Definition and Diagnostic Criteria of Dry Eye Disease: Historical Overview and Future Directions

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The first comprehensive definition of DED was published in 1995 on the basis of consensus from the National Eye Institute (NEI) Industry Working Group on Clinical Trials in DED.1 In the report, DED is defined as follows:

“Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.”

The definition clearly states that changes in the tear film are the cause of DED, which subsequently cause irritating symptoms and epithelial abnormalities. It also suggests that tear deficiency and excessive evaporation are the major causes of DED. This concept was reflected in the classification in this publication. DED was divided into two major categories involving tear deficient and evaporative, and then was further subclassified into a range of intrinsic and extrinsic causes. It is important that the definition uses the term “disorder” and not “disease.” This definition and classification scheme have influenced subsequent DED studies and clinical approaches, including the Preferred Practice Pattern reported by the American Academy of Ophthalmology in 20133 and others.3–5

The second major progress was made in the early 2000s, and the results were published in the report of the International DEWS. In 2005, the report states:

“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.”

This definition proposes several differences from the previous NEI report. First, DED was considered to be a disease caused by abnormalities in either tears or the ocular surface. Tears were not considered to be the sole cause of DED, and changes in the epithelium could cause abnormalities in tears. In this regard, DED was considered to be a dysfunction of the integrated functional unit comprising the lacrimal glands, ocular surface, eyelids, and sensory and motor nerves.8 Second, DED might cause visual disturbances.9–11 Third, increased osmolarity and ocular surface inflammation were included in the DED definition.12–14 Inclusion of these pathogenic factors in the definition of DED was new and contrasted with previous NEI reports. The definition caused controversy among researchers regarding whether the inflammation and hyperosmolarity had a causal or causal relationship with DED. The classification system of the DEWS report basically revised the 1995 NEI report, with aqueous-deficient DED and evaporative dry eye as the major two subtypes (Fig. 1). Aqueous-deficient was further classified into Sjögren and non-Sjögren categories. Evaporative dry eye was subclassified into intrinsic and extrinsic categories, and they were further classified as resulting from a range of causes.

In a recent revision, published in 2017, dealing with the DED definition and classification in the DEWS II report, the following definition of DED is provided:

“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.”

This definition is basically a minor revision of DEWS, which used the term “homeostasis of the tear film” to suggest that a
FIGURE 1. Major etiological causes of DED proposed by the DEWS of the TFOS 2006. The left box illustrates the influence of the environment on risk of an individual developing DED. Note that aqueous-deficient dry eye has two major subtypes: Sjögren and non-Sjögren syndrome DED. Evaporative dry eye is subdivided into intrinsic and extrinsic causes, and can be further classified into subgroups. Reprinted with permission from Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15:276–283. © 2017 Elsevier Inc.

FIGURE 2. Tests to diagnose and monitor DED proposed by DEWS II of the TFOS. The test starts with screening questions for DED, followed by a series of examinations, such as slit-lamp biomicroscopy, osmolarity, BUT measurement, and staining tests. Then, further tests for subtype classification, including meibomian gland/lid margin changes and tear volume examinations, are performed. Reprinted with permission from Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017;15:539–574. © 2017 Elsevier Inc.
In the diagnosis report, DEWS II listed a variety of diagnostic tests, which included questionnaires, tear film tests, epithelial abnormalities, and others. Although the report did not propose specific diagnostic criteria, it indicated the most appropriate (efficacious) tests to diagnose and monitor DED (Fig. 2).

There are other groups that proposed definitions and/or diagnostic criteria. In 2006, a panel of international DED specialists established a consensus using the Delphi approach. In this report, the use of “dysfunctional tear syndrome (DTS)” instead of DED was proposed. The report concluded that treatment strategies should rely on symptoms and signs rather than tests. The panel defined clinical signs to be considered in assessing the severity of DTS, which were used to develop a severity-based treatment algorithm. A major aim of the report was to establish a treatment algorithm; no specific definition or diagnostic criteria were suggested.

The Korean Corneal Study Group suggested a DED definition and treatment algorithm in 2014. In the report, they define DED as “a disease of the ocular surface that is associated with tear film abnormalities.” They proposed diagnostic criteria involving one or more symptoms (either irritating or visual symptoms), plus at least one objective sign including either ocular surface staining or tear film instability.

