New Korean Guideline for the Diagnosis and Management of Dry Eye Disease

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ABSTRACT

New Korean guidelines for the diagnosis and management of dry eye disease were developed based on literature reviews by the Korean Dry Eye Guideline Establishment Committee, a previous dry eye guideline by Korean Corneal Disease Study Group, a survey of Korean Dry Eye Society (KDES) members, and KDES consensus meetings. The new definition of dry eye was also proposed by KDES regular members. The new definition by the regular members of the KDES is as follows: "Dry eye is a disease of the ocular surface characterized by tear film abnormalities and ocular symptoms". The combination of ocular symptoms and an unstable tear film (tear break-up time <7s) was considered as essential components for the diagnosis of dry eye. Schirmer test and ocular surface staining were considered adjunctive diagnostic criteria. The treatment guidelines consisted of a simplified stepwise approach according to aqueous deficiency dominant, evaporation dominant, and altered tear distribution subtypes. New Korean guidelines can be used as a simple, valid, and accessible tool for the diagnosis and management of dry eye disease in clinical practice.

KEYWORDS: Dry eye disease; Diagnosis; Treatment; Clinical guideline
Introduction

Dry eye has historically been thought to be due to inadequate tear production or impaired tear film stability. In 1995, the National Eye Institute/Industry Workshop defined dry eye as follows: "Dry eye is a disorder of the tear film due to lack of tears or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort". [1] It is noteworthy that this definition used the term "disorder" rather than "disease". In 2006, the Delphi panel proposed a new term for dry eye disease (DED) as “dysfunctional tear syndrome (DTS)”, and a diagnosis of severity based on symptoms and signs. [2] In 2007, a consensus for dry eye was made at Dry Eye WorkShop (DEWS) supported by the Tear Film and Ocular Surface Society (TFOS). First TFOS DEWS definition was as follows: “Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.” [3] The original TFOS DEWS was the first to address that dry eye was a disease entity, not a disorder. [3] The Delphi panel and TFOS DEWS recommended treatment guidelines based on severity level of dry eye. [2, 4] In 2017, the definition of dry eye in TFOS DEWS II was determined as follows: “Dry eye is 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.” [5] The etiologic classification of DED consisted of the two predominant and non-mutually exclusive categories; aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE) in TFOS DEWS II. [5] Additionally, staged management was suggested rather than severity based management of dry eye. [6] Meanwhile, Asia Dry Eye Society (ADES) emphasized the importance of tear film instability in dry eye and in 2017 defined dry eye as follows: “Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage.” [7] ADES also reported dry eye classification based on target tear components (aqueous tears, lipid layer, secretory mucin, and membrane associated mucin) and recommended tear film-oriented therapy (TFOT). [7, 8]

Clinical guidelines for dry eye in South Korea were first established in 2014. [9] Korean Corneal Disease Study Group (KCDSG) published guidelines for the diagnosis according to the symptoms and signs of dry eye based on the severity (Levels I-IV) and recommended treatment methods according to the level. [9] (Table 1 and 2) The Korean Dry Eye Society (KDES) was founded in August 2016 to contribute to dry eye research, international academic interaction, and public education and awareness, and 60 regular members were initially elected among
Korean cornea specialists in 2017. Since the establishment of the first Korean Dry Eye Guideline, [9] the extensive revision of the existing guideline has become necessary due to changes in dry eye treatment patterns, the release of new treatment drugs, various diagnostic devices, and insurance issues.

The purpose of this study was to present concise and intuitive clinical guidelines for dry eye for Korean ophthalmologists. The Korean Dry Eye Guideline Establishment Committee (DH Kim, Y Eom, CH Yoon, HS Lee, HS Hwang, JH Kim, T Kim, JS Song, and KC Yoon) in KDES developed the new dry eye guidelines based on literature reviews, a survey of KDES members, and KDES consensus meetings.

