厚生労働科学研究費補助金（医療技術評価総合研究事業）

# 世界ドライアイ診断基準の作成と我が国への応用に関する研究

平成18年度　総括研究報告書

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（総括）研究報告書

# 世界ドライアイ診断基準の作成と我が国への応用

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研究要旨

１９９５年に第１回目の世界ドライアイワークショップにてドライアイの定義と分類が定められた。それより１０年が経過し、世界中のドライアイ研究者の間よりこれを見直そうという動きが２００４年より具体化し、世界ドライアイワークショップが結成（DEWS）された。定義と診断基準に限らず、検査、疫学調査、基礎研究、治療の各分野にわたる広い範囲で現在にいたるまで検討が行われてきている。DEWSの方向性もかなり固まってきたことでその流れを参考しながら我が国の新しい定義と基準を作成することになった。
２００６年度より世界ドライアイワークショップで提案された世界のドライアイ定義と診断基準は日本ドライアイ研究会にてさらに検討され、日本のドライアイの定義は““ドライアイとは様々な要因による涙液及び角結膜上皮の慢性疾患であり、眼不快感や視覚障害を伴う”という“自覚症状ならびに視覚障害”の概念が含まれるものに変わった（別紙１）。ここ１０年間ドライアイの不定愁訴が中心となる新しいタイプのドライアイ（コンピューター作業によるものなど）が非常に多くなってきていると言われている。世界ドライアイワークショップで日本におけるドライアイの頻度に関する疫学調査や研究が非常にすくないことや大規模の疫学調査が殆どなされてないことが指摘されている。新ドライアイ定義に自覚症状が含まれたことで疫学調査も調査のみによって行なうことが十分可能となり、ドライアイの頻度をより容易に評価できるようにもなったと思われる。前年度はVDT作業者の会社員におけるドライアイprevalence studyでは３５４９例中男性の２６．９％、女性の４８％に重症のドライアイの自覚症状が存在していることが明らかになった。自覚症状を聴取することには１）疫学的調査、２）ドライアイの診断、３）ドライアイの治療判定などいくつかの目的がある。

## A．研究目的

本研究の目的は以下のように要される：１）ドライアイの不定愁訴を日本ドライアイ診断基準に加え、世界の診断基準との統一性を得る。２）我が国においてドライアイの自覚症状はどれだけ問題になっているか、またその頻度を把握するため、ドライアイの疫学調査を実施する。３）日本に応用できるドライアイの symptom questionnaire(調査表)を作成し、涙液機能検査とともに疫学調査を実施しながら旧ドライアイ診断基準と新診断基準を比較する。４）世界ドライアイワークショップ(DEWS)で決まったドライアイの新診断基準、定義とその分類、また日本のドライアイ疫学調査にて得られた研究結果について医師の知識を高めるため、日本眼科学会、日本ドライアイ研究会が主催するシンポジユームや公開講座を行なう。５）世界ドライアイワークショップの最終報告書を日本語に訳し、ドライアイ研究会やドライアイワークショップウェッブサイトで一般市民向けの情報も提供する。

## B．研究方法

１）２００６年５月４日から６日の間に米国マイアミ市で再度世界ドライアイワショップが開催され、世界における新診断基準が統一され、ドライアイの定義、診断における検査法の、世界におけるドライアイのepidemiology、ドライアイ分野における基礎研究や治療の現状について最終報告の形が決まった。２００６年６月１８日、２００７年２月１日世界ドライアイワークショップ理事会員(Tony Bron, Christophe Baudouin, Murat Dogru, Ilene Gipson, Michael Lemp, Dan Nelson, Kelly Nichols, Steven Pflugfelder, Debra Schaumberg, Janine Smith, David Sullivan, Kazuo Tsubota)国際電話会議が行なわれ、世界ドライアイワークショップ最終報告書のフォーマットと内容が見直され、２００７年４月にThe Ocular SurfaceというTear Film and Ocular Surface Societyの機関誌に出版されることが決定された。DEWSの最終報告書を別紙２にて示す。

２）２００５年度はVDT作業者の会社員におけるドライアイprevalence studyでは３５４９例中

男性の２６．９％、女性の４８％に重症のドライアイの自覚症状が認められた。この研究の対象症例は年齢２０歳以上のものだけだったので２００６年度は若者におけるドライアイprevalence も理解するため３４３３人の高校生を対象に４ヶ所の高校（日大桜ヶ丘高校・男女、志木高等学校・男子、女子高、慶應義塾高等学校-男）でSchaumberg questionnaireにてドライアイ調査が行なわれた。

３）本年度はドライアイの定義は“ドライアイとは様々な要因による涙液及び角結膜上皮の慢性疾患であり、眼不快感や視覚障害を伴う”という“視覚障害”の概念も含まれたため、視機能障害に関する自覚症状を含む新ドライアイ調査表が作成された。新調査表は環境因子、視覚障害、ドライアイの独特な自覚症状の質問がふくまれており、それぞれ日常生活にあたえる影響を評価できるものである（別紙３）。また、ドライアイの重症度スコアーも検出できるようになっている。本調査表を利用し、慶應義塾大学医学部眼科外来に検診およびドライアイ診療にこられる症例を対象に疫学調査を開始した。これら症例にまた涙液機能検査を施行し、旧診断基準と新診断基準によってドライアイのprevalenceはどのように変更されたかという点も検討中である。

Ｃ．研究結果

結果１）世界ドライアイワークショップ最終報告書の要約：

**ドライアイの定義と分類**：世界の新定義は” 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.“となっております（別紙２ページ９）。新定義はドライアイに様々な原因があること、ドライアイは自覚症状、視機能障害を有することを強調している。またドライアイの原因による分類（ページ１１）、発症機序による分類（ページ２０）、ドライアイの重症度による分類（ページ２２）、三つの分類が提案なされている。

**ドライアイの疫学**：ここ10年間世界各国地で実施された疫学調査と各々の国のドライアイの発症率や有病率がまとめられている（ページ２９）。台湾とインドネシアにドライアイの大規模の疫学調査の実施があり、日本にはないことが指摘なされている。またドライアイの様々なリスクファクターが詳細に挙げられている。ここ１０年間ドライアイの様々な疫学調査に使われた問診表の特徴などが詳細にdiscussionされている。

**ドライアイの診断**：ドライアイ診断に用いられる各検査法の特徴、望ましいやりかた、感受性などが詳細に挙げられている（ページ４７）。またどのような組み合わせでこれら検査を施行すると効率よく診断できるかについてもアドバイスが見られる。検査を正しく行なう順位も指摘されている（ページ５１）

**ドライアイ治験や臨床トライアルのデザインとガイドライン**：
ドライアイの臨床治験や臨床studyの望ましい進め方（ページ６６）が挙げられている。また、理想なstudy／治験に含めないと行けない採用と除外基準も書かれている。

**ドライアイの治療**：ここ１０年間確立されているドライアイの様々な治療について、詳細な検討がなされている。またドライアイの重症度によってどのように治療行なえば良いかについての提案が見られる（ページ８３）。

**ドライアイの基礎研究**：ここ１０年間なされているドライアイ分野における殆どの研究、動物実験のまとめが丁寧にあげられ、ドライアイの発症機序、病態についての様々な考え方が挙げられている。

（DEWSの本報告書は現在The Ocular SurfaceというTear Film and Ocular Surface Society機関雑にて印刷中であり、４月下旬までには出版されることになっている。出版される次第、日本語に訳し、日本国内でも公開する予定である。DEWSの報告書のcopyrightはエティスコミュニケーションズが有している）

結果２）高校生におけるドライアイの頻度：
３４３３人の高校生を対象におこなわれた 今回の疫学調査では男性の４．３%、女性の８%は既に医師によるドライアイの診断をうけており、女性では重症のドライアイ自覚症状を有するものは男性に比べ比較的多い（２４．４%）結果となっている（別紙４）。今回医師のドライアイ診断を受けているものならびに診断をうけておらずドライアイの重症の自覚症状を訴えるものにおいてコンタクトレンズ装用がドライアイの有意なリスクファクターになっていることが明らかになっている。本データは高校生におけるドライアイの実態についての初めての大規模の疫学調査である。
結果３）２００６年度は標準となると思われる症状聴取項目がふくまれている問診表が作成された。現在慶應義塾大学眼科にて実施が始まっており、眼鏡処方やドライアイ専門外来にかかった１５例30眼が対象となっている（女性：９人、男性：６人；平均年齢：６８．８歳）。現在の結果では新診断基準にてドライアイ確定例とされたものは全体の５９%、旧診断基準にて確定例とされるものは全体の６９%をしめしており、確定例の診断率がやや低下しているようである。その原因としては生体染色スコアーのカットオッフ値を１点から３点にあげたことが考えられるがまだ症例数がすくないため、強調できない結果となっている。２００７年度は日本予防医学会の協力を得て、予防医学会の検診センター、慶應病院で症例数を３００人に増やして改めて検討する予定である。また、日常生活にドライアイ自覚症状（５１%）ならびに視覚的自覚症状が（４０%）主に影響を与えている結果となっている（別紙５）。ドライアイ確定例となったものではドライアイの重症度スコアは５６．８±１７．１ドライアイ疑い例では４３．２±２１．２となっており確定例では比較的高度な値を認めた。今後重症度スコアーと涙液機能検査の間の相関性を検討する予定である。