A European group also proposed diagnostic criteria for severe DED. In this report, Baudouin and associates proposed that patients with a high ocular surface disease index (OSDI; >33) and increased corneal fluorescein score (≥3) were considered to have severe DED, whereas an OSDI <33 with a fluorescein score ≥3, OSDI ≥33 with a fluorescein score = 2, or an OSDI ≥33 with a fluorescein score <2 were considered as severe DED if there were different DED findings, such as impaired corneal sensitivity, a breakup time (BUT) <5 seconds, and additional criteria (Fig. 3).

**Recent Progress Regarding the Concept of DED in Japan**

The first definition and diagnostic criteria of DED were proposed by the Japan Dry Eye Society (JDES) in 1995, the same year that the NEI report was published. In this report, DED is defined as “Ocular surface epithelial damage caused by qualitative or quantitative abnormalities of tears.” Diagnostic criteria were also proposed (Table 1). The definition and criteria had some similarities to those proposed by the NEI report; however, there were two distinct differences. First, the Japanese definition did not include the presence of subjective symptoms, based on the observation that end-stage DED patients with keratinized ocular surfaces seldom complained of irritating symptoms. Second, the Japanese dry eye guideline proposed cutoff values involving alterations in tears (Schirmer’s I test value ≤5 mm, cotton thread test ≤10 mm, or a BUT ≤5 seconds) as well as epithelial damage (fluorescein score ≥1 point [maximum = 3] or Rose Bengal staining scores ≥3 points [maximum = 9]).

The second version of the Japanese dry eye definition and criteria was published in 2006. In the report, dry eye is defined as follows: “Dry eye is the chronic disease in tears and corneal/conjunctival epithelia caused by various factors. It may accompany irritating symptoms and/or visual disturbances.” This definition differs from the previous version in that abnormalities in tears and ocular surface epithelia were considered to be reciprocal, forming a vicious cycle. It also suggests that multiple intrinsic or extrinsic factors contribute to the development of DED, including decreased tear secretion, Meibomian gland dysfunction, and wearing of contact lenses. The Japanese 2006 report included diagnostic
Definition and Diagnostic Criteria of Dry Eye Disease

Table 1. Diagnostic Criteria of the JDES, 1995 Version

<table>
<thead>
<tr>
<th>Category 1. Abnormalities of Tear:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Schirmer's test I ≤ 5 mm</td>
</tr>
<tr>
<td>2. Cotton thread test ≤ 10 mm</td>
</tr>
<tr>
<td>3. Breakup time ≤ 5 seconds</td>
</tr>
</tbody>
</table>
凡其之一表明阳性。

<table>
<thead>
<tr>
<th>Category 2. Ocular Surface Epithelial Damage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fluorescein score ≥ 1 point (maximum of 3 points)</td>
</tr>
<tr>
<td>2. Rose Bengal score ≥ 3 points (maximum 9 points)</td>
</tr>
</tbody>
</table>
凡其之一表明阳性。

诊断为DED:
1. 明显性干眼症（category 1和2均阳性）
2. 可能性干眼症（category 1或2阳性）

图4. DED诊断标准由JDES（2006版）提出，包括三个成分：主观症状、泪液功能和毒性染色测试。所有三项均阳性者被归类为“明显性干眼症”，而仅两项阳性者则被归类为“可能性干眼症”。

Awareness of “Short BUT-Type Dry Eye”

自第二种干眼症定义和标准自其发布以来，许多日本DED专家已认识到所称为“短BUT型干眼症”（sBUT干眼症）的重要性。这种类型的DED由泪液缺乏引起的积极症状和泪液BUT（5秒）的降低所致，但无明显性病变。据报告，441名561名办公室工作人员（78.6%）的泪液BUT（5秒）降低，约有50%被归类为sBUT干眼症。23,24 前期研究曾报道短泪液BUT干眼症的严重程度与典型水肿不足干眼症相当。25–27 尽管sBUT干眼症在2006年被定义为“可能性干眼症”，但这些发现表明sBUT干眼症应以类似方式管理，即“明显性干眼症”。Tsubota曾进一步详细阐述sBUT干眼症。

