>
<td>94</td>
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<tr>
<td></td>
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<td>59</td>
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<td>Tomlinson et al.63</td>
<td>&gt;312 mOsmol/L</td>
<td>66</td>
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<td>34</td>
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<tr>
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<td>52</td>
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<td></td>
<td>Osmolarity</td>
<td>Sullivan11</td>
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<td>95</td>
<td>6</td>
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<td>Lysozyme assay</td>
<td>van Bijsterveld56</td>
<td>Dia ≤21.5 mm</td>
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<td>1</td>
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<td>Fering</td>
<td>Norm12</td>
<td>Area &lt;0.06 mm²/µL</td>
<td>94</td>
<td>75</td>
<td>6</td>
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<tr>
<td></td>
<td>Lactoferrin</td>
<td>Lucca et al.13</td>
<td>&lt;90 µg/dL</td>
<td>35</td>
<td>70</td>
<td>65</td>
<td>17</td>
<td>86</td>
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<td>Combined Tests (Parallel)</td>
<td>Schirmer or rose bengal</td>
<td>Farris55</td>
<td>&lt;1 mm/min or any</td>
<td>77</td>
<td>49</td>
<td>23</td>
<td>21</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Schirmer or TBUT</td>
<td>Farris55</td>
<td>&lt;1 mm/min or any</td>
<td>78</td>
<td>56</td>
<td>22</td>
<td>24</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Schirmer or TBUT or rose bengal</td>
<td>Farris55</td>
<td>≤10 sec</td>
<td>80</td>
<td>49</td>
<td>20</td>
<td>22</td>
<td>93</td>
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<tr>
<td>Combined tests (series)</td>
<td>Schirmer and osmolarity</td>
<td>Farris55</td>
<td>≤1 mm/min and</td>
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<td>88</td>
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<tr>
<td></td>
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<td>&gt;312 mOsmol/L</td>
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<td>&gt;30 and &gt;312 mOsmol/L</td>
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<td>Discriminant function</td>
<td>Craig44</td>
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<td>4</td>
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<td>99</td>
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</table>

Sensitivities (Sens), specificities (Spec), false-negatives (False–ves), positive predictive values (PPV), negative predictive values (NPV), and overall accuracies (OA) of different tests, singly and in combination, and discriminant function are shown. TERTC-DEQ, Texas Eye Research and Technology Center Dry Eye Questionnaire; TBUT, tear break-up time; FIBUT, fluorescein break-up time; NIBUT, noninvasive tear break-up time; TMS-BUT, topographic modeling system tear break-up.

of most tests and their inability to measure specifically the change in tear physiology in the multifactorial condition of dry eye.10

The purpose of this study was to assess as directly as possible tear physiology and meibomian gland function in a range of dry eye conditions in an attempt to optimize the diagnosis by determining the most suitable single test or battery of diagnostic tests. The study complied with the guidelines in the Declaration of Helsinki for research involving human subjects. All participants provided signed informed consent.

Methods

Subjects

Two groups of subjects were recruited for the study, including those with dry eye and normal subjects with no symptoms or signs of anterior eye disease. Patients with dry eye were referred from two Glasgow hospitals to the Tear Physiology Unit in Glasgow Caledonian University for tear evaluation. Clinical diagnosis of dry eye was made by the referring ophthalmologists (KR, CD) on the basis of symptoms, clinical observations, Schirmer I test, tear break-up time, and autoantibody tests (in the case of Sjogren's syndrome). All the patients had positive dry eye symptoms. Patients treated with tear supplementation were instructed not to use any solutions for 48 hours before tear evaluation. The dry eye group was made up of patients defined by the ophthalmologists in the following subgroups: Sjogren's syndrome, graft-versus-host disease (GVHD), or the general category other dry eye. Patients with blepharitis were excluded from the study.