Ｄ．考察

１）世界と日本のドライアイの定義は以下のように確立された：

A)”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.“

B) “ドライアイとは様々な要因による涙液及び角結膜上皮の慢性疾患であり、眼不快感や視覚障害を伴う”

世界ドライアイワークショップの動きにより最終報告が作成された。現在この報告書を日本語に訳して公開する準備を進めている。本報告書によりドライアイの診断の効率が高まること、これまで以上にドライアイの病態の理解が深まることが期待される。

２）日本の高校生におけるドライアイの実態についての初めての大規模の疫学調査を実施した。ドライアイの頻度は女性では比較的高く、コンタクトレンズ装用がドライアイの有意なリスクファクターになっていることが明らかになった。

３）ドライアイ疫学調査の標準となると思われる症状聴取項目がふくまれている問診表が作成された。この問診表を用いての疫学調査と涙液機能を測定しているstudyは現在進行中である。この問診表を用いてドライアイが日常生活にあたえる影響を評価でき、ドライアイの重症度スコアーも検出できるようになると思われる。

Ｅ．結論

ドライアイの新診断基準と定義の確立に伴って、ドライアイの診断の効率が高まること、これまで以上にドライアイの病態の理解が深まることが期待される。また本研究によって標準となる症状聴取項目の設定することが期待でき、日本国民におけるドライアイならびにその自覚症状の実態も明らかになってくると思われる。

F．健康危険情報
（分担研究報告書には記入せずに、総括
研究報告書にまとめて記入）

なし

G．研究発表

1.　論文発表

Miki Uchino[1,2] MD, Murat Dogru[1,3] MD, Yuichi Uchino[1,2] MD, Kazumi Fukagawa[1,2] MD, Shigeto Shimmura[1,2]MD, Toshihiko Satou[4] MD,MPH, Toru Takebayashi[5] MD,MPH, Debra A. Schaumberg[6], SCD, MPH, Kazuo Tsubota[1,2] MD。**Prevalence of Dry Eye Syndrome among Japanese VDT users** [1] Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan [2] Ryogoku Eye Clinic, Tokyo, Japan[3] Department of Ophthalmology, Tokyo Dental College, Chiba, Japan[4] Department of Public Health, Kitazato University School of Medicine, Kanagawa, Japan [5] Department of Public Health, Keio University School of Medicine, Tokyo, Japan[6] Division of Preventive Medicine, Brigham and Women's Hospital, and the Schepens Eye Research Institute, Harvard Medical School, Boston, USA
現在Lancet投稿規定で執筆が完成しており、co-authorのハーバード大学医学部のSchaumberg先生のご閲覧を
頂いている。

2.　学会発表
（発表誌名巻号・頁・発行年等も記入）
内野ら。VDT作業者におけるドライアイ関連不定愁訴の出現頻度と関連因子。第６０回日本臨床眼科学会２００６年１０月５日−８日。２００６年日本眼科学会学会誌１９１ページ

H．知的財産権の出願・登録状況
（予定を含む。）
1．特許取得
特になし

2．実用新案登録
ない

3.その他
特になし

研究成果の刊行に関する一覧表レイアウト

書籍

| 著者氏名 | 論文タイトル名 | 書籍全体の編集者名 | 書　籍　名 | 出版社名 | 出版地 | 出版年 | ページ |
|---|---|---|---|---|---|---|---|
| なし | なし | なし | なし | なし | なし | なし | なし |
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雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| ドライアイ研究会 | ２００６年ドライアイ診断基準 | あたらしい眼科 | ２４ | １８１ | ２００７ |
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総説

# 2006年ドライアイ診断基準

*Definition and Diagnosis of Dry Eye 2006*

島﨑　潤*（ドライアイ研究会**）

**ドライアイ研究会：世話人代表：坪田一男（慶應義塾大学）　世話人：木下　茂（京都府立医科大学）　大橋裕一（愛媛大学）　下村嘉一（近畿大学）　田川義継（北海道大学）　濱野　孝（ハマノ眼科）　高村悦子（東京女子医科大学）　横井則彦（京都府立医科大学）　渡辺　仁（関西ろうさい病院）　島﨑　潤（東京歯科大学）（順不同）

## I　ドライアイ診断基準見直しの経緯

ドライアイ研究会が，1995年にドライアイの定義と診断基準を発表してから10年が経過した[1]．同じ診断基準にのっとって臨床研究を行うことが，ドライアイ研究を進めるうえで欠かせない，という認識のもとに前回の発表を行ったが，この10年間でその目的は十分に果たしたと考えている．

この10年はドライアイ研究にとって非常に多くの進歩が見られた．新しい診断機器の導入，涙腺，涙液，オキュラーサーフェスに関する基礎的・臨床的研究の進歩，ドライアイの内科的・外科的治療の開発など，多方面で新しい知見が得られた．そのかなりの部分が，わが国の研究者からもたらされたことはまことに喜ばしい．さらに，一般の人々の間でのドライアイの認知も大幅に進んだ．最近では自分がドライアイではないか，といって来院される受診者も珍しくなくなった．これらドライアイを取り巻く環境の変化に応じて，10年前に発表したドライアイの定義・診断基準の見直しを図ることとし，今回，ドライアイ研究会のメンバーによる協議の結果，改訂版を発表するに至った．

アメリカでも日本と時を同じくして，1995年にNational Eye Instituteのサポートのもとに，Dr Lempが中心となってドライアイの定義と分類が定められた[2]．10年が経過し，世界中のドライアイ研究者の間よりこれを見直そうという動きが2004年より具体化し，Dry Eye Workshop（通称DEWS）が結成された．定義と診断基準に限らず，検査，疫学調査，基礎研究，治療の各分野にわたる広い範囲で現在に至るまで検討が行われている（http://www.tearfilm.org/dewshome.html）．DEWSにおけるドライアイの定義・診断基準の決定は，まだ最終結論を得るに至っていないが，方向性はかなりまとまってきているので，今回，ドライアイ研究会としてはこの流れを参考にして新しい基準を作成することとした．

## II　診断基準改訂に当たっての立場

今回の改訂に当たっては，以下の3つの点を特に留意した．

### 1．世界の基準との整合性

上述のように，世界的にドライアイの定義・診断基準の見直しが行われており，わが国もこれに参加している．今回のドライアイ研究会の改訂は，わが国のドライアイの定義と診断基準を定めるために行われたが，世界の動きとの整合性を図ることは，日本発の研究を国際的に広めていくうえでも重要と考えられる．したがって，特にドライアイの定義を定めるに当たっては，DEWSでの討議を意識した．もちろんまったくの翻訳ではなく，ニュアンスが多少異なる部分もある．また診断基準

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別紙1

など，わが国のほうがむしろ検討が進んでいる部分も多い．今回，わが国での基準が定められて広く用いられるようになれば，これをもとに世界に情報を発信して世界の診断基準に影響を与えることも期待される．

### 2. 検査法と診断基準

10年前の論文でも同様のことを述べたが，診断基準に用いられる検査法は，「ほとんどの施設で日常的に行うことができる」ものを取り上げた．いかに優れた検査法であっても，一部の施設でしか行うことができないのでは，診断基準に含める意味がないと考えた．したがって，検査機器や診断法の進歩によっては，今後の新たな検査法が取り入れられることは十分考えられる．

### 3. 診断基準とカットオフ値

ドライアイの検査法には絶対的なものがないことはよく知られている．個々の方法の感度・特異度は十分でなく，再現性にも問題がある．そのなかで最善の基準をもって判定が行われるべきであるのは当然のことである．たとえば，シルマー法で何ミリより少なければ異常とするか，についての基準（カットオフ値の設定）は，エビデンスに基づいて行われるべきと考える．1995年の基準は，その時点でのドライアイ専門家の意見を元に定められた．これが適当であったかどうかの検討もドライアイ研究会で行ってきたが，十分な結論が得られたとはいえない．この点については今後も研究を続けていき，より良い基準を作ることが重要と考えている．したがって今回の改訂では，明らかに変更したほうがよいと意見が一致したものを除いて，カットオフ値の変更は行わなかった．今後の研究によって新たなデータが得られれば，これについても変更される可能性がある．

## III ドライアイの定義

今回の討議により，ドライアイの定義は**表1**のように改訂された．10年前の定義「涙液（層）の量的・質的異常によって引き起こされる角結膜上皮障害」と比較すると，いくつかの大きな変化があったことがわかる．一つは，自覚症状を有することが定義に含まれた点である．

**表1 ドライアイの定義**（2006年，ドライアイ研究会）

| |
|---|
| ドライアイとは，様々な要因による涙液および角結膜上皮の慢性疾患であり，眼不快感や視機能異常を伴う |

日常診療においても，涙液分泌の少ない患者がすべて眼不快感を訴えるわけではない．ドライアイ治療の目的の多くが，患者の自覚症状の軽減にあることを考えると，自覚症状を有することが定義に含まれたのは自然のことといえる．ちなみにNEI（National Eye Institute）の定義[2]でも自覚症状は含まれており，新しいDEWSの討議でも症状を有することが定義として明記されている．