**Proposed New Definition of Dry Eye**

Dry eye disease was defined in a previous Korean guideline as “a disease of the ocular surface that is associated with tear film abnormalities.” [9] The concise definition, mention of symptoms, and addition of the ocular surface and tear film were derived from face-to-face discussions between regular members of KDES. The final consensus meeting was held in Busan on 11th February, 2023, and the new definition agreed upon by the regular members of the KDES is as follows: "Dry eye is a disease of the ocular surface characterized by tear film abnormalities and ocular symptoms". Ocular symptoms include dryness, discomfort, foreign body sensation, pain, blurring, and visual fluctuation. [9] KDES members agreed that ocular surface inflammation and tear film instability are major contributors to dry eye. In addition, tear hyperosmolarity was agreed to be an important element in the pathogenesis of DED. Fifty-eight percent and thirty-six percent of KDES members responded that tear film instability and ocular surface inflammation were the most important causes of dry eye, respectively. Tear film abnormalities included tear film instability due to evaporation and aqueous deficiency and altered tear distribution due to various abnormal anatomical changes around the ocular surface.

**Proposed Diagnosis of Dry Eye**

The practical diagnostic guideline for dry eye according to the new definition was discussed at the consensus meetings in 2017, 2018, 2019 and 2023. All KDES members agreed that a dry eye patient should be diagnosed if he or she has at least one symptom and one objective sign. Fluorescein tear break-up time (TBUT), Schirmer's
test, and ocular surface staining were the most commonly performed tests to diagnose dry eye in KDES member survey. Members responded that TBUT was the most important finding in tear film instability among TBUT, non-invasive tear breakup time (NIBUT), and tear breakup patterns. In the TFOS DEWS II diagnostic test battery, NIBUT<10s is included as a diagnostic criterion, and TBUT can be used only when NIBUT is not available. [10] ADES sets the criterion for unstable tear film as TBUT ≤5s. [7] Meanwhile, the multinational Ocular Dryness Disease Severity (ODISSEY) European Consensus Group established a practical algorithm for severe dry eye in 2014. [11] Ocular symptoms (OSDI≥33) and ocular surface staining (corneal fluorescein staining≥3) were primary diagnostic criteria. [11] The consensus among KDES members regarding the diagnosis of dry eye is as follows. 1) the cut-off value of TBUT needs to be adjusted in the range of 5-10 seconds, 2) Schirmer test < 10mm has low sensitivity, 3) the mixed form of ADDE and EDE needs to be expressed, and 4) the subtype of altered tear such as lid abnormalities should be addressed. Additionally, The KDES member survey identified TBUT<7s as the most appropriate criterion for tear film instability in South Korea. Fifty-five percent of all KDES members agreed that symptoms and TBUT (TBUT<7s) should be included as essential criteria in the Korean Dry Eye Guideline, and Schirmer test and ocular surface staining are considered as adjunctive criteria. Accordingly, a diagnostic battery as shown in Figure 1 was determined. The combination of ocular symptoms and an unstable tear film (TBUT<7s) is considered sufficient to make a diagnosis of dry eye. Decreased tear volume (Schirmer's test <10 mm) and ocular surface staining were reported as secondary diagnostic factors (+). Based on the results of tear volume, TBUT, and tear distribution, dry eye subtypes are classified as aqueous deficiency dominant, evaporative dominant, and altered tear distribution in new Korean dry eye guideline. (Figure 1) Sjögren's syndrome and meibomian gland dysfunction (MGD)-related dry eye are representative of the aqueous-deficient and evaporative-dominant subtypes, respectively. (Figure 1) Altered tear distribution subtype include lid abnormality, conjunctivochalasis, and abnormal blinking. (Figure 1) Although the TFOS DEWS II definition included corneal neuropathic pain, [5, 10] the KDES members decided to exclude neuropathic pain from the diagnosis of dry eye due to no objective sign. In addition, it was agreed that the following are appropriate as auxiliary elements of the Korean Dry Eye Diagnosis Guideline: 1) dry eye symptom questionnaire, 2) strip meniscometry, 3) tear meniscometry using optical coherence or slit lamp biomicroscope, 4) conjunctival impression cytology, 5) corneal sensitivity, 6) tear osmolarity, 7) tear MMP-9 level, 8) tear film interferometry, and 9) meibography.