Normal subjects were recruited initially by a general e-mail notice within the university. The inclusion criteria for normal subjects were less than two symptoms on the McMonnies Dry Eye Questionnaire,13 noninvasive tear break-up time (NIBUT)56 of greater than 10 seconds, and a Schirmer I test score11,14 of >5 mm in 5 minutes. Subjects who had worn contact lenses and those with external ocular diseases in the previous 6 months were excluded from the study. None of the normal subjects had ever used tear supplements before. Signed consent was obtained from all the subjects and patients before recruitment into the study.

Investigations

In addition to the initial dry eye assessment performed at the hospital with the use of conventional clinical tests, tear analysis was performed at the Tear Physiology Unit at Glasgow Caledonian University on all subjects. The specific measures included, tear quality, tear film break-up time, meibum indices, and meibomian gland function.

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Tear film quality analysis in an attempt to improve diagnostic efficacy. Combined in parallel and series Discomfort, severity Conjunctival injection — (None to mild) — (Variable) — (Moderate to varied widely with the tests. MGD, meibomian gland dysfunction; TFBUT, tear fluorescein break-up time.

**Analysis of Data**

The results obtained for individual measurements of tear quality, evaporation, turnover, volume and osmolarity, and meibomian gland function were assessed for their effectiveness in defining dry eye. Cutoffs and referent values for dry eye were obtained for individual measurements of tear quality, evaporation, turnover, volume and osmolarity between normal subjects and those with dry eye, the use of these aspects and frequency turnover, volume, and osmolarity, and meibomian gland function were analyzed by comparisons of means in normal subjects and patients with dry eye. Cutoffs and referent values for dry eye were initially obtained from the intercept of the frequency distributions of each tear measurement for dry eye and normal groups. Receiver operating characteristics (ROC) curves were plotted to determine the sensitivity and specificity of the measurement in defining dry eye. The results for individual tear measurements were combined in parallel and series and by discriminant function analysis in an attempt to improve diagnostic efficacy.

**Results**

Forty-one patients with dry eye (17 men and 24 women; average age, 51.63 ± 13.81 years) of which 17 (2 men and 15 women; average age, 52.35 ± 11.81 years) had a diagnosis of Sjögren’s syndrome by the referring ophthalmologist as, 12 (12 men, average age, 47.01 ± 13.09 years) of GVHD, 12 (3 men and 9 women; average age, 55.25 ± 16.77 years) as general dry eye (aqueous deficient and/or evaporative); and 32 normal subjects (12 males and 20 females, average age, 52.31 ± 14.38 years), were examined. The mean and standard deviations of values obtained in assessments of these groups are shown (Table 2). Patients with dry eye were also classified into different groups in a severity matrix (Table 3), based on the dry eye severity scale proposed by Behrens et al. and adopted by the recent Dry Eye Workshop (DEWS) report.

**Normal and Dry Eyes**

All the measured variables were tested for normality. Tear evaporation, turnover rate, osmolarity, and volume were normally distributed. A two-sample t-test showed that there were statistically significant differences between normal subjects and patients with dry eye for tear turnover rate (TTR; \( P < 0.001 \)), tear evaporation \( (P = 0.001), \) and osmolarity \( (P < 0.001), \) but not for tear volume \( (P = 0.234) \). The frequency distribution of tear film quality grade was determined by \( \chi^2 \) test, and no significant difference was seen between the groups \( (P = 0.717) \). The distribution of meibomian gland dropout score was not normal, and so a nonparametric test (Mann-Whitney U test) was used to test for significant differences between the subject groups. No significant difference was seen in the mean meibomian gland dropout scores \( (P = 0.691) \) between normal subjects and patients with dry eye. Abnormal meibomian gland function (meibomian gland dropout score ≥ 2), was present in 14% of normal subjects and 20.4% of patients with dry eye.

As significant differences had been demonstrated for tear turnover, evaporation, and osmolarity between normal subjects and those with and dry eye, the use of these aspects of tear physiology were assessed for their effectiveness in diagnosis.

