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Tear volume based diagnostic classification for tear dysfunction

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Abstract

Dysfunction of one or more components of the lacrimal functional unit results in an unstable tear film that can trigger eye irritation or cause ocular surface disease. There are distinct differences in the pattern of cornea and conjunctival disease and inflammation between aqueous deficient and aqueous sufficient tear dysfunction. There are accurate commercially available methods to measure tear volume. Diagnostic classification based on tear volume can guide therapy and identify patients with higher risk of developing disabling ocular surface disease or irritation.

Keywords

Tear dysfunction; Dry eye; optical coherence tomography; therapy

Introduction

Tear production, distribution and clearance are regulated by the Lacrimal Function Unit that consists of the main and accessory lacrimal glands, the Meibomian glands, the conjunctiva, eyelids and blink apparatus.¹ Tear dysfunction develops when one or more of these components is no longer able to maintain a stable tear film.¹ Tear dysfunction is one of the most common eye conditions with a reported prevalence of 6 – 43 million in the United States, depending on the diagnostic criteria.^{2–6} Tear dysfunction causes eye irritation and visual symptoms, including photophobia and blurred and fluctuating vision. Tear dysfunction can cause pathological changes to the ocular surface epithelium with disruption of corneal epithelial barrier function and loss of mucus secreting conjunctival goblet cells. It may also decrease quality of life and in the most severe cases, it can cause functional and occupational disability. Indeed, the impact of dry eye on quality of life was rated to be equivalent to unstable angina using utility assessments.⁷

Tear dysfunction can result from a myriad of causes. Disease or dysfunction of the lacrimal glands results in aqueous tear deficiency (ATD), while aqueous tear production and tear volume are typically normal in Meibomian gland disease and conditions altering tear distribution, such as conjunctivochalasis. Consequently, there is no need to stimulate

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aqueous tear production or block tear drainage in patients with a normal or elevated tear volume. Consensus-based classification schemes for dry eye and tear dysfunction have been proposed. An international Delphi panel proposed a classification of tear dysfunction with 3 major subsets: without lid margin disease, with lid margin disease and altered tear distribution.⁸ One problem with this classification scheme is that lid margin disease is prevalent in older individuals, is difficult to grade objectively and is frequently not accompanied by eye irritation or ocular surface disease. The International Dry Eye Workshop (DEWS I) took a different approach by proposing two major categories of dry eye: aqueous deficiency and increased tear evaporation, the latter caused primarily by meibomian gland disease (MGD).⁹ While evidence of increased tear evaporation has been found in MGD^{10–12}, there are no commercially available instruments to measure tear evaporation rate and the evidence suggests that increased tear evaporation alone is not sufficient to decrease tear volume below normal levels in patients with MGD.¹³ A more practical approach is to stratify tear dysfunction by objective measurement of tear volume into aqueous deficient and aqueous sufficient groups. Evidence supports this approach to classification because studies have found distinct differences between aqueous deficient and sufficient groups in pattern and severity of ocular surface disease, conjunctival goblet cell density, response to desiccating environmental stress, corneal sensitivity, blink rate and profile of inflammatory mediators in tears and conjunctiva.^{13–18} The advent of simple, rapid, noninvasive commercially available methods to measure tear volume facilitate the use of diagnostic and treatment guidelines based on tear volume. Rationale for this approach and guidelines for treating tear dysfunction associated with low or normal aqueous volume are presented herein.

Why use tear volume to classify tear dysfunction?