さらに今回，「眼不快感」だけでなく，「視機能異常」もドライアイの症状と定められたことも大きな特徴である．ドライアイの多くは，視機能異常をきたすことはないといわれてきたが，近年の研究で運転やVDT（visual display terminal）作業など，瞬目が少なくなるような環境では，持続開瞼によって不正乱視の増大，視力低下が生じることが明らかとなってきた[3,4]．日常診療でも，ドライアイ患者が漠然とした見づらさを訴えることはよく経験されるが，矯正視力には異常がないことが多かった．今回の定義で視機能異常が含まれたことは，ドライアイ検査法の進歩が，ようやく患者の訴えを検出できるまで進歩したことの表れといえる．また，スティーブンス・ジョンソン症候群などの重症ドライアイでは，眼表面の著明な角化によって逆に異物感や乾燥感などの眼不快感を訴えなくなることが経験されるが，こうした場合も視機能異常を伴うことが定義に定められたことで矛盾がなくなった．

今回，ドライアイの原因が多岐にわたる「多因子による疾患」であることが明記された．これまでも「ドライアイ症候群」という単語もあるように，多くの因子がその発症や増悪に関わっていることが指摘されていたが，今回この点を定義に含めたことでさらに明確となった．

## IV 診断基準

今回定められた診断基準を**表2，3**に示す．10年前のものと比べると，以下の点で違いがある．

### 1. 自覚症状を有することが診断基準に含まれた

定義のところでも述べたが，ドライアイの自覚症状（視機能異常を含む）を有することが，診断の必須項目となった．内容をよく吟味すれば疫学的調査（ドライアイの頻度や性差など）もアンケートのみによって行うことは十分可能であることが示されている[5~8]．ここで問題となるのが，どういった症状をいかにして捉えるか，という点である．患者側から訴えるもののみを取り上げ

表 2　ドライアイの診断基準

1. 涙液の異常
   ① シルマー試験 I 法にて 5 mm 以下
   ② 涙液層破壊時間 (BUT) 5 秒以下
   ①, ②のいずれかを満たすものを陽性とする
2. 角結膜上皮障害*
   ① フルオレセイン染色スコアー 3 点以上 (9 点満点)**
   ② ローズベンガル染色スコアー 3 点以上 (9 点満点)**
   ③ リサミングリーン染色スコアー 3 点以上 (9 点満点)**
   ①, ②, ③のいずれかを満たすものを陽性とする

*生体染色スコアリングを臨床研究に用いる場合は，用いる治療法や薬剤の特性を考慮して，適宜改変して用いることが望ましい．
**図 1 参照．

表 3　ドライアイ診断における確定例と疑い例

| | | | | |
|---|---|---|---|---|
| ①自覚症状 | ○ | ○ | × | ○ |
| ②涙液異常 | ○ | ○ | ○ | × |
| ③角結膜上皮障害 | ○ | × | ○ | ○ |
| ドライアイの診断 | 確定 | 疑い | 疑い | 疑い* |

*涙液の異常を認めない角結膜上皮障害の場合は，ドライアイ以外の原因検索を行うことを基本とする．

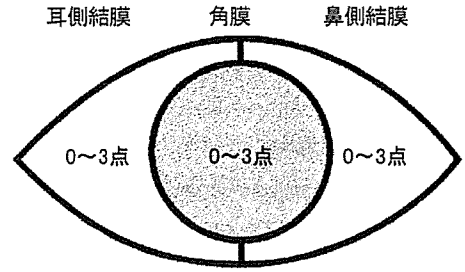


図 1　角結膜上皮障害スコアリング (フルオレセイン，ローズベンガル，リサミングリーンとも)
耳側球結膜，角膜，鼻側球結膜における染色の程度を各々 3 点満点で判定し，これを合算して 9 点満点として計算する．

表 4　涙液層破壊時間 (BUT) 検査の方法

- 点眼するフルオレセイン溶液の量は最小限にする
- 時間の測定はストップウォッチやメトロノームで正確に行う
- 検査は 3 回行って，その平均をとる
- 涙液層の破綻は，角膜全体のどこかに生じたときに陽性とする

るのか，医師側から積極的に聞くのか，あるいは問診表などの形式をとるのかによって，自覚症状をもつ者の割合は大きく左右される．自覚症状を聴取することには，(1) 疫学的調査，(2) ドライアイの診断，(3) ドライアイの治療判定，などいくつかの目的がある．それぞれによって聴取項目や方法が異なることは当然である．この点については，ドライアイ研究会が中心となって標準となる症状の聴取項目の設定がなされる見通しである．この問題は DEWS でも独立したワーキンググループのもとでディスカッションが行われている．これによってさらに統一されたドライアイ診断が行われることが期待される．

また，ドライアイの定義に含まれた視機能異常を検出する方法の確立も望まれる．従来の視力検査では検出することができなかった異常を調べる検査法として，tear film stability analysis system や実用視力などが提唱されている[4,9,10]が，その検査法や解析法はいまだ検討中であり，検査機器の入手法とともにその確立が望まれる．

## 2. 涙液検査

涙液異常の検査法としては，シルマー法と涙液層破壊時間 (BUT) が選ばれた．以前の診断基準に含まれていた綿糸法 (10 mm 以下が異常) は，国際的に広く行われているとはいえないことと，必ずしも涙液貯留量を反映しているとはいえない[11]などの理由で今回の基準からは省かれた．ただし，コンタクトレンズ装用の適否のスクリーニングなどの場での有用性はあると考えられるので，検査法そのものの意義が否定されたわけではない．

検査法の標準化も大きな問題として取り上げられた．シルマー法，BUT 検査ともにいろいろなバリエーション，判定方法があり，これを標準化しないと一定の基準で判定したことにならない．シルマー法は，点眼麻酔を用いない第 I 法で自然瞬目状態で測定することが推奨されたが，用いる試験紙の種類や試験紙の挟み方，検査時に涙液をふき取るかどうかなど，施設によって微妙な差異がある．また BUT 検査はさらにバリエーションが大きく，用いるフルオレセイン染色液の濃度と量，時間の測定法，繰り返して結果を平均化するか，涙液 break-up の判定法などさまざまである．研究会で推奨する方法を表 4 に示すが，これらの検査法の標準化に向けてさらなる啓発と基礎的検討が必要であることが示された．

## 3. 角結膜上皮障害の検査

染色試験によって角結膜上皮障害の判定を行うことには変わりがないが，その判定基準と用いる染色液について若干の変更があった．まず，フルオレセイン染色試験の判定方法では，従来の角膜上の染色を 3 点満点で判定

して1点以上を陽性とする基準から，角膜と結膜を9点満点で判定して3点以上を陽性とする基準に改められた(表3，図1)．ドライアイにおいては，結膜上皮の障害が角膜上皮障害より高率に認められ，点眼や涙点プラグなどの治療を行った後も結膜染色が残存する傾向が強い．従来，結膜上皮障害は，ローズベンガル染色によって判定することが推奨され，今回もこの判定基準はそのまま残された．フルオレセインとローズベンガルの染色メカニズムが異なることは報告されているが，日常診療においては，フルオレセイン染色によっても結膜上皮障害を十分に判定しうると考えられる．フルオレセインによる結膜上皮障害をさらに詳細に検討・記録するには，ブルーフリーフィルターなどを使用する方法もある[12]．結膜の異常に目を向けることが，ドライアイ診療において重要であることが示されたといえる．また，ローズベンガルとともに，リサミングリーンも角結膜上皮障害の判定に用いることができることが示された[13]．ローズベンガルの染色スコアは，シェーグレン症候群の診断基準にも用いられているが，点眼後の疼痛を訴える例が多く，特に光毒性が強いため日常診療には用いにくいという欠点があった．リサミングリーンはこうした障害が少なく，特別な観察フィルターも必要がないため，その有用性があると判断された．

この上皮障害スコアリングとそのカットオフ値の正当性についても，今後の研究結果によっては変更がありうることを再度確認のために記しておく．また，生体染色液による上皮障害スコアリングを臨床研究に用いる場合は，用いる治療法や薬剤の特性を考慮して，適宜改変して用いることが望ましい．

## ま と め

今回10年ぶりに改訂された，新しいドライアイの定義と診断基準を紹介した．いまだ発展途上であり，今後の研究の進展をまたなくてはならない部分も多いが，新しい基準を用いることで，これまで以上にドライアイの病態の理解が深まることが期待される．

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# The Definition and Classification of Dry Eye Disease:
## *Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007)*

**ABSTRACT The aim of the DEWS Definition and Classification Subcommittee was to provide a contemporary definition of dry eye disease, supported within a comprehensive classification framework. A new definition of dry eye was developed to reflect current understanding of the disease, and the committee recommended a three-part classification system. The first part is etiopathogenic and illustrates the multiple causes of dry eye. The second is mechanistic and shows how each cause of dry eye may act through a common pathway. It is stressed that any form of dry eye can interact with and exacerbate other forms of dry eye, as part of a vicious circle. Finally, a scheme is presented, based on the severity of the dry eye disease, which is expected to provide a rational basis for therapy. These guidelines are not intended to override the clinical assessment and judgment of an expert clinician in individual cases, but they should prove helpful in the conduct of clinical practice and research.**

**KEYWORDS definition, DEWS, dry eye disease, Dry Eye WorkShop, etiopathogenesis, mechanism, severity grading**

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Proprietary interests of Subcommittee members are disclosed on pages **(EDITOR; INSERT PAGE NUMBERS)**

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### I. INTRODUCTION

The Definition and Classification Subcommittee reviewed previous definitions and classification schemes for dry eye, as well as the current clinical and basic science literature that has increased and clarified knowledge of the factors that characterize and contribute to dry eye. Based on its findings, the Subcommittee presents herein an updated definition of dry eye and classifications based on etiology, mechanisms, and severity of disease.