The Development of 2016 Dry Eye Definition

2016年，干眼症定义和标准的修订版由JDES提出，旨在与亚洲其他眼科专家共享泪液不稳定的重要性。自亚洲干眼症学会（ADES）在2012年成立后，包括中国、韩国和日本的眼科干眼症专家进行了讨论，发布了ADES干眼症定义和标准的共识。29 在这份报告中，DED定义为，“干眼症是一系列因素导致的泪液不稳定，引起各种症状和/or视觉障碍，可能伴有眼表损伤。”这一定义清楚地表明了泪液不稳定是DED的核心成分。除了可能存在主观症状，包括视觉障碍外，眼表损伤已不再重要。新标准。

2006 Japanese Diagnostic Criteria for Dry Eye

1. Subjective Symptoms
2. Tear Functions
   1) Schirmer test I ≤ 5 mm (5 minutes)
   2) Tear film break up time (BUT) ≤ 5 seconds
   * Subject who meets either criteria 1 or 2 is considered to fulfill that criteria.
3. Vital Staining
   Lissamine green, Rose Bengal, fluorescein staining *
   * A staining score of more than 3 points out of 9 is considered to be positive.

图4. DED诊断标准由JDES（2006版）提出，包括三个成分：主观症状、泪液功能和毒性染色测试。所有三项均阳性者被归类为“明显性干眼症”，而仅两项阳性者则被归类为“可能性干眼症。”
were also published along with the ADES/JDES definition. According to the criteria, patients were considered to have DED when they had DED symptoms and decreased BUT (≤5 seconds). Neither Schirner’s value nor the presence of epithelial damage was a part of the criteria.

As the new dry eye definitions/criteria of the ADES/JDES report are highly dependent on BUT measurements, training in the proper use of this test is of key importance. BUT measurements can sometimes be unreliable if an excessive amount of fluorescein solution is used, or a solution that may alter the tear film quality. Assessment of the appropriate cutoff value of the BUT may also be required. The JDES/ades report proposed a cutoff value of ≥5 seconds, whereas the DEWS II report proposed a cutoff value of >10 seconds.

**Comparison of the Current Definition/Criteria Between DEWS II and ADES/JDES**

The dry eye definitions proposed by the DEWS II and ADES/JDES have both similarities and differences (Table 2). Both definitions share the similar concept that tears and ocular surface epithelia form a communal environment, and disruption of the environment results in the development of DED; however, the core concepts of DED differ. The DEWS II definition included multiple potential pathogeneses in DED, including hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities as well as tear film instability. The DEWS II report emphasized the pathophysiology of DED, whereas the ADES/JDES report emphasized the diagnostic value of the physician’s observations. The ADES/JDES report therefore placed the emphasis on “visible changes,” whereas the DEWS II report placed the emphasis on “invisible changes.” The differences could have been the result of differences in committee members. The DEWS II committee was composed of both clinicians and researchers, whereas the ADES/JDES committee was composed exclusively of clinicians.

**Future Directions**

There has been rapid progress in basic and clinical research on DED over the past several decades, which has been reflected in changes in the definition and diagnostic criteria of DED. It should be noted, however, that all of the previous reports were generated based on expert consensus. Although some used systematic methods for decision making, such as voting or Delphi methods, they are regarded as “authority-based” rather than “evidence-based.” In addition, some of the reports had financial support from pharmaceutical companies, which may have influenced the direction of the discussion. Further progress in dry eye research would generate more comprehensive and clinically relevant dry eye definitions and criteria.

The JDES recently proposed the concept of “tear film-oriented diagnosis (TFOD)” and “tear film-oriented treatment (TFOT)” (see a later chapter). In this concept, it is important to distinguish which tear film components (lipid, aqueous tear, and mucins) are compromised, and subsequent treatments should use to compensate for the corresponding abnormal components. Observation of the tear film breakup pattern may provide important insight into identifying abnormal components. This concept is discussed in detail by Yokoi and Georgiev. Poor correlations between signs and symptoms in DED have been a challenging issue in DED research. Many recent studies have emphasized the importance of neurosensory abnormalities in DED, as indicated in the DEWS II report; however, no clinically useful method for assessing this component is currently available. The goal of DED treatment is to alleviate the patient’s discomfort, so future research should be directed toward developing diagnostic measures that correlate with the patient’s symptoms. The current definitions and criteria of DED should then be revised in accordance with the progress of such studies.

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**References**