It is easy to explain why patients with ATD and moderate ocular surface vital dye staining have irritation symptoms. On the other hand, it is puzzling why some “dry eye” patients who are experiencing constant severe eye irritation are found to have a normal or even elevated tear meniscus. Some of these patients may even complain of tearing and appear to have a wet eye. This paradox combined with the increasing evidence that tear instability is associated with ocular surface inflammation, served as the basis for the conclusion of the International Delphi panel that not all dry eye is due to a deficient tear volume and that tear dysfunction is a more encompassing term than dry eye for disorders of the lacrimal functional unit.⁸ There are key differences in cornea and conjunctival disease between patients with low and normal/high tear volume. ATD, particularly when accompanied by systemic autoimmunity (e.g. Sjögren’s syndrome) and loss of reflex tearing is associated with greater ocular surface vital dye staining, reduced conjunctival goblet cell density, lower levels of lacrimal growth factors (e.g. epidermal growth factor - EGF) in tears, higher tear MMP-9 activity and greater expression of T helper associated cytokines (IFN- γ and IL-17) in the conjunctiva.^{14,15,17,19,20} Patients with chronic ATD and corneal epithelial disease have been noted to have cornea nerve degeneration and reduced corneal sensitivity, even in the face of increased irritation symptoms.^{18,21–23} In contrast patients with conjunctivochalasis often have normal or elevated tear meniscus height and require surgical excision of the redundant conjunctiva to reestablish tear dynamics and eye comfort.^{24,25} These findings

support use of a tear volume based classification to identify patients at risk of developing sight threatening corneal disease and to recommend appropriate therapy

Practical Tear volume based approach to classification of tear dysfunction

An algorithm for classification of tear dysfunction based on tear volume is presented in Figure 1. Patients with tear dysfunction typically present with irritation symptoms, including dryness, foreign body sensation, grittiness or burning. They often report that dry and drafty environmental conditions exacerbate their eye irritation. Eye irritation may be accompanied by complaints of blurred or fluctuating vision or visual complaints alone. Certain patients with long standing or severe corneal epithelial disease may develop degeneration of corneal nociceptors and have reduced corneal sensitivity. Some of these patients are relatively symptom free. Paradoxically, others may complain of severe discomfort due to neuropathic pain.²⁶

Patients with complaints of eye irritation or blurred vision can be sub classified into ATD or aqueous normal groups by imaging the tear meniscus dimensions as an indicator of tear volume.²⁷ Tear meniscus imaging (as well as tear and corneal surface imaging) should be performed prior to instilling any drops or manipulating the eye. Tear meniscus dimensions can be measured by optical coherence tomography (OCT) or from a reflected image using commercially available instruments.^{25,27,28} OCT is a rapid, accurate and reproducible method to image tear meniscus dimensions and the latest generation instruments have an optical resolution of 5 microns.²⁹ The tear meniscus height, width or cross-sectional area can be measured. Because meniscus height has been found to correlate with meniscus area, height is the most commonly used measurement. Representative tear meniscus images taken by OCT in subjects with tear dysfunction who have aqueous deficiency or normal tear volume are shown in Figure 2. The mean tear meniscus height in normal subjects ranging in age from 19–82 years was found to be 348µm in a study reported by Tung and colleagues which was very similar to the mean height (330µm) in a normal population in Japan.^{13,30} Mean TMH was found to be lower in ATD (205µm), whereas, it was not statistically different from the control group in patients with MGD (313µm).¹³ A significant inverse correlation was found between inferior TMH and change in severity of irritation symptoms and ocular surface dye staining in patients who were exposed to experimental desiccating environmental stress, indicating that patients with a low tear volume are more susceptible to develop worsen irritation and ocular surface disease when they are exposed to a dry, drafty environment.¹⁶ The tear meniscus image can also be examined for particulate debris (as shown in Figure 2B) which may represent desquamated epithelium, clumped protein/mucus or inflammatory cells, that increase with tear dysfunction, inflammation and delayed clearance.