**Table 2. Results of Tear and Gland Assessments in Normal and Dry Eye**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal</th>
<th>Dry Eye</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR (%/min)</td>
<td>15.24 ± 5.66</td>
<td>7.75 ± 5.94</td>
<td>&lt;0.001</td>
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<tr>
<td>Evaporation (g/m²/h)</td>
<td>20.97 ± 10.06</td>
<td>37.89 ± 26.48</td>
<td>0.001</td>
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<tr>
<td>Osmolarity (mOsmol/L)</td>
<td>308.39 ± 9.29</td>
<td>328.71 ± 13.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tear volume (mL)</td>
<td>7.98 ± 3.54</td>
<td>7.08 ± 2.85</td>
<td>0.234</td>
</tr>
<tr>
<td>Meibomian gland dropout score</td>
<td>0.56 ± 0.57</td>
<td>0.78 ± 0.99</td>
<td>0.691</td>
</tr>
<tr>
<td>Tear film quality (mg/100mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>6.25</td>
<td>9.76</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>15.63</td>
<td>39.02</td>
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</tr>
<tr>
<td>Grade 3</td>
<td>56.25</td>
<td>12.19</td>
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<tr>
<td>Grade 4</td>
<td>21.87</td>
<td>29.27</td>
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</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
<td>9.76</td>
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</table>

Data are the mean ± SD.

**Table 3. Patients with Dry Eye Grouped in the Four Severity Levels**

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1 (Mild, episodic, with stress)</th>
<th>2 (Moderate, episodic or chronic)</th>
<th>3 (Severe, frequent, or constant)</th>
<th>4 (Severe, disabling, and constant)</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort, severity and frequency</td>
<td>8</td>
<td>11</td>
<td>13</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>27 (None or episodic mild fatigue)</td>
<td>3 (Annoying or activity-limiting episodic)</td>
<td>1 (Annoying, chronic and/or constant limiting activity)</td>
<td>3 (Constant and/or possibly disabling)</td>
<td>34</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>(None to mild)</td>
<td>(None to mild)</td>
<td>(+/-)</td>
<td>(+/+/+)</td>
<td></td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>(None to mild)</td>
<td>(Variable)</td>
<td>(Moderate to marked)</td>
<td>(Marked)</td>
<td></td>
</tr>
<tr>
<td>Corneal staining (severity/location)</td>
<td>4 (None to mild)</td>
<td>7 (Variable)</td>
<td>16 (Marked central)</td>
<td></td>
<td>27</td>
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<tr>
<td>Corneal/tear signs</td>
<td>9 (None to mild)</td>
<td>10 (Mild debris, ↓ meniscus)</td>
<td>6 (Filamentary keratitis, mucus clumping, ↑ tear debris)</td>
<td>8 (Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration)</td>
<td>33</td>
</tr>
<tr>
<td>Lid/meibomian glands</td>
<td>25 (MGD variably present)</td>
<td>9 (MGD variably present)</td>
<td>6 (Frequent)</td>
<td>1 (Trichiasis, keratinization, symblepharon)</td>
<td>41</td>
</tr>
<tr>
<td>TFBUT (s)</td>
<td>5 (Variable)</td>
<td>13 (≥10)</td>
<td>8 (≥5)</td>
<td>4 (Immediate)</td>
<td>30</td>
</tr>
<tr>
<td>Schirmer (mm/5 min)</td>
<td>5 (Variable)</td>
<td>9 (≥10)</td>
<td>14 (≥5)</td>
<td>13 (≥2)</td>
<td>41</td>
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</tbody>
</table>

Numerical data are the number of subjects at each level. Groups were determined by results of different clinical tests based on the severity matrix proposed by Behrens et al. Not all of these investigations were performed on each patient to establish a positive diagnosis. The tests were conducted only as required at the discretion of the ophthalmologist. It can be seen that the number of patients falling into different severity levels varied widely with the tests. MGD, meibomian gland dysfunction; TFBUT, tear fluorescein break-up time.
Distribution curves of TTR, evaporation, and osmolarity were plotted for normal subjects and patients with dry eye. As an example, the values for TTR are shown in Figure 1.