### II. GOALS OF THE DEFINITION AND CLASSIFICATION SUBCOMMITTEE

The goals of the DEWS Definition and Classification Subcommittee were to develop a contemporary definition of dry eye disease and to develop a three-part classification of dry eye, based on etiology, mechanisms, and disease stage.

The manner of working of the committee is outlined in the introduction to this issue of *The Ocular Surface*. Further details are published on the TFOS-DEWS web-site [details of web site].

### III. DEFINITION OF DRY EYE DISEASE

The committee reviewed the definition and classification presented at the 1995 National Eye Institute (**NEI**)/Industry Dry Eye Workshop, which was: *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.*[1]

The committee agreed that the definition could be improved in the light of new knowledge about the roles of tear hyperosmolarity and ocular surface inflammation in dry eye and the effects of dry eye on visual function. Initially two definitions were developed and presented to members of the workshop. These "general" and "operational" definitions overlapped to some extent, and, therefore, in this final report, these versions have been combined to produce the following definition:

> *Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,*[2-4] *visual disturbance,*[5-7] *and tear film instability*[8-10] *with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film*[11-14] *and inflammation of the ocular surface.*[15,16]



別紙2

**OUTLINE**



Dry eye is recognized as a disturbance of the *Lacrimal Functional Unit* (**LFU**), an integrated system comprising the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that connect them.[17] Trigeminal sensory fibers arising from the ocular surface run to the superior salivary nucleus in the pons, from whence efferent fibers pass, in the *nervus intermedius,* to the pterygopalatine ganglion. Here, postganglionic fibers arise, which terminate in the lacrimal gland, nasopharynx, and vessels of the orbit. Another neural pathway controls the blink reflex, via trigeminal afferents and the somatic efferent fibers of the seventh cranial nerve. Higher centers feed into the brainstem nuclei, and there is a rich sympathetic supply to the epithelia and vasculature of the glands and ocular surface.

This functional unit controls the major components of the tear film in a regulated fashion and responds to environmental, endocrinological, and cortical influences. Its overall function is to preserve the integrity of the tear film, the transparency of the cornea, and the quality of image projected onto the retina.[17-20] At the 2007 Dry Eye WorkShop, it was noted that the corneal and conjunctival epithelia are in continuity, through ductal epithelia, with the acinar epithelia of the main and accessory lacrimal glands and the meibomian glands, which themselves arise as specialized invaginations from the ocular surface. Also, these epithelia have the same embryological derivation. This broader concept, which has additional features, has been termed the *Ocular Surface System* and is discussed further in the "Research" chapter of this issue.[21]

An important aspect of the unit is the part played by sensory impulses, which arise from the ocular surface, in the maintenance of resting tear flow. Currently, it is considered that waking tear flow is a reflex response to afferent impulses deriving particularly, but not entirely, from the ocular surface.[22] Sensory input from the nasal mucosa also makes a contribution.[23] Disease or damage to any component of the LFU (the afferent sensory nerves, the efferent autonomic and motor nerves, and the tear-secreting glands) can destabilize the tear film and lead to ocular surface disease that expresses itself as dry eye. Tear film stability, a hallmark of the normal eye, is threatened when the interactions between stabilizing tear film constituents are compromised by decreased tear secretion, delayed clearance, and altered tear composition. Ocular surface inflammation is a secondary consequence. Reflex tear secretion in response to ocular irritation is envisioned as the initial compensatory mechanism, but, with time, inflammation accompanying chronic secretory dysfunction and a decrease in corneal sensation eventually compromises the reflex response and results in even greater tear film instability. Perturbation of the LFU is considered to play an important role in the evolution of different forms of dry eye.

The distinctions *aqueous-deficient dry eye* and *evaporative dry eye* were removed from the definition, but are retained in the etiopathogenic classification.

## IV. CLASSIFICATION OF DRY EYE DISEASE

### A. Background

Vitali, writing about the harmonized classification criteria for Sjogren syndrome (**SS**) remarked that classification criteria are not necessarily appropriate for use in diagnosis and may lead to misclassification of a disease, particularly its early stages.[24] In an individual patient, a classification scheme can provide a guide, but an expert clinician, applying appropriate diagnostic criteria, is needed to establish a diagnosis.

Although the NEI/Industry Workshop classification[1] has served as a useful and durable scheme for over a decade, it does not reflect newer knowledge on pathophysiological mechanisms, effects on vision, and the utility of an assessment of severity of disease. Recently, two new classification schemes were published, and these were used as source documents by the committee. These include: the Triple Classification[25,26] and the report of the Delphi panel.[27]

The Triple Classification evolved from reports presented

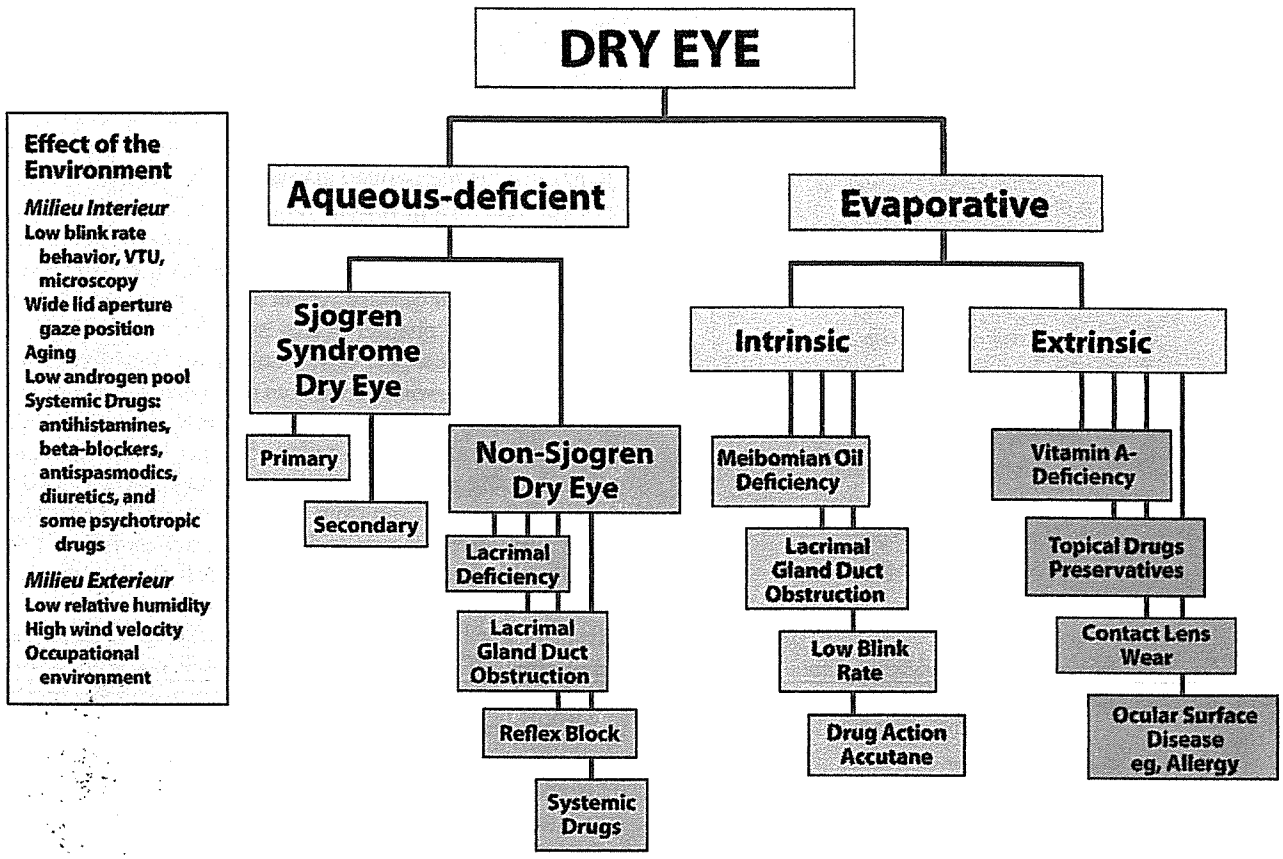


**Figure 1. Major etiological causes of dry eye.**

**The left hand box illustrates the influence of environment on the risk of an individual to develop dry eye. The term "environment" is used broadly, to include bodily states habitually experienced by an individual, whether it reflects their "milieu interieur" or is the result of exposure to external conditions which represent the "milieu exterieur." This background may influence the onset and type of dry eye disease in an individual, which may be aqueous-deficient or evaporative in nature.**

**Aqueous-deficient dry eye has two major groupings, Sjogren syndrome dry eye and non-Sjogren syndrome dry eye.**

**Evaporative dry eye may be intrinsic, where the regulation of evaporative loss from the tear film is directly affected, eg, by meibomian lipid deficiency, poor lid congruity and lid dynamics, low blink rate, and the effects of drug action, such as that of systemic retinoids. Extrinsic evaporative dry eye embraces those etiologies that increase evaporation by their pathological effects on the ocular surface. Causes include vitamin A deficiency, the action of toxic topical agents such as preservatives, contact lens wear and a range of ocular surface diseases, including allergic eye disease. Further details are given in the text.**

at the 14th Congress of the European Society of Ophthalmology.[25] After further clinical experience, an updated version was published in 2005, which presented three separate schemes: one based on etiopathogenesis; one based on the glands and tissues targeted in dry eye; and one based on disease severity.[26]

The committee felt that the concept of three different schemes serving different purposes was attractive, but it was noted that evidence-based referencing was limited. For this reason, the scheme as a whole was not adopted, but many conceptual aspects were incorporated into the committee's final schemes.