TMH was found to be increased in eyes with conjunctivochalasis because the redundant conjunctiva protrudes into the inferior tear meniscus (as shown in Figure 2C) where it serves as a mechanical barrier that interferes with horizontal movement of tears along the lower lid margin and may push the border of the tear meniscus further anteriorly on the lid margin.²⁴ Because conjunctivochalasis has been found to be worse in the temporal and nasal conjunctiva, it typically sequesters tears in the center of the lower lid.²⁹ Anterior migration

of the tear meniscus and increased osmolarity and concentration of inflammatory mediators in tears can cause changes to the lid margin and meibomian gland orifices.^{31,32} We measured TMH and the location of Marx's line, that is normally present just posterior to the mucocutaneous junction and meibomian gland orifices on the lower lid, in eyes with MGD, of which 96% had grade 1 or higher conjunctivochalasis temporally using a reported grading scheme.³³ Relative to the posterior lid margin, we found Marx's line had the greatest anterior displacement in the temporal zone. Significant positive correlations were found between length of anterior displacement of Marx's line in the temporal zone and central tear meniscus height, anterior length, and area (Fig 3 A and B). These findings highlight the importance of identifying altered tear dynamics associated with conjunctivochalasis and MGD early so surgical reduction/excision of CCh can be considered before structural changes of the lid margin and/or meibomian gland orifices develop.

Tear instability should be evaluated as a measure of tear dysfunction which is compromised in all types of tear dysfunction.¹⁴ Tear stability can be measured by non-invasive imaging methods or by the traditional fluorescein tear break up time.^{28,34} Confirmation of tear instability is particularly important in patients with normal or increased TMH. If tear break up time is found to be normal in this group, the patient should be examined for other causes of irritation, such as exposure, allergy, superior limbic keratoconjunctivitis, lid malposition or tear drainage obstruction.

The ATD and aqueous normal groups can be further stratified by etiology. ATD can be subclassified based on presence of systemic disease into non-autoimmune, autoimmune (primarily Sjögren's syndrome based on consensus criteria³⁵) or other systemic inflammatory disease, such as Steven's Johnson syndrome or graft-vs-host disease (GVHD). Those in the normal or elevated groups should have thorough examination of their lid margins and meibomian glands. Signs of MGD, such as expressibility, secretion quality, plugging and lid margin vascularity have been reported by the Meibomian gland workshop.³⁶ The cornea and conjunctiva should be examined for conditions that alter tear spread or distribution. These include conjunctivochalasis, pinguecula, pterygium and cornea fibrotic conditions, such as basement membrane disease and nodular degeneration. This examination may also reveal signs of conjunctival inflammation or scarring, or lid or punctal abnormalities.

Grading Severity of Ocular Surface Disease

Severity of ocular surface disease can be assessed with vital stains. Fluorescein is the easiest dye to visualize in the cornea, while lissamine green produces optimal staining of the conjunctiva. A number of schemes have been reported to grade severity of cornea and conjunctival dye staining.^{13,37,38}

The Schirmer test, although recognized for its variability from induced reflex tearing, blinking or eyelid closure, can provide an indication of the lacrimal gland's capacity to reflex tear when the test is performed without anesthesia (Schirmer 1) or with nasal stimulation.¹⁴ Reflex tearing is often lost early in the disease course of Sjögren syndrome and inability to reflex tear is associated with worse ocular surface disease.^{18,39} Topographic

corneal regularity indices, such as the Klyce surface regularity (SRI) and surface asymmetry (SAI) indices have been found to increase in tear dysfunction and to correlate with the severity of corneal epithelial disease and visual function.⁴⁰ Conjunctival goblet cells produce mucins and a variety of immunomodulatory and homeostatic factors.⁴¹ Reduced conjunctival goblet cell density has been observed in ATD and there is a significant inverse correlation between goblet cell density and severity of conjunctival lissamine green staining and expression of IFN- γ .^{14,20} Goblet cells can be measured in conjunctival impression cytology stained with periodic acid Schiff reagent or antibodies to the goblet cell mucin MUC5AC.^{15,20,42} Reduced corneal sensitivity can be the cause or consequence of ATD and is associated with worse corneal epithelial disease, irritation symptoms and risk of developing persistent/recurrent corneal epithelial defects.¹⁸ Corneal sensitivity can be evaluated by contact or non-contact methods.¹⁸ Increased tear matrix metalloproteinase (MMP-9) activity has been reported to correlate with severity of corneal epithelial disease.¹⁹ While there are no currently available clinical assays to measure MMP-9 activity, there is an approved point-of-care MMP-9 tear immunoassay that detects levels of MMP-9 about a certain threshold.^{43,44} In one clinical series, this test was positive in 39% of patients experiencing ocular irritation; however, a positive result did not correlate with severity of ocular surface dye staining, so this test may prove to be a useful method to identify higher levels of ocular surface inflammation in symptomatic patients.⁴⁴