**Single Test Results in the Diagnosis of Dry Eye**

Figure 1 shows that TTR was lower in patients with dry eye than normal subjects. The intercept of the distribution curves for normal subjects and patients with dry eye was found to be at 12%/min. To evaluate the effectiveness of TTR in determining whether a subject has dry eye or is normal, an ROC curve was plotted from the TTR values of these two groups of subjects (Fig. 2). The area under the curve was found to be 0.84 (95% CI: 0.75–0.94). The sensitivity and specificity of a cutoff value of 12%/min as derived from the ROC curves was found to be 0.80 and 0.72, respectively, and the positive (PPVs) and negative (NPVs) predictive values were 0.79 and 0.74, respectively. The overall accuracy of this cutoff in discriminating between normal subjects and patients with dry eye was found to be 76.71%

A similar process was applied to tear evaporation and osmolarity, with the intercepts determined from the distribution curves. ROC curves were plotted, and the effectiveness of single tear measures in differentiating normal subjects from dry eye determined. These results are shown in Table 4.

Single tests may be used to diagnose dry eye but combinations in parallel or series may improve the efficacy of diagnosis. This approach has the merit that there are distinct differences in diagnostic test results in different subgroups of patients with dry eye, which can aid clinicians in differential diagnosis of tear film disorders.

Combination Test Results in the Diagnosis of Dry Eye

The ability to differentiate persons with dry eye from normal subjects by combining, in parallel and series, objective measures of tear physiology was determined. Tests combined in parallel required a positive result on one test for diagnosis of dry eye; in series, all tests had to be positive. This approach has the merit that there are distinct differences in diagnostic test results in different subgroups of patients with dry eye, which can aid clinicians in differential diagnosis of tear film disorders.

Discriminant function analysis was also performed, to improve the efficacy of diagnosis and to identify the most suitable combination of tests. A forward linear step-wise model was used to exclude the parameters that offered little or no contribution to the diagnosis. All the measured parameters including TTR, tear evaporation, osmolarity, volume, film quality, and meibomian gland dropout scores were included in the analysis. The step-wise model removed tear film quality and meibomian gland dropout scores from the canonical function, leaving TTR, tear evaporation, and osmolarity as significant contributing factors in the diagnosis of dry eye (Table 5). A discriminant function incorporating three variables is acceptable.

The most significant, single contributory measure to this function was osmolarity (with a standardized canonical discriminant function coefficient of 0.628), followed by TTR (coefficient, -0.528) and evaporation (coefficient, 0.343).
The group to which the patient was allocated by the analysis was determined by inputting the values of TTR, evaporation (Evap), and osmolarity (Osm) into the following nonstandardized canonical equation derived from the discriminant function analysis:

\[
F = -0.09 \times \text{TTR} + 0.016 \times \text{Evap} + 0.052 \times \text{Osm} - 16.25
\]

The weighted midpoint of the group centroids of normal subjects and dry eye was found to be 0.4 on the study sample. This value was used as a cutoff for the function with discriminant score of more than 0.4 indicative of dry eye. This function classified 86.3% of the cases correctly. On cross-validation (i.e., when each case is classified by the functions derived from all other cases except that particular case), it was seen that 83.6% of the cases were classified correctly (Table 4). This value was used as a cutoff for the function with discrimination causing significant aqueous deficiency.

The derived discriminant function from discriminant analysis was applied to the data from the tested subject, and the predicted group membership was determined. The discriminant function correctly classified 86.3% of the subjects and the cross-validation, 83.6%.

