“Dry Eye” Is the Wrong Diagnosis for Millions

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ABSTRACT
The clinical perspective that dry eye is, at best, an incomplete diagnosis and the benefit of an etiology-based approach to dry eye are presented. To provide context for this perspective, the historical and current definition of dry eye is reviewed. The paradigm shift introduced by the Meibomian Gland Dysfunction (MGD) Workshop, that MGD is likely the leading cause of dry eye, is discussed in combination with the advancements in the diagnosis and treatment of MGD. To facilitate discussion on the benefit of an etiology-based approach, a retrospective observational analysis was performed on deidentified data from eligible, fully consented, refractory dry eye patients, where conventional sequelae-based dry eye treatment had failed. In this refractory population, the diagnosis of MGD, which directed treatment to evacuating gland obstructions and rehabilitating gland function, was successful. The clinical perspective that “dry eye” is the wrong diagnosis for millions is provocative. However, the MGD-first approach has the potential to revolutionize the timing of diagnosis and the choice of frontline therapy in most patients with dry eye. Additionally, the ability to screen for MGD in its earliest stages, during routine care, expands the scope of clinical practice to include early intervention. For most patients, we are no longer constrained to delay diagnosis until the tear film has decompensated and the cascade of inflammation has ensued. We do not have to wait for our patients to tell us there is a problem.

Key Words: meibomian gland dysfunction, dry eye, ocular surface disease

The past decade has seen remarkable advances in many areas of eye care. However, in the field of dry eye, our progress has been relatively slow. We remain challenged by the apparent complexity of both diagnosis and management of dry eye.1–3 The authors believe that the lack of significant advancement in dry eye can be traced, in part, to the origins of its discovery and the international consensus to define dry eye by its sequelae (signs and symptoms). Specifically, the 65-year-old culture that dry eye is primarily attributed to a lack of aqueous production,4 in combination with a sequelae-based approach to diagnosis and management, continues to thwart our therapeutic efficacy.5,6

What Is Dry Eye?
The National Eye Institute defined dry eye as the following: “Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.”5 It is notable that the definitions are nonspecific. The intent of the “global” definition was not to include an etiology but rather identify a state. The state was recognized as manifesting any one or a group of sequelae. Although no clear etiology was established in either definition, the earlier report stated that aqueous deficiency was the basis of the overwhelming majority of dry eye and thus recommended that treatments be targeted to tear replacement and controlling inflammation.5,6

In 2007, the International Dry Eye Workshop offered the following: “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.”1 This definition also contains no mention of etiology but is highly specific in its listing of the six sequelae: symptoms of discomfort, visual compromise, tear film instability, ocular surface damage, increased osmolarity, and inflammation. As such, currently, dry eye is a diagnosis of sequelae (signs and symptoms).

Identifying, measuring, and managing the sequelae of a disease are critical to disease management. However, diagnoses that offer no direction for the treatment of an etiology but rather direct the treatment to measuring and managing the sequelae of the disease are known to be complex and problematic to manage.7 Dry eye is...
no exception. If one examines the risk factors for dry eye, they span the entire spectrum, from innumerable systemic conditions to daily computer use, from hormones to contact lens wear, from low humidity environments to cancer therapy. “Dry eye” is as nonspecific a diagnosis as back pain or headache. A recent commentary on dry eye states that it is best viewed as a general failure of the lacrimal functional unit to protect the ocular surface from environmental stress. This places almost anyone at risk for dry eye.

How Did We Get Here?

Dry eye itself and the concept of lacrimal insufficiency as the etiology for dry eye were first introduced in 1950 when a group of patients with Sjögren disease manifested symptoms of “dry eye” in addition to the other known manifestations of the disease. Thus, our initial discovery of the condition was birthed from a select group of patients that did experience a dysfunction of the lacrimal gland.

Since that time, our awareness of the condition has exploded. Over the last 50 years, multiple etiologies have been proposed such as mucin deficiency, inflammation, the role of hormones, and, more recently, meibomian gland dysfunction (MGD). Despite these various proposals, the historical belief that the lacrimal insufficiency is the primary driver of the condition continues to direct our current treatment methods and impedes treatment efficacy. The number one prescribed frontline therapy for dry eye is some form of tear replacement for the amelioration of symptoms.