The Delphi Panel was a consensus group that met to review the classification of dry eye.[27] The panel proposed changing the name of *dry eye disease* to *dysfunctional tear syndrome*, suggesting that the name more accurately reflected pathophysiological events in dry eye. However, although the committee felt that the term embraced the essential features of the disease, they concluded that retention of the name *dry eye* had much to recommend it and that its use was embedded in the literature. The committee also rejected a subdivision based on the presence or absence of lid disease, because it is frequently difficult to identify the relative contribution of lid disease to a particular case of dry eye.

The majority of the Definition and Classification Subcommittee was in favor of adopting a severity grading based on the report of the Delphi Panel, recognizing it as a comprehensive approach that could form the basis of therapy according to severity of the disease. As noted above, the Triple Classification also presented a severity grading.

### B. Etiopathogenic Classification of Dry Eye Disease

The etiopathogenic classification developed by the Subcommittee is an updated version of that presented in the NEI/Industry Workshop Report and reflects a more contemporary understanding of dry eye disease (Figure 1).

As in the 1995 report, the term *dry eye* is regarded as synonymous with the term keratoconjunctivitis sicca (**KCS**).

The classification has the following features:

The left hand box in Figure 1 illustrates the influence of environment on an individual's risk of developing dry eye. The term *environment* is used broadly to include physiological variation between individuals (their *milieu interieur*), as well as the ambient conditions that they encounter (their *milieu exterieur*).

The *milieu interieur* implies physiological conditions particular to an individual that could influence their risk of dry eye. For instance, a normal subject may have a low natural blink rate, or the blink rate may be slowed for behavioral or psychological reasons.[28] Slowing of the blink rate increases the blink interval and increases the period of evaporative loss between each blink.[29]

Similarly, the natural height of the palpebral aperture in the primary position varies between individuals and between ethnic groups.[30] The aperture is also wider in upgaze than downgaze.[31] Evaporative loss per eye increases with increasing palpebral width and is, therefore, increased in upgaze.[32]

Extensive evidence supports a role for the sex hormones in the etiology of dry eye[33] with the generalization that low levels of androgens and high estrogen levels are risk factors for dry eye. Biologically active, androgens promote lacrimal and meibomian gland function.[33] Androgen deficiency is associated with dry eye[34] and may be prevented by topical or systemic androgen therapy.[35-38] Dry eye occurs in patients exposed to anti-androgens in the treatment of prostatic cancer,[39,40] and women with complete androgen insensitivity syndrome show an increase in the signs and symptoms of dry eye, associated with evidence of meibomian gland and goblet cell dysfunction.[41-43] A significantly depleted androgen pool in "non-autoimmune" dry eye associated with meibomian gland dysfunction (**MGD**) has been reported.[44] Also, as noted elsewhere in this issue,[45] female sex and postmenopausal estrogen therapy are important risk factors for dry eye,[46,47] and women with premature ovarian failure suffer from the symptoms and signs of dry eye, although their tear production is not affected.[48]

Lacrimal tear secretion is reduced by a number of systemic drugs, and these effects may be looked upon as disturbances of the *milieu interieur*. Their details are discussed later in this report. Aging is associated with physiological changes that may predispose to dry eye, including decreased tear volume and flow, increased osmolarity,[49] decreased tear film stability,[50] and alterations in the composition of the meibomian lipids.[51]

The *milieu exterieur* involves the occupational and external environments, which may represent risk factors for the development of dry eye. Evaporative water loss from the eye is increased in conditions of low relative humidity, occurring either as part of natural variation at different geographic locations or in special circumstances created by air-conditioning, air travel, or other artificial environments.[52] Similarly, tear evaporation is increased by exposure to high wind velocity, and this mechanism has been incorporated into some of the newer experimental models of dry eye.

Occupational factors may cause a slow blink rate, representing a risk for dry eye in those working with video display terminals.[53] Other activities associated with decreased blinking and an increase in palpebral width, including that associated with upgaze, have been reported to carry a risk for the development of dry eye symptoms.

The major classes of dry eye, as in the 1995 workshop,[1] are still held to be aqueous tear-deficient dry eye (**ADDE**) and evaporative dry eye (**EDE**). The category ADDE refers chiefly to a failure of lacrimal secretion, and this approach is retained. However, it should be recognized that a failure of water secretion by the conjunctiva could also contribute to aqueous tear deficiency. The class EDE has been subdivided to distinguish those causes that are dependent on intrinsic conditions of the lids and ocular surface and those that arise from extrinsic influences.

Dry eye can be initiated in any of these classes, but they are not mutually exclusive. It is recognized that disease initiated in one major subgroup may coexist with or even lead to events that cause dry eye by another major mechanism. This is part of a vicious circle of interactions that can amplify the severity of dry eye. An example might be that all forms of dry eye cause goblet cell loss and that this, in turn, will contribute to loss of tear film stability, to surface damage and evaporative water loss, and to symptoms resulting from a loss of lubrication and surface inflammatory events.

The major classes and subclasses of dry eye are described below.

### 1. Aqueous Tear-Deficient Dry Eye (Tear Deficient Dry Eye; Lacrimal Tear Deficiency)

Aqueous tear-deficient dry eye implies that dry eye is due to a failure of lacrimal tear secretion. In any form of dry eye due to lacrimal acinar destruction or dysfunction, dryness results from reduced lacrimal tear secretion and volume.[54,55] This causes tear hyperosmolarity, because, although the water evaporates from the ocular surface at normal rates, it is from a reduced aqueous tear pool. Tear film hyperosmolarity causes hyperosmolarity of the ocular surface epithelial cells and stimulates a cascade of inflammatory events involving MAP kinases and NF*k*B signalling pathways[56,57] and the generation of inflammatory cytokines (interleukin (**IL**)-1$\alpha$; -1$\beta$; tumor necrosis factor (**TNF**)-$\alpha$) and matrix metalloproteinases (**MMP**-9).[58] When lacrimal dysfunction is due to lacrimal gland infiltration and inflammation, inflammatory mediators generated in the gland are assumed to find their way into the tears and be delivered to the ocular surface. However, when such mediators are detected in the tears, it is not usually possible to know whether they derive from the lacrimal gland itself or from the ocular surface (conjunctiva and cornea).

It is uncertain whether evaporation is reduced[59] or increased[59-64] in ADDE. It is possible that this is determined by the stage of the disease. Some studies suggest that the reservoir of lid oil is larger in non-Sjogren syndrome dry

**Table 1.** Revised international classification criteria for ocular manifestations of Sjogren syndrome

| |
|---|
| **I. Ocular symptoms:** a positive response to at least one of the following questions:<br>1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?<br>2. Do you have a recurrent sensation of sand or gravel in the eyes?<br>3. Do you use tear substitutes more than 3 times a day? |
| **II. Oral symptoms:** a positive response to at least one of the following questions:<br>1. Have you had a daily feeling of dry mouth for more than 3 months?<br>2. Have you had recurrently or persistently swollen salivary glands as an adult?<br>3. Do you frequently drink liquids to aid in swallowing dry food? |
| **III. Ocular signs:** that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:<br>1. Schirmer I test, performed without anesthesia (≤5 mm in 5 minutes)<br>2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system) |
| **IV. Histopathology:** In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 $mm^2$ of glandular tissue[18] |
| **V. Salivary gland involvement:** objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:<br>1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)<br>2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts[19]<br>3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer[20] |
| **VI. Autoantibodies:** presence in the serum of the following autoantibodies:<br>1. Antibodies to Ro(SSA) or La(SSB) antigens, or both |

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eye (**NSSDE**)[65] and that the tear film lipid layer is thicker,[66] but dynamic studies of the tear film lipid layer in ADDE have shown that spreading of the lipid layer is delayed in the interblink.[67,68] Additionally, in severe ADDE, spreading may be undetectable by interferometry, suggesting a major defect in the tear film lipid layer. Delayed or absent spreading of the tear film could lead to an increase in water loss from the eye.

ADDE has two major subclasses, SS dry eye (SSDE) and non-SS dry eye.