<table>
<thead>
<tr>
<th>Test Cutoff</th>
<th>Sens %</th>
<th>Spec %</th>
<th>False–ves %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>OA%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR &lt;12%/min</td>
<td>80</td>
<td>72</td>
<td>20</td>
<td>79</td>
<td>74</td>
<td>76.7</td>
</tr>
<tr>
<td>Evap &gt;33 g/m²/h</td>
<td>51</td>
<td>96</td>
<td>49</td>
<td>84</td>
<td>41</td>
<td>67.1</td>
</tr>
<tr>
<td>Osm &gt;317 mOsml/L</td>
<td>78</td>
<td>78</td>
<td>22</td>
<td>86</td>
<td>73</td>
<td>79</td>
</tr>
</tbody>
</table>

Combined tests (parallel):
- TTR or Evap: <12%/min or >33 g/m²/h or >317 mOsml/L: 95, 62.5, 5, 76.5, 86, 80
- TTR or Osm: <12%/min or >317 mOsml/L: 93, 59, 7, 74.5, 86, 78
- TTR or Evap or Osm: <12%/min or >33 g/m²/h or >317 mOsml/L: 100, 66, 0, 81, 100, 86

Combined tests (series):
- TTR and Evap: <12%/min and >33 g/m²/h: 36.5, 100, 63.5, 100, 55, 64
- TTR and Osm: <12%/min and >317 mOsml/L: 63, 90, 37, 90, 66, 75
- TTR and Evap and Osm: <12%/min and >33 g/m²/h and >317 mOsml/L: 38, 100, 62, 100, 52, 63

Discriminant function (F*)
- TTR, Evap and Osm >0.4: 93, 88, 7, 58, 99, 89

Specificity (Spec), sensitivity (Sens), false negatives (False–ves), positive predictive values (PPV), negative predictive values (NPV) and overall accuracies (OA) of different tests including tear turnover rate (TTR), evaporation (Evap) and osmolarity (Osm), singly and in combination, used in the diagnosis of dry eye. The intercepts found in the distribution curves between normal subjects and patients with dry eye for these tests were considered to be the cut-off value for dry eye.

\[ F = -0.09 \times \text{TTR} + 0.016 \times \text{Evap} + 0.052 \times \text{Osm} - 16.25 \]

The clinical and laboratory tests used for assessing the physiological characteristics of tears in this study have been shown

<p>| Table 6. Classification Results of the Original and Predicted Group Memberships of Normal Subjects and Those with Dry Eye |</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Original Count</th>
<th>Normal</th>
<th>Dry Eye</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8</td>
<td>4</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>6</td>
<td>35</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>87.5</td>
<td>12.5</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>14.6</td>
<td>85.4</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Cross-validated (a)
- Normal | 28 | 4 | 32 |
- Dry eye | 8 | 33 | 41 |
- % | 87.5 | 12.5 | 100.0 |
- Dry eye | 19.5 | 80.5 | 100.0 |

The derived discriminant function from discriminant analysis was applied to all subjects, and the subjects were reclassified as having normal or dry eyes in predicted group membership. In cross-validation, the function derived from all the subjects other than the tested subject was applied to the data from the tested subject, and the predicted group membership was determined. The discriminant function correctly classified 86.3% of the subjects and the cross-validation, 83.6%.
Fluorescein clearance measures have been reported to give equivalents of these tests have been, or are being, developed. In clinical practice. However, several more clinically applicable tests used in this study are expensive and not widely available than osmolarity if used singly for the diagnosis of dry eye. But, significantly if assessments of tear turnover (production), evaporation, and osmolarity are included in a diagnostic battery of tests. Also, tear physiology tests are repeatable and reliable, unlike the currently used diagnostic tests. It has been shown previously that there is a low site-to-site and day-to-day intra-individual variation in the results of evaporation. Fluorophotometry and its simpler alternative, the fluorescein clearance test, are considered to be the gold standard for measuring TTR. It is therefore reasonable to argue that tear physiology tests can advance our ability to diagnose dry eye disease.

The determination of the effectiveness of any diagnostic test is made by considering the sensitivity and specificity of the test, which are characteristics of the test itself, and the predictive value of the test, which is influenced by the prevalence of the disease. In the case of dry eye disease which has a prevalence of ~15% in general populations of Caucasians, these measures of effectiveness apply to an extent. As illustrated in Tables 1 and 3, the choice of a test and its cutoff value for diagnosis of dry eye changes the relative values of sensitivity and specificity. Physiological factors and the seriousness of the condition must be taken into account when choosing a test and its cutoff value. In diagnostic tests for dry eye, it is preferable to optimize overall accuracy and combine this with high sensitivity (and NPV).