Proposed Treatment Guideline of Dry Eye
Previous guideline by KCDSG presented treatment methods according to the level of severity. [9] Most of the KDE members mentioned that the previous guidelines were not appropriate for the recent clinical setting, as level 2 drugs were used preemptively in some of the level 1 patients, and sometimes level 3 treatments were used if necessary. KDE members agreed that it is appropriate to include the following as Korean Dry Eye Treatment Guidelines: 1) education and environmental modifications, 2) elimination of offending medications, 3) artificial tears and ointment, 4) lipid-containing agent, 5) lid hygiene and warm compresses, 6) dietary modifications, 7) topical corticosteroids, 8) topical immunomodulatory drugs (cyclosporine A, etc.), 9) topical secretagogues (diquafosol, rebamipide, etc.), 10) dietary modifications, 11) blood derivatives (autologous serum, platelet-rich plasma, etc.), 12) therapeutic contact lens, 13) punctal occlusion, 14) moisture goggles, 15) surgical approaches, 16) thermal pulsation therapy (Lipiflow, iLux, etc.), and 17) intense pulsed light (IPL). In addition, there has been enough discussion about which of stepwise and subtype-based treatment would be appropriate, and how many steps would be appropriate. It was also mentioned that clinical procedures such as punctal occlusion and IPL should be classified separately from general steps. Forty-four percent of KDE members supported simplified stepwise subtype-based treatment guideline. The support rates for the 4-step stepwise subtype-based treatment and the stepwise treatment without subtype discrimination were 34 and 18%, respectively. Accordingly, the Korean Dry Eye Guideline Establishment Committee established a two-step stepwise treatment guideline based on the new dry eye subtype, and the procedures were separately classified as shown in Figure 2. The treatment guideline is simplified to step 1 or 2, and the subtype-based treatments are suggested for dry eye subtype in new Korean dry eye diagnostic guideline. This guideline emphasizes various treatment options can be used initially, as needed.

Discussion

The new Korean guidelines for dry eye are simple, intuitive, and easy to use in clinical practice. Previous and contemporary evidence-based concepts in the diagnosis and management of dry eye were considered in developing these guidelines. [1-11] The new definition of dry eye by KDE is “Dry eye is a disease of the ocular surface characterized by tear film abnormalities and ocular symptoms”. Ocular symptoms and tear film instability (TBUT<7s) are primary criteria in diagnosing dry eye, and Schirmer’s test and ocular surface staining are
classified into auxiliary components. There are three subtypes of dry eye in this new guideline: 1) Aqueous Deficiency Dominant, 2) Evaporative Dominant, and 3) Altered Tear Distribution. These subtypes can cover all patients with dry eye except of corneal neuropathic pain. The new treatment guidelines are simplified to step 1 or step 2 according to the subtypes of dry eye, and the clinical procedure has been separated. Table 3 compared KDES, ADES, and TFOS DEWS II clinical guidelines of dry eye. We think that the new Korean dry eye guideline is simple, intuitive, understandable, and comprehensive compared to ADES and TFOS DEWS II guidelines.

Ocular symptoms and tear film instability are only included in the new Korean definition of dry eye. While the TFOS DEWS II and ADES definitions included the term "multifactorial," the new Korean definition did not. Because many studies about dry eye have already shown that dry eye is a multifactorial disease and all KDES members already accept this as a matter of course, we did not use this term for concise expression. [12-26] Previously, ocular surface staining was considered an essential part of diagnosis. [1, 2] However, ocular surface staining is not required for the definitive diagnosis of dry eye. In a previous Japanese clinical study, 76% of dry eye patients had a negative ocular surface staining, but 95% of them had an unstable tear film (TBUT ≤ 5s). [7, 27] Retrospective medical records of 1,691 Korean patients with dry eye showed that 47.5% of them were Level I with minimal ocular surface staining. [9] Eom et al.’s study also demonstrated that 54.4% of 158 Korean patients with dry eye were also Level I. [28] Mean TBUT values in patients with Level I were 3.2 ± 1.5s. Additionally, KDES members agreed that tear film abnormality is a term that could include the concepts of unstable tear film and altered tear distribution. Accordingly, ocular symptoms and tear film abnormalities are considered to be sufficient to constitute the definition of dry eye.