### *a. Sjogren Syndrome Dry Eye*

Sjogren syndrome is an exocrinopathy in which the lacrimal and salivary glands are targeted by an autoimmune process; other organs are also affected. The lacrimal and salivary glands are infiltrated by activated T-cells, which cause acinar and ductular cell death and hyposecretion of the tears or saliva. Inflammatory activation within the glands leads to the expression of autoantigens at the surface of epithelial cells (eg, fodrin, Ro and La)[69] and the retention of tissue-specific CD4 and CD8 T-cells.[70] Hyposecretion is amplified by a potentially reversible neurosecretory block, due to the effects of locally released inflammatory cytokines or to the presence of circulating antibodies (eg, anti-M3 antibody) directed against muscarinic receptors within the glands.[71-73]

There are two forms of SS, and classification criteria have recently been harmonized in a European-American collaboration.[74] *Primary SS* consists of the occurrence of ADDE in combination with symptoms of dry mouth, in the presence of autoantibodies, evidence of reduced salivary secretion and with a positive focus score on minor salivary gland biopsy.[75,76] Details of the criteria are presented in Table 1. *Secondary SS* consists of the features of primary SS together with the features of an overt autoimmune connective disease, such as rheumatoid arthritis, which is the most common, or systemic lupus erythematosis, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary sclerosis, or mixed connective tissue disease. Diagnostic criteria for each of these connective tissue disorders have been published.[77]

The precise triggers leading to autoimmune acinar damage are not known in full, but risk factors include genetic profile,[78] androgen status[79] (a low androgen pool favoring an inflammatory environment within the target tissues), and exposure to environmental agents, ranging from viral infections affecting the lacrimal gland to polluted environments. A nutritional deficiency in omega-3- and other unsaturated fatty acids and unsupplemented intake of vitamin C has also been reported in patients with SS.[80] It is generally accepted that environmental factors leading to increased evaporative water loss from the eye (eg, low humidity, high wind velocity, and increased exposure of the ocular surface) may act as a trigger by invoking inflammatory events at the ocular surface through a hyperosmolar mechanism (see Section V).

The ocular dryness in SSDE is due to lacrimal hyposecretion and the accompanying characteristic inflammatory changes in the lacrimal gland, together with the presence of inflammatory mediators in the tears and within the conjunctiva.[81] It is not known whether the conjunctival changes are due to an autoimmune targeting of this tissue or whether they are due to the effect of inflammatory mediators released from the lacrimal glands into the tears.

The frequency of MGD is higher in patients with SS than in the normal population; thus, a defective tear film lipid layer may contribute to dry eye by leading to excess evaporation.[82]

### *b. Non-Sjogren Syndrome Dry Eye*

Non-Sjogren syndrome dry eye is a form of ADDE due to lacrimal dysfunction, where the systemic autoimmune features characteristic of SSDE have been excluded. The most common form is age-related dry eye, to which the term KCS has sometimes been applied in the past. However, as noted earlier, the term KCS is now used to describe any form of dry eye. In the 1995 Dry Eye Workshop report, it was referred to as *primary lacrimal disease*,[1] but this term has not been generally adopted. The different forms of NSSDE are briefly discussed below (Table 2).

**Table 2.** Conditions associated with non-Sjogren syndrome dry eye

| |
|---|
| **Primary lacrimal gland deficiencies** |
| Age-related dry eye |
| Congenital alacrima |
| Familial dysautonomia |
| **Secondary lacrimal gland deficiencies** |
| Lacrimal gland infiltration |
| Sarcoidosis |
| Lymphoma |
| AIDS |
| Graft vs host disease |
| Lacrimal gland ablation |
| Lacrimal gland denervation |
| **Obstruction of the lacrimal gland ducts** |
| Trachoma |
| Cicatricial pemphigoid and mucous membrane pemphigoid |
| Erythema multiforme |
| Chemical and thermal burns |
| **Reflex hyposecretion** |
| Reflex sensory block |
| Contact lens wear |
| Diabetes |
| Neurotrophic keratitis |
| Reflex motor block |
| VII cranial nerve damage |
| Multiple neuromatosis |
| Exposure to systemic drugs |

#### 1) Primary Lacrimal Gland Deficiencies

*Age-Related Dry Eye (ARDE):* There is some uncertainty as to whether tear dynamics are affected by age in the normal population.[83] Mathers et al showed significant age-related correlations for tear evaporation, volume, flow, and osmolarity,[49] but no such relationship was noted by Craig and Tomlinson[84] or in other reports of tear turnover,[85] tear evaporation[86,87] and lipid layer.[88] ARDE is a primary disease. With increasing age, in the normal population, there is an increasing infiltration of the lacrimal glands with T-cells.[89] It is considered that in ARDE, these infiltrating T-cells target the lacrimal acinar and ductal cells, leading to their destruction, and probably cause a neurosecretory block, much as described for SSDE. ARDE resembles SSDE in that it is due to the gradual destruction or dysfunction of lacrimal tissue by infiltrating CD4 and CD8 T-cells. Its clinical features resemble those of SSDE, but, in general, its age of onset is later, its rate of progression slower, and its severity generally less marked than in SSDE.

*Congenital Alacrima:* Congenital alacrima is a rare cause of dry eye in youth.[90] It is also part of certain syndromes,[91] including the autosomal recessive, triple A syndrome (Allgrove syndrome), in which congenital alacrima is associated with achalasia of the cardia, Addison's disease, central neurodegeneration, and autonomic dysfunction. It is caused by mutations in the gene encoding the protein ALADIN, which plays a role in RNA and/or protein trafficking between the nucleus and cytoplasm.[92,93]

*Familial Dysautonomia:* Lacrimal dysfunction is a major feature of the autosomal recessive disorder, familial dysautonomia (Riley Day syndrome), in which a generalized insensitivity to pain is accompanied by a marked lack of both emotional and reflex tearing, within a multisystem disorder. There is a developmental and progressive neuronal abnormality of the cervical sympathetic and parasympathetic innervations of the lacrimal gland and a defective sensory innervation of the ocular surface, which affects both small myelinated (Aδ) and unmyelinated (C) trigeminal neurons.[94,95] The chief mutation affects the gene encoding an IκB kinase-associated protein.

#### 2) Secondary Lacrimal Gland Deficiencies

*Lacrimal gland infiltration*: Lacrimal secretion may fail because of inflammatory infiltration of the gland, as in:

*Sarcoidosis*: Infiltration of the lacrimal gland by sarcoid granulomata may cause dry eye.[96]

*Lymphoma*: Infiltration of the lacrimal gland by lymphomatous cells causes dry eye.[97]

*AIDS*: Dry eye may be caused by lacrimal gland infiltration by T-cells. However, in AIDS-related dry eye, unlike the situation in SSDE, there is a predominance of CD8 suppressor cells, rather than CD4, helper cells.[98]

*Graft vs host* disease (**GVHD**): Dry eye is a common complication of GVHD disease, occurring typically around 6 months after hematopoietic stem cell transplantation. It is caused in part by lacrimal gland fibrosis due to colocalization of periductal T-lymphocytes (CD4 and CD8) with antigen-presenting fibroblasts.[99,100]

*Lacrimal gland ablation*: The ducts of the main lacrimal gland pass through its palpebral part, so that excision of the palpebral part will be expected to have the same effect as excision of the main gland. Dry eye may be caused by partial or complete ablation of the lacrimal gland at any age, but is not an obligatory consequence, presumably because accessory gland and conjunctival secretion may compensate in some cases.[55] It is, therefore, of interest that ablation of the main lacrimal gland in squirrel monkeys, while reducing both basal and reflex tear secretion, does not in itself lead to dry eye in that species.[101]

*Lacrimal gland denervation:* Parasympathetic denerva-

tion of the human lacrimal gland may cause dry eye,[102] and, experimentally in the rat, it causes reduced tear flow and lacrimal protein secretion and activates inflammatory changes in the gland.[103] The accessory glands are innervated similarly to the main and palpebral lacrimal glands[104] and are assumed to be under similar reflex control; however, evidence for this is lacking.

### 3) Obstruction of the Lacrimal Gland Ducts

Obstruction of the ducts of the main palpebral and accessory lacrimal glands leads to aqueous-deficient dry eye and may be caused by any form of cicatrising conjunctivitis (Table 2). In these disorders, it is not uncommon for conjunctival scarring to cause a cicatricial obstructive MGD. In addition, lid deformity influences tear film spreading by affecting lid apposition and dynamics. Specific conditions are discussed below.

*Trachoma:* Trachoma is a cause of blindness on a global scale, in which corneal opacity and blindness are caused by a combination of tarsal and conjunctival scarring, trichiasis and a cicatrizing meibomian gland obstruction. Dry eye is part of the overall picture, resulting from lacrimal duct obstruction, lid malapposition, and a deficient tear film lipid layer.[105]

*Cicatricial pemphigoid and mucous membrane pemphigoid:* Cicatricial and mucous membrane pemphigoid are mucocutaneous disorders characterized by blistering of the skin and mucous membranes, leading to severe and progressive conjunctival scarring. Dry eye may be caused by lacrimal obstruction, cicatricial MGD, and/or poor lid apposition.[106-108]

*Erythema multiforme:* This is an acute, self-limited mucocutaneous disorder usually precipitated by drugs, infection or malignancy. Conjunctival scarring can lead to dry eye in the manner outlined above.[109]

*Chemical and thermal burns:* Diffuse burns may cause sufficient scarring to cause dry eye.[110]

### 4) Reflex Hyposecretion

#### *a) Reflex Sensory Block (Tables 2 and 3)*

Lacrimal tear secretion in the waking state is due in large part to a trigeminal sensory input arising chiefly from the nasolacrimal passages and the eye. When the eyes open, there is an increased reflex sensory drive from the exposed ocular surface. A reduction in sensory drive from the ocular surface is thought to favor the occurrence of dry eye in two ways, first, by decreasing reflex-induced lacrimal secretion, and, second, by reducing the blink rate and, hence, increasing evaporative loss.[111] Experimental evidence has shown that trigeminal denervation in the rabbit modifies the regulation of lacrimal protein secretion.[112]

Bilateral sensory loss reduces both tear secretion and blink rate. Bilateral, topical proparacaine decreases the blink rate by about 30% and tear secretion by 60-75%.[22] It should be kept in mind that part of the reduction in secretion may be due to local anesthesia of secretory nerve terminals supplying the palpebral and accessory lacrimal glands (Belmonte C: personal communication).