On the basis of the results of this study (Table 4), the most appropriate single test for dry eye diagnosis would be osmolarity (giving overall accuracy of 79%, sensitivity of 78%, and NPV of 73%) and in parallel a combination of TTR, evaporation, and osmolarity (giving 86% overall accuracy, a 100% sensitivity, with 100% NPV). For a screening test for dry eye, the same single and combined tests would be chosen, with the combined test having improved sensitivity over the single test (100% vs. 80%). The choice of a weighted combination derived from discriminant function analysis would give comparable sensitivity, NPV, and (slightly) improved overall accuracy to the parallel combination of tests for use in diagnosis but would be less effective as a screening test because of its reduced PPV. The test results in the present study compare very favorably with the effectiveness of other objective tests, as reported in the literature. From Tables 1 and 4, it can be seen that tear physiology tests are more effective in diagnosing dry eye than the commonly used tests, such as Schirmer and TBUT. The best diagnostic test in the literature would appear to be the lysozyme assay, yielding the highest reported overall accuracy combined with high sensitivity and NPVs. However, this study involved patients with severe dry eye and was probably influenced by significant spectrum bias, leading to overestimation of the test’s sensitivity. In the present study, patients classified as having general dry eye had borderline dry eye and those with Sjögren’s syndrome and GVHD had moderate to severe dry eye, according to the clinical criteria, making the dry eye sample more inclusive of the general dry eye population. Therefore, the recommended cutoff values of the tear physiology tests in this study are suitable for diagnosing less severe forms of dry eye. However, it should be noted that several severe cases of aqueous-deficiency dry eye were included in our sample, and this may have led to the higher weighting of TTR in the discriminant function in comparison to tear evaporation. Also, the sample was from a secondary/tertiary eye care center. Correct diagnosis of moderate to severe dry eye is more essential in such settings, as misdiagnosis can have a huge impact on QOL and productivity of a patient. Further diagnostic mechanisms are essential for diagnosing a milder form of the disease within primary eye care.

It must be remembered that the results of diagnostic efficacy in this and previous studies (Table 1) are generally affected by selection bias, because efficacy was assessed on the data from the patient samples on which the cutoff values for diagnosis were derived and not from an independent sample of new patients. However, as this applied to all the single and combinations of tests compared, the findings of relative effectiveness in this study are valid. Another difficulty with studies of diagnostic efficacy in diseases with no gold standard is that the classification of patients by any new test is compared with...
a potentially flawed standard. In this case the comparison is with the ophthalmological diagnosis based on conventional clinical tests (Schirmer, TIBUT, vital staining and auto antibodies). This problem will remain in the diagnosis of dry eye, as in many other diseases, until a gold standard is defined.

Blepharitis, a condition mainly caused by bacterial infections and/or dysfunction of the meibomian gland, has been found to be associated with dry eye. However, as blepharitis is an independent clinical entity that shares only some of the signs and symptoms of dry eye, patients with this disease were excluded from the study.

Another problem of diagnosis in dry eye is the issue of subtyping. The function derived by discriminant analysis for separating dry eye from normal was found to be more accurate than any of the individual tests or parallel or series combinations of tests, as it had higher sensitivity, specificity, and overall predictive values. Its effectiveness is similar to that previously reported by Craig et al. (1995:36:ARVO Abstract 4823) in discriminating between normal subjects and patients with dry eye associated with rheumatoid arthritis. The previous study discriminating between normal subjects and patients with dry eye, reported by Craig et al. (1995:36:ARVO Abstract 4823), was excluded from the study.

36. Vitali C, Moutsopoulos HM, Bombardieri S. The European commuity study group on diagnostic criteria for Sjogren’s syndrome:


44. Craig JP. Tear physiology in the normal and dry eye. 1995.

45. Farris RL. Tear osmolarity: a new gold standard?