Previous diagnostic guideline by KCDSG was modified from the dry eye severity grading scheme of the DEWS. [3] and ocular surface staining was weighted in grading the disease severity. [9] Ocular signs might include conjunctival injection, lid abnormalities (blepharitis, trichiasis, keratinization, and symblepharon), and tear film abnormalities (debris, decreased tear meniscus, and mucus clumping), [9] however these signs are not considered in the grading of dry eye in previous Korean guideline. Since grading schemes were excluded from the new Korean guidelines, simple and clear diagnostic criteria were required. As mentioned above, there are many dry eye patients who demonstrate no ocular staining in Korea. There are wide intra-patient variations in the Schirmer-1 test, and the test is not routinely performed on every dry eye patient in the office. [9] Therefore, most KDES members agreed that tear breakup time was the most meaningful sign in dry eye. NIBUT which is a diagnostic criterion in TFOS DEWS 2, has a disadvantage because all Korean ophthalmologists cannot apply it. Fluorescein tear breakup time (TBUT) is the most widely used sign that can be easily checked in the office, although the variability in
the volume of fluorescein or observer may affects TBUT. It is known that NIBUT was significantly longer than TBUT in patients with dry eye and the mean difference between NIBUT and TBUT was 2.0s (95% CI: 1.1-3.4s). Therefore, TBUT<7s is considered as the most appropriate diagnostic sign for dry eye in KDES member survey. The combination of ocular symptoms and TBUT<7s is considered sufficient to cover overall dry eye patients in Korea. Meanwhile, ADES guideline classified dry eye as aqueous deficient, increased evaporation, and decreased wettability dry eye. [13] KDES members agreed that although decreased wettability may be an important factor in dry eye, a major drawback is that there is still no method to easily measure it in the clinical setting. It was also commented that the ADES diagnostic guidelines do not sufficiently include entities for altered tear distribution. Accordingly, KDES guideline classified dry eye subtypes as aqueous deficiency dominant, evaporation dominant, and altered tear distribution.

TFOS DEWS II management reported that many treatment options for dry eye are poorly supported by Level 1 studies. [6] Nevertheless, environmental and dietary modifications, elimination of offending factors, artificial tears, ointment, topical agents including corticosteroids, secretagogues, immunomodulators, and blood derivatives, lid hygiene, warm compress, punctal occlusion, intense pulsed light, and thermal pulsation therapy, etc. are helpful for dry eye patients. [6, 8, 9, 30] Previous treatment guideline by KCDSG presented a stepladder approach according to severity level. [9] However, because of the heterogeneity in characteristics of dry eye patients, it is important for ophthalmologists to compound various treatments appropriately for individual dry eye patients. In recent KDES consensus meetings, most KDES members favoured a stepwise treatment guideline such as the TFOS DEWS II, [6] but about half of the members supported the more simplified guidelines that take into account the subtypes of dry eye according to the new diagnostic guideline. In the clinical setting in Korea, the procedure can also be performed preemptively, so the procedural part is separated. Topical secretagogues such as diquafoisol and rebamipide are not approved in the United States, making them clinically difficult to prescribe to dry eye patients. On the other hand, topical immunomodulators such as topical cyclosporine and lifitegrast are not approved in Japan. Both topical secretagogues and immunomodulators can be prescribed for dry eye patients only in South Korea. We believe that an immediate and effective treatment for dry eye patients can be achieved under the new simplified treatment guideline.