A Paradigm Shift

In 2011, the International Meibomian Gland Dysfunction Workshop Report concluded that MGD may well be the leading cause of dry eye throughout the world. This was in direct opposition to the aforementioned National Eye Institute report stating that aqueous deficiency dry eye due to lacrimal dysfunction was the vast majority of dry eye. They further hinted that their findings might necessitate change by the following commentary: “There are rare occasions in a field of science when significant advances occur in leaps and bounds, rather than in small, deliberate steps. This moment is imminent in the field of meibomian gland dysfunction, and therefore in dry eye disease.”

Although it has been intellectually accepted that the majority of dry eye is caused by MGD, our clinical approach has not shifted substantially. This may in part be attributed to a lack of awareness of new metrics and therapies for diagnosing and managing MGD. It may also be because MGD has not yet been incorporated into any internationally accepted definition of dry eye as the leading cause of dry eye.

MGD Is Prevalent and Treatable

There have been numerous studies documenting the overwhelmingly high prevalence of MGD in dry eye and other populations. To mention a few, Hom et al. reported 39% of asymptomatic subjects had MGD. Lemp et al. found that 86% of patients with dry eye of known cause had MGD. Shimazaki et al. found 65% of eyes with ocular discomfort had MGD, and Foulks et al. reported that the prevalence of MGD is as high as 60%. The lack of understanding that MGD is nonobvious in its early stages, and that it can only be detected if meibomian gland function and structure are actively assessed, has contributed to the low awareness of the prevalence of MGD. Further, the lack of metrics to accurately assess function and structure have only recently been introduced at the clinic level. As such, future prevalence data are likely to be even higher than are currently reported.

The treatments for MGD have evolved dramatically over the last decade. It has been understood for more than 150 years that the core therapy for dysfunctional meibomian glands is to remove obstructions and thickened secretions from within glands. We now also understand that front surface heating of the eyelids is minimally effective and likely best reserved for adjunctive therapy. The recent discovery that heat can be efficaciously applied to the inner palpebral conjunctival surface directly over the meibomian glands has revolutionized treatment of MGD and dry eye.

This treatment approach, tested in multiple clinical trials, is so effective that a single dose therapy has been shown to have sustained efficacy (reduced dry eye symptoms and improved gland function) for 6 to 12 months and longer. Treatments for MGD have become progressively more efficacious, providing a viable treatment of dry eye that can reliably reduce dry eye symptoms and other dry eye sequelae such as elevated osmolarity, tear film instability, and ocular surface staining. There are other novel therapies for MGD that have been reported in the literature but they do not currently have US Food and Drug Administration clearance for the treatment of MGD. Treatment of dry eye resulting from the recognition that the most prevalent etiology of dry eye is MGD has resulted in a new era of success in what was an enigmatic and frustrating area of multiple treatments with minimal success.

An Etiology-Based Approach to Even the Most Refractory Cases

There is a single peer-reviewed abstract on the benefit of treating MGD in patients with refractory dry eye symptoms by heating and evacuating the meibomian gland obstructions. This study showed that a significant proportion of post-refractive surgery patients with refractory dry eye symptoms were successfully treated by using a single 12-minute dose of vectored thermal pulsation for MGD. The results remained positive for up to 6 months. After 6 months, a subset of the patients began to show regression. There was no mention of any additional therapy. The successful treatment of refractory dry eye after LASIK by treating MGD, where all other dry eye therapy had failed, is in alignment with the perspective that MGD is the leading cause of dry eye.