**Table 3.** Causes of ocular sensory loss

| |
|---|
| Infective |
| Herpes simplex keratitis |
| Herpes zoster ophthalmicus |
| Corneal surgery |
| Limbal incision (extra-capsular cataract extraction) |
| Keratoplasty |
| Refractive surgery |
| PRK |
| LASIK |
| RK |
| Neurotrophic Keratitis |
| Vth nerve/ganglion section/injection/compression |
| Topical agents |
| Topical anaesthesia |
| Systemic medications |
| Beta blockers |
| Atropine-like drugs |
| Other causes |
| Chronic contact lens wear |
| Diabetes mellitus |
| Aging |
| Trichlorethylene toxicity |

*Contact Lens Wear:* A reduction in corneal sensitivity occurs in wearers of hard- and extended wear- contact lenses (**CL**s), possibly contributing[11,113] to dry eye symptoms in this group of patients. In some studies, increased tear osmolarity has been recorded in association with CL wear.[113,114] In a rabbit model, trigeminal denervation increases tear film osmolarity and causes the morphological changes characteristic of dry eye.[115] Similar arguments have been put forward to advance the concept of LASIK dry eye[116,117]; although there is evidence to support the concept, counter arguments have been put forward to suggest that at least some of the patients who are symptomatic after LASIK surgery have a neurotrophic deficiency[118] or neuralgic disorder.[119]

*Diabetes:* Diabetes mellitus has been identified as a risk factor for dry eye in several studies, including large population studies.[120-123] The prevalence was 18.1% in diabetics compared to 14.1% in non-diabetics in the Beaver Dam study,[121,122] in which the diagnosis of dry eye or dry eye symptoms were self-reported. A similar prevalence (diabetics 20.6%, non-diabetics 13.8%) was reported in a study based on frequency of use of ocular lubricants.[123] This study also noted an association between poor glycemic control (as indicated by serum HbA1C) and frequency of drop use. Goebbels[124] found a reduction in reflex tearing (Schirmer test) in insulin-dependent diabetics, but no difference in tear film breakup time or basal tear flow by fluorophotometry.

It has been suggested that the association may be due to diabetic sensory or autonomic neuropathy, or to the occurrence of microvascular changes in the lacrimal gland.[123]

*Neurotrophic keratitis:* Extensive sensory denervation of the anterior segment, involving the cornea and the bulbar and palpebral conjunctiva, as a component of herpes zoster ophthalmicus or induced by trigeminal nerve section, injection,

or compression or toxicity, or, can lead to neurotrophic keratitis. This condition is characterized by features of dry eye, such as tear instability, diffuse punctate keratitis, and goblet cell loss, and also, most importantly, the occurrence of an indolent or ulcerative keratitis, which may lead to perforation.[115,125]

The sensory loss results in a reduction of lacrimal secretion[126] and a reduction in blink rate. In addition, it is envisaged that there is a loss of trophic support to the ocular surface[125] after sensory denervation, due to a deficient release of substance-P or expression of nerve growth factor.[127-131]

**Table 4.** Meibomian gland diseases causing evaporative dry eye

| Category | Disease | References |
|---|---|---|
| **Reduced number** | Congenital deficiency<br>Acquired—MGD | Bron et al[137] |
| **Replacement** | Dystichiasis | Bron et al[137] |
| | Dystichiasis lymphedema syndrome | Brooks et al[138]<br>Kiederman et al[139] |
| | Metaplasia | |
| **Meibomian Gland Dysfunction** | | |
| Hypersecretory | Meibomian seborrhoea | Gifford[140]<br>Cowper[141] |
| Hyposecretory MGD | Retinoid therapy | Mathers et al[142] |
| Obstructive MGD | Primary or secondary | Bron et al[143] |
| | Focal or diffuse | Bron et al[143] |
| | Simple or cicatricial | Foulks and Bron[134] |
| | Atrophic or inflammatory—<br>note association with dermatoses | Pflugfelder et al[144] |
| Simple MGD: Primary, or Secondary to: | | |
| Local disease | Anterior blepharitis | |
| Systemic disease | Acne rosacea; seborrhoeic dermatitis; atopy; icthyosis; psoriasis; | McCulley Dougherty[145]<br>McCulley[146] |
| Syndromes | Anhydrotic ectodermal dysplasia; ectrodactyly syndrome; Turner syndrome | Baum et al[147]<br>Mondino et al[148] |
| Systemic toxicity | 13-cis retinoic acid | Mathers et al[142]<br>Lambert and Smith[149,150] |
| | Polychlorinated biphenyls | Ikui[151]<br>Ohnishi et al[152,153] |
| | Epinephrine (rabbit) | Jester et al[154] |
| Cicatricial MGD: Primary, or Secondary to: | | |
| Local disease | Chemical burns; trachoma; pemphigoid; erythema multiforme; acne rosacea; VKC and AKC | |

### *b) Reflex Motor Block*

Central damage to the VII cranial nerve, involving the nervus intermedius, leads to dry eye due to loss of lacrimal secretomotor function. The nervus intermedius carries postganglionic, parasympathetic nerve fibers (of pterygopalatine ganglion origin) to the lacrimal gland. Dry eye is due to lacrimal hyposecretion in addition to incomplete lid closure (lagophthalmos). Multiple neuromatosis has also been reported as a cause of dry eye.[132]

An association between systemic drug use and dry eye has been noted in several studies, with decreased lacrimal secretion being the likely mechanism. Responsible agents include: antihistamines, beta blockers, antispasmodics, and diuretics, and, with less certainty, tricyclic antidepressants, selective serotonin reuptake inhibitors, and other psychotropic drugs.[122] Additional associations with drying medications were reported by Schein et al, unrelated to the disease for which they were used.[133] Use of ACE (angiotensin converting enzyme) inhibitors was associated with a lower incidence of dry eye, and no relationship was found with calcium channel blockers or cholesterol-lowering drugs.[122]

## 2. Evaporative Dry Eye

Evaporative dry eye is due to excessive water loss from the exposed ocular surface in the presence of normal lacrimal secretory function. Its causes have been described as *intrinsic*, where they are due to intrinsic disease affecting lid structures or dynamics, or *extrinsic*, where ocular surface disease occurs due to some extrinsic exposure. The boundary between these two categories is inevitably blurred.

### *a. Intrinsic Causes*

#### 1) Meibomian Gland Dysfunction

Meibomian gland dysfunction, or posterior blepharitis, is a condition of meibomian gland obstruction and is the most common cause of evaporative dry eye.[134-136] Its multiple causes and associations are listed in Table 4 and include dermatoses, such as acne rosacea, seborrhoeic dermatitis, and atopic dermatitis. Less common but important associations include the treatment of acne vulgaris with isotretinoin, which leads to a reversible meibomian gland atrophy, loss of acinar density on meibography, and reduced volume and increased viscosity of expressed excreta.[142] Additionally, exposure to polychlorinated biphenyls, through ingestion of contaminated cooking oils, causes a chronic disorder with gross and extensive acneiform skin changes, meibomian seborrhoea with thick excreta and glandular cyst forma-

tion. Other organs are affected.[152,153,155] Meibomian duct keratinization occurs in the experimental model.[149,150]

MGD can be primary or secondary, simple or cicatricial. In simple MGD, the gland orifices remain located in the skin of the lid, anterior to the mucocutaneous junction. In cicatricial MGD, the duct orifices are drawn posteriorly onto the lid and tarsal mucosa and, hence, are unable to deliver oil to the surface of the tear film. Diagnosis is based on morphologic features of the gland acini and duct orifices, presence of orifice plugging, and thickening or absence of expressed excreta. Methods exist to grade the degree of MGD,[143] measure the degree of gland dropout (meibography),[156,157] and the amount of oil in the lid margin reservoir (meibometry).[65,158] Evidence from several sources suggests that MGD of sufficient extent and degree is associated with a deficient tear film lipid layer, an increase in tear evaporation, and the occurrence of an evaporative dry eye.

It is important to recognize the effect of lid commensal organisms on meibomian lipid composition and its potential effect on tear film lipid layer stability. Shine and McCulley have shown that constitutional differences in meibomian lipid composition exist in different individuals.[159,160] They identified one group of subjects with low levels of cholesterol esters and esters of unsaturated fatty acids (ie, the "normal-cholesterol absent" group: N[CA]), and another group with high levels of these fractions ("normal-cholesterol present" group: N[CP]). In the latter group, esterases and lipases produced by normal lid commensals (coagulase-negative staphylococci [CoNS], *Propionobacterium acnes* and *S aureus*) can release fatty acids and mono- and diglycerides into the tear film, which may be a source of irritation or of soap formation, said to be responsible for producing "meibomian foam."[161] It should also be noted that *S. aureus* growth can be stimulated by the presence of cholesterol and that, in a study by Shine and McCulley, there were twice as many staphylococcal strains on the lid margins of those normal subjects whose meibomian lipid was cholesterol-rich, than in the cholesterol-poor group.[160] Factors such as these may influence the microbial load and type on normal lid margins and influence the development of blepharitis.

