Special Issue

The International Workshop on Meibomian Gland Dysfunction: Introduction

Kelly K. Nichols

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 (MGD)—and therefore in dry eye disease. The goals of the International Workshop on Meibomian Gland Dysfunction were twofold: first, to develop a consensus understanding of the meibomian gland in health and disease; second, to disseminate the knowledge broadly to further the field.

Over the past several years, although the body of knowledge about dry eye has been expanding, it has become clear that significant detail and direction relative to the impact of the meibomian gland in dry eye have been lacking. The Tear Film and Ocular Surface Society (TFOS; http://www.tearfilm.org), a nonprofit organization, launched the International Workshop on Meibomian Gland Dysfunction (www.tearfilm.org/mgdworkshop/index.html) in conjunction with generous industry sponsors that supported the workshop process through unrestricted grants, allowing volunteers to come together to plan, execute, translate, and present the findings of the workshop at a variety of meetings worldwide.

Objectives

International workshops, such as the Dry Eye Workshop (DEWS) and this workshop on MGD, provide a consensus overview of the field as a snapshot in time. In addition to an exhaustive international literature–based review of the salient clinical, translational, and basic research, new concepts—often assimilated through the process of refining the reports—are also included here. Thus, this report is the most current, definitive summary of the meibomian gland in health and disease. As such, the objectives defined by the Steering Committee were as follows:

- to develop a contemporary understanding of the definition and classification of MGD;
- to conduct an evidence-based evaluation of meibomian gland structure and function in health and disease;
- to critically assess the structure of meibomian lipid and the interaction of the secreted lipid with additional components of the tear film;
- to evaluate the prevalence and associated risk factors for MGD;
- to assess methods of diagnosis, evaluation, and grading of severity of MGD;
- to evaluate existing recommendations and provide a diagnostic/therapeutic algorithm for the management and therapy of MGD;
- to evaluate existing clinical trials of pharmaceutical interventions for the treatment of MGD and provide recommendations for future clinical trial design; and
- to create an executive summary of recommendations for future research in MGD.

Process

More than 50 international experts participated in the workshop, which occurred over a 2-year period. The initial steering committee meeting was held in November 2008, at which time subcommittee chairs and committees were selected on the basis of expertise within the field. After the appointments, the steering committee and the subcommittees met via conference call, Skype, and in person to create draft outlines, assign writing topics, and create draft subcommittee reports. The draft outlines were reviewed by the membership at an MGD workshop meeting after the Association for Ophthalmology and Visual Science (ARVO) annual meeting in May 2009. After that meeting, draft reports were written and circulated for review by the membership at large, including members of the industry liaison committee. Each subcommittee reviewed comments, and suggestions were incorporated into the reports. The "final" draft reports were reviewed by the writing committee at a meeting in April 2010. The committee used this meeting to identify areas in the reports that required harmonization, when overlap classification was needed. After this process and revision by the subcommittees with writing committee guidance, the finalized reports were submitted to the subcommittees for final approval. The steering committee members, writing committee members, subcommittee chairs, and subcommittee members are listed in Tables 1 and 2.

Overarching Issues and Forward-Looking Statements

Assembling a group of experts in any field provides the opportunity for discussion, agreement, and disagreement, all of which tend to move a field forward. During the MGD Workshop process, each subcommittee grappled with the controversies within each topical area. Several of the key issues are identified in the following sections. In addition, several appear in more than one report, indicating that there are overarching topics related to MGD that we have yet to fully understand.

Relation of MGD and Dry Eye Disease

It is believed that MGD may be the most common cause of evaporative dry eye and may also have some association with

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Table 1. Steering Committee

Chair: Kelly K. Nichols (USA)*
Vice-chair: Gary N. Foulks (USA)*
Organizer: David A. Sullivan (USA)*
Consultant: Anthony J. Bron (UK)*
Members: Ben J. Glasgow (USA), Murat Dogru (Japan), Kazuo Tsubota (Japan), and Michael A. Lemp (USA)
Operations Manager: Rose M. Sullivan (USA)
Managing Editor: Michelle Dalton (USA)*

* Members of the Writing Committee.

aqueous-deficient dry eye. Overview reports on dry eye have suggested "meibomian oil deficiency" as an intrinsic factor associated with the disease. The field now understands that the meibomian gland is a key component in the etiology of dry eye and contributes to the evaporative status of the tear film. Most clinicians now assess the lid/meibomian glands in a severity-grading scheme for dry eye, which includes terminology such as "MGD variably present" to "frequent" and "trichiasis, keratinization, symblepharon" at the severe end of the scale. The inclusion of meibomian gland pathophysiology indicates a consensus that the meibomian gland plays a role in dry eye disease.

What is perhaps less clear is the causative relation involved, as well as the binomial classification of dry eye (aqueous-deficient versus evaporative). From a clinical perspective, patients can present with various degrees of MGD and aqueous deficiency and of the two currently accepted forms of dry eye, evaporative dry eye is thought to be significantly more common than aqueous-deficient dry eye. One could hypothesize that abnormalities in meibomian gland structure or function (e.g., lipid quality and/or quantity) are the leading contributors to dry eye disease. Several key questions should be answered, including but not limited to the following:

1. Can MGD be considered a leading cause of dry eye?
2. Can aqueous-deficient dry eye and evaporative dry eye co-exist? Further, can aqueous-deficient dry eye lead to evaporative dry eye, and vice versa?
3. Should MGD be diagnosed and managed within the dry eye paradigm or as an independent condition?
4. Should MGD be considered to be a separate entity or within the dry eye context when evaluating the prevalence of dry eye?
5. Can symptom-based definitions of dry eye discriminate between aqueous-deficient dry eye and evaporative dry

Table 2. Subcommittees

Definition and Classification of MGD

Co-Chairs: J. Daniel Nelson (USA) and Jun Shimazaki (Japan)
Steering Committee (SC) Liaison: Gary N. Foulks (USA)
Members: José M. Benitez-del-Castillo (Spain), Jennifer P. Craig (New Zealand), James P. McCulley (USA), and Seika Den (Japan)

Anatomy, Physiology, and Pathophysiology of the Meibomian Gland

Chair: Erich Knop (Germany)
SC Liaison: David A. Sullivan (USA)
Members: Nadja Knop (Germany), Tom Millar (Australia), and Hiroto Obata (Japan)

Tear Film Lipids, and Lipid-Protein Interactions, in Health and Disease

Chair: Kari B. Green-Church (USA)
SC Liaison: Ben J. Glasgow (USA)
Members: Stefano Barabino (Italy), Douglas Borchman (USA), Igor Butovich (USA), Friedrich Paulsen (Germany), and Mark Willcox (Australia)

Epidemiology of, and Associated Risk Factors for, MGD

Chair: Debra A. Schaumberg (USA)
SC Liaisons: Kelly K. Nichols (USA)
Members: Jason J. Nichols (USA), Eric B. Papas (Australia), Louis Tong (Singapore), and Miki Uchino (Japan)

Evaluation, Diagnosis and Grading of Severity of MGD

Chair: Alan Tomlinson (Scotland)
SC Liaisons: Murat Dogru (Japan) and Anthony J. Bron (UK)
Members: Donald R. Korb (USA), Shiro Amano (Japan), Jerry R. Paugh (USA), E. Ian Pearce (Scotland), Richard Yee (USA), Norihiko Yokoi (Japan), and Reiko Arita (Japan)

Management and Therapy of MGD

Chair: Gerd Geerling (Germany)
SC Liaisons: Kazuo Tsubota (Japan) and Kelly K. Nichols (USA)
Members: Christophe