To further assess the benefits of an etiology-based approach (specifically MGD; Fig. 1) in refractory dry eye, where the conventional sequelae-based approach had failed, we conducted a retrospective study of deidentified data on recalcitrant dry eye patients over a 1-year period. These patients specifically sought our expertise, often in desperation, because conventional dry eye treatment had not improved their symptoms or findings. The goal of the retrospective analysis was to evaluate what percentage of these patients had improved MG function and improved dry eye symptoms (a criterion of six or fewer lower eyelid functional meibomian glands constituted MGD). We also wished to determine how effective our standard “MGD First” approach had
been in helping these recalcitrant dry eye treatment participants with their symptoms. This was not a formally designed study and we do not wish to convey that identifying and treating MGD should be implemented while ignoring all other potential etiologies for “dry eye,” or at the expense of measuring and managing sequelae of dry eye. Our retrospective analysis was to determine the efficacy of an etiology-based approach focused on the meibomian glands, in even the most refractory dry eye patients.

Retrospective analysis was performed on deidentified data from eligible, fully consented, refractory dry eye patients at a single clinical center in Boston, MA, during 2013 and 2014 (n = 47; 12 male and 35 female subjects). A comprehensive dry eye workup, combined with an MGD-directed treatment approach, was performed on all patients. The primary measures for the analysis were the number of functional glands and the symptom scores before and after treatment. The final follow-up was 9 to 12 months after treatment.

The mean (±SD) age was 50.9 (±16.5) years (range, 18 to 80 years). The mean (±SD) number of doctors visited by the 47 patients before visiting our clinic was 2.5 (±1.5) (range, 1 to 7). The mean number of different therapies prescribed by the prior practitioners and used by the patients before their baseline visit was 3.5. Forty-five of the 47 patients had MGD. The mean (±SD) number of functional meibomian glands before treatment was 3.3 (±2.0) (range, 0 to 9), improving after treatment to 6.3 (±2.2) (range, 0 to 12) (p < 0.0001, paired t test). The mean (±SD) symptom score before treatment was 13.9 (±5.2) (range, 5 to 28), improving after treatment to 8.4 (±4.2) (range, 2 to 18) (p < 0.0001, paired t test). Thirty-eight (81%) of the 47 participants had improved meibomian gland function (by at least one additional

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**FIGURE 1.**
A schematic for an etiology-based approach to the diagnosis and management of dry eye.

**FIGURE 2.**
An etiology-based approach, facilitating early intervention of MGD.
DISCUSSION

In 1946, Wolff concluded the following: The meibomian glands "are essentially the glands proper to the cornea, which in the interests of vision have been moved out of the way." Wolff was a visionary. The clinical science to substantiate that the health of the ocular surface is indeed dependent on healthy meibomian gland function has taken several decades to emerge.

With the expanding body of clinical science, in combination with the MGD Workshop report, the authors' clinical perspective has evolved to question the validity of dry eye as the primary diagnosis in, not all, but the majority of cases. There are always exceptions (e.g., Stevens-Johnson syndrome, Sjögren rheumatoid arthritis, Bell palsy, etc.) where MGD is not the primary diagnosis. However, even in these cases, MGD remains highly prevalent. Meibomian gland dysfunction is hypothesized to occur through the mechanisms of tear film decompensation and evaporative stress. MGD should be the primary diagnosis as it would appropriately direct treatment toward rehabilitating meibomian gland function as the necessary long-term goal while measuring and managing the sequelae of dry eye in the short term.

The "rule out MGD first" approach has the potential to revolutionize the timing of diagnosis and the choice of frontline therapy in most patients with dry eye. With an etiology that can be screened for during routine care, the scope of clinical practice is expanded to include early intervention. Certainly, we can identify MGD in its earliest stages. We are not constrained to delay diagnosis until the tear film has been compensated and the cascade of inflammation has ensued, that is, waiting for our patients to tell us there is a problem (Fig. 2). The authors believe that the evidence is compelling and that the present practice of diagnosis and treatment of patients presenting with "dry eye" should change. Despite the increased use of drugs in the past decade, treatment dedicated to the historically accepted lacrimal dysfunction has achieved only limited success, and the diagnosis of dry eye, through manifest sequelae, has diverted our attention from treating the root cause and causes of the condition.

Our clinical perspective is that dry eye is likely the wrong diagnosis for millions. Although provocative, this statement will, at worst, encourage the reader to further contemplate why dry eye diagnosis and management remains an enigma. At best, it will encourage a shift to an etiology-based approach and, ultimately, this perspective should also serve to stimulate a culture of early diagnosis and intervention.

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