### 2) Disorders of Lid Aperture and Lid/Globe Congruity or Dynamic

An increase in the exposed evaporative surface of the eye occurs in craniostenosis, endocrine and other forms of proptosis, and in high myopia. Endocrine exophthalmos and, specifically, increased palpebral fissure width, is associated with ocular drying and tear hyperosmolarity.[162] Increasing palpebral fissure width correlates with increased tear film evaporation.[61] Increased ocular surface exposure also occurs in particular gaze positions, such as upgaze,[163] and in activities that induce upgaze, such as playing pool, where, while aiming, the head is inclined downward and the eyes are in extreme upgaze.

Drying of the ocular surface due to poor lid apposition or to lid deformity, leading to exposure or poor tear film resurfacing, are accepted causes of ocular surface drying, but they have received little formal study.[164] Dry eye problems may be caused by problems of lid congruity after plastic surgery of the lids.[165]

### 3) Low Blink Rate

Drying of the ocular surface may be caused by a reduced blink rate, which lengthens the period during which the ocular surface is exposed to water loss before the next blink.[166] Methods have been developed to record the blink rate and to relate this to the development of dry eye. [163] This may occur as a physiological phenomenon during performance of certain tasks of concentration, eg, working at video terminals[167] or microscopes, or it may be a feature of an extrapyramidal disorder, such as Parkinson disease (**PD**).

The reduced blink rate in PD is due to a decrease in the dopaminergic neuron pool of the substantia nigra and is proportional to disease severity.[168] Reduced blink rate is regarded by some authors as the basis of dry eye in PD.[169] Biousse et al found blink rate and tear film breakup time (**TFBUT**) to be significantly reduced in untreated, early-onset PD patients with a significantly increased frequency of dry eye symptoms, whereas the Schirmer test and rose bengal staining measurements were no different in PD patients than in controls.[170] However, other authors report a reduced lacrimal secretion in PD,[171-173] and abnormalities of tear film stability, fluorescein and rose bengal staining, tear meniscus height, and meibomian gland function.[173]

Tamer et al reported dry eye symptoms in 87.5% of PD patients versus 20.6% of age-matched controls, with a mean total number of abnormal dry eye tests of $3.10 \pm 1.8$ in PD, versus $0.35 \pm 0.9$ in controls. ($P < 0.001$). Each test was significantly abnormal in PD patients versus controls, and all the tear tests (except meibomian gland function and meniscus height) showed a significant correlation with a PD severity index. The overall number of abnormal tests in PD patients was inversely related to the blink rate.

On the basis of these findings, Tamer et al postulated several mechanisms by which PD may induce dry eye. 1) Reduced blink rate and impaired meibomian oil delivery to the tear film can increase evaporative loss. They also suggest that a reduced blink rate could impair the clearance of lipid-contaminated mucin.[174] 2) Experimentally, androgens are required for the normal functioning of both the lacrimal[175,176] and meibomian glands, [177,178] and there is clinical evidence that dry eye symptoms are promoted by blockade of androgen receptors.[43] The levels of circulating androgens are low in a large proportion of PD patients,[179] and it is suggested that this may contribute to lacrimal and meibomian dysfunction. 3) In addition, decreased reflex tearing in PD has been attributed to autonomic dysfunction, reflecting the presence of Lewy bodies in the substantia nigra, sympathetic and peripheral parasympathetic ganglia.[180] Magalhaes et al found evidence of autonomic failure in about a third of patients with PD.

In conclusion, it is possible that dry eye disease in PD has multiple causes.

### *b. Extrinsic Causes*

#### 1) Ocular Surface Disorders

Disease of the exposed ocular surface may lead to imperfect surface wetting, early tear film breakup, tear hyperosmolarity, and dry eye. Causes include vitamin A deficiency and the effects of chronically applied topical anesthetics and preservatives.

*Vitamin A Deficiency:* Vitamin A deficiency may cause dry eye (xerophthalmia) by two distinct mechanisms. Vitamin A is essential for the development of goblet cells in mucous membranes and the expression of glycocalyx mucins.[181,182] These are deficient in xerophthalmia, leading to an unstable tear film characterized by early tear film break up. Vitamin A deficiency can cause lacrimal acinar damage, and, therefore, some patients with xerophthalmia may have a lacrimal, aqueous tear-deficient dry eye.[183]

*Topical Drugs and Preservatives:* Many components of eye drop formulations can induce a toxic response from the ocular surface. Of these, the most common offenders are preservatives, such as benzalkonium chloride (**BAC**), which cause surface epithelial cell damage and punctate epithelial keratitis, which interferes with surface wettability. Use of preserved drops is an important cause of dry eye signs and symptoms in glaucoma patients, and it is usually reversible on switching to nonpreserved preparations.[184] Therefore, frequent applications of preserved artificial tear preparations should be avoided.

Topical anesthesia causes drying in two ways. It reduces lacrimal secretion by reducing sensory drive to the lacrimal gland and also reduces the blink rate. It has also been suggested that anesthesia of those lacrimal secretory nerve terminals close to the surface of the upper fornix (innervating the palpebral and accessory portions of the lacrimal gland) may also be blocked by topical anaesthetics (Belmonte C: personal communication).

Chronic use of topical anesthetics can cause a neurotrophic keratitis leading to corneal perforation.[185,186]

#### 2) Contact Lens Wear

Contact lens wear is prevalent in the developed world, with 35 million wearers cited in the USA in the year 2000.[187] The causes of CL-related symptoms and of lens intolerance are, therefore, of personal and general economic importance. The primary reasons for CL intolerance are discomfort and dryness.[188,189] In recent years, a number of questionnaires have been developed to identify dry eye symptoms in CL wearers.[45,190-192] Use of such questionnaires has indicated that about 50% of CL wearers report dry eye symptoms[191-194] CL wearers are 12 times more likely than emmetropes and five times more likely than spectacle-wearers to report dry eye symptoms.[195]

In a large cross-sectional study of CL wearers (91% hydrogel and 9% gas permeable lenses), several factors were found to be associated with dry eye diagnosed using the Contact Lens Dry Eye Questionnaire (**CLDEQ**). Pre-lens tear film (**PLTF**) thinning time was most strongly associated with dry eye (dry eye: 8.23 ± 5.67 seconds; non-dry eye: 11.03 ± 8.63 seconds. [$P = 0.0006$]), followed by nominal CL water content and refractive index.[114]

The pre-lens lipid layer thickness was less in dry eye subjects and correlated well with the pre-lens tear film thinning time. This, together with poor lens wettability, could be a basis for a higher evaporative loss during lens wear and was attributed to potential changes in tear film lipid composition, rather than to a loss of meibomian gland oil delivery.

Patients wearing high water-content hydrogel lenses were more likely to report dry eye. This is a controversial area in the literature. In a study of the effects of five hydrogel lenses on tear film physiology, Thai et al found that all the examined soft CL materials increased the evaporation rate and decreased the tear film thinning time.[196] The surface wetting ability of the CL materials was the same, regardless of special surface lens treatments. Efron et al found that patients wearing low water CLs, which maintained their hydration, were free from symptoms.[197] However, other studies reported no correlation between CL hydration and dry eye symptoms[189] and no relationship between lens hydration and tear film thinning time and dry eye symptoms[198] or evaporative water loss.[199] Dry eye was associated with a higher tear osmolarity, but not in the range normally associated with dry eye tear hyperosmolarity. The authors commented that this lower value might have been caused by reflex tearing at the time of sampling.[114]

Women were found to report dry eye more frequently than men, with 40% of the men and 62% of the women classified as having dry eye ($P < 0.0001$).[114] The reasons for this were not explored, but potential contributing factors were considered to be hormone fluctuations during the menstrual cycle or after the menopause and use of oral contraceptives or hormone replacement therapy. It was also noted that symptom reporting by women, in general, tends to be higher than that by men.[200] Some studies show no effect of oral contraceptives or hormone levels on a range of tear parameters.[201]

Glasson et al[202] showed that intolerance to hydrogel lenses in normals correlates with a shorter blink interval, noninvasive TFBUT and phenol red thread test length and a lower tear meniscus height and area; this has had predictive power in people presenting for CL fitting. A formula linking symptoms (using the McMonnies Dry Eye Questionnaire), non-invasive tear break up time (NITFBUT), and tear meniscus height predicted potential intolerant subjects with a sensitivity of 100%, specificity of 57%, and accuracy of 78%. Intolerance was also associated with an increase in degraded lipid products, phospholipase A2, and lipocalin in tear samples.[203] These studies suggest that features compatible with a dry eye state may predispose an individual to CL intolerance

The variations in visual performance with soft CLs may be due to light scattering produced by changes in the hydration levels of the lens or changes in the tear film over the lens.[204,205] Decreases in retinal image quality have been inferred from the modulation transfer function induced by the drying tear film and observed with the Schack-Hartman