Conclusion
the new Korean dry eye guideline can be used as a simple, valid, and accessible tool for the diagnosis and management of dry eye in clinical practice, even for general ophthalmologists. We are convinced that the guideline of this paper may be used as a basis for further discussions for the diagnosis and management of dry eye.

CONFLICTS OF INTEREST

None of the authors had any proprietary or conflicting interests in any of the methods or materials described in this article.

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REFERENCES


Figure legends

Figure 1. A new diagnostic battery of dry eye by Korean Dry Eye Society

Figure 2. Treatment guideline based on the new dry eye subtype by Korean Dry Eye Society
Table 1. Korean Corneal Disease Study Group guidelines for the diagnosis of dry eye disease

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
<th>Level IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular symptoms</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
<td>Daily life limited</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
<td>Daily life limited</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Signs*</th>
<th>Staining score†</th>
<th>Grade II</th>
<th>Grade III</th>
<th>&gt;Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBUT</td>
<td>Variable</td>
<td>6-10 sec</td>
<td>1-5 sec</td>
<td>Immediate</td>
</tr>
<tr>
<td>Schirmer-1</td>
<td>Variable</td>
<td>&lt;5 to ≤10 mm</td>
<td>&lt;2 to ≤5 mm</td>
<td>&lt;2 mm</td>
</tr>
</tbody>
</table>

Positive ocular signs may include conjunctival injection, lid abnormalities (blepharitis, trichiasis, keratinization, and symblepharon), and tear film abnormalities (debris, decreased tear meniscus, and mucus clumping). However, these findings are not considered in the grading of disease severity; †Oxford system.
<table>
<thead>
<tr>
<th>Severity level</th>
<th>Treatment recommendation*</th>
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</table>
| Level I        | Patient education, environmental control  
Check systemic medications (ex. anti-histamines, anti-depressants, or beta-blockers) Fluid intake, psychological support  
Artificial tears (preserved or non-preserved)  
4 Times a day, or incremental according to patients’ symptoms Allergy treatment, when necessary |
| Level II       | Non-preserved artificial tears  
Anti-inflammatory therapy (ex. topical Cyclosporine A or topical corticosteroids) Oral supplements; essential fatty acid (ex. omega-3-fatty acid or gamma linoleic acid) Gels/ointment (may be used in level I patients, when necessary) |
| Level III      | Autologous serum  
Oral tetracycline (may be used in level II patients) Punctual plug/occlusion  
Contact lenses, goggles |
| Level IV       | Surgery  
Systemic anti-inflammatory medication |

*Accompanying ocular surface disease such as blepharitis or ocular allergies should be treated for any level.
Table 3. Comparison of Korean Dry Eye Society (KDES), Asia Dry Eye Society (ADES), and Tear Film and Ocular Surface Society (TFOS) Dry Eye WorkShop (DEWS) II guidelines for dry eye

<table>
<thead>
<tr>
<th>Parameter</th>
<th>New Korean dry eye guideline by KDES</th>
<th>ADES diagnostic guideline</th>
<th>TFOS DEWS II guideline</th>
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<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Dry eye is a disease of the ocular surface that is characterized by tear film abnormalities and ocular symptoms.</td>
<td>A multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage.</td>
<td>A multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.</td>
</tr>
<tr>
<td><strong>Diagnostic criteria</strong></td>
<td>Ocular symptoms &amp; decreased TBUT (TBUT&lt;7s)</td>
<td>Ocular symptoms &amp; decreased TBUT (TBUT≤5s)</td>
<td>Ocular symptoms &amp; one objective sign (ocular surface staining, decreased NIBUT or TBUT[&lt;10s], decreased Schirmer-1 test [≤ 10 mm])</td>
</tr>
<tr>
<td><strong>Treatment guideline</strong></td>
<td>Simplified stepwise subtype-based approach</td>
<td>Tear film oriented therapy</td>
<td>Stepwise approach</td>
</tr>
</tbody>
</table>