Tear volume based treatment recommendations

Treatment recommendations for tear dysfunction based on tear volume are presented in the Table. These are adapted from previously published consensus recommendations of the Delphi panel and Dry Eye Workshop.^{8,45} Anti-inflammatory agents are suggested to treat for both aqueous deficiency and aqueous normal conditions. Additional therapies, such as punctal occlusion, secretagogues, nasal neurostimulation, are recommended for ATD to increase tear volume. Autologous blood products (serum, plasma, plasma rich in growth factors) can increase concentrations of deficient tear factors (e.g. epidermal growth factor) in patients with lacrimal gland disease.^{45–47} Cyclosporin A has been found to increase conjunctival goblet cell density (CsA).^{42,48} Therapy based on tear volume identifies patients who are likely to benefit from therapies that increase tear volume and beneficial tear factors while avoiding the adverse effects of punctal occlusion in patients with normal tear volume.

In summary, diagnostic classification of tear dysfunction based on tear volume is clinically practical, identifies patients with similar patterns of disease and provides rationale for prescribing more targeted therapy.

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Tear Volume Based Classification of Tear Dysfunction

Figure 1.

Tear volume based diagnostic classification for tear dysfunction. Patients presenting with irritation or vision-related symptoms consistent with tear dysfunction are stratified into aqueous deficient or aqueous normal based on tear meniscus height (TMH). These conditions are further stratified based on clinical features or additional diagnostic tests. GVHD = graft vs. host disease, MGD = Meibomian gland disease, AKC= atopic keratoconjunctivitis, CCh = conjunctivochalasis, EBMD = epithelial basement membrane disease

Figure 2.

Tear meniscus height (TMH) imaged with optical coherence tomography (OCT) in eye with severe aqueous deficiency and no measurable meniscus (A.), meibomian gland disease with delayed tear clearance and particulate debris in the tears with a normal TMH (B.), and conjunctivochalasis with redundant conjunctival prolapsed into the central tear meniscus and anterior displacement of the tear meniscus on the lower lid margin.

Figure 3. Correlations between central tear meniscus height (A.) and area (B.) with furthest anterior migration of Marx's line (stained with lissamine green) in the temporal lower eye lid margin.

Table

Tear volume based treatment recommendations

Aqueous Tear Deficiency	Aqueous Normal/Elevated	
	Meibomian Gland Disease	Conjunctivochalasis
Levels 1 & 2 Artificial tears/lubricants Punctal plugs EFA Anti-inflammatory therapy [*] Nasal neurostimulation	Thermocompression (manual or automated) EFA Anti-inflammatory therapy [*] Anti-protease/lipase [¥]	Anti-inflammatory [*] Ablation or excision
Levels 3 & 4 Permanent punctal occlusion Anti-proteases [¥] Secretagogues Nasal neurostimulation Blood products Therapeutic contact lens Tarsorrhaphy		

Adapted from the International Delphi Panel and Dry Eye Workshop.^{8,45}

EFA: essential fatty acids [docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), gamma linolenic acid (GLA)]

^{*} azithromycin, corticosteroids, cyclosporine A, lifitegrast, tetracyclines^{49–51}[¥] corticosteroids, tetracyclines (also inhibits bacterial lipases), azithromycin^{52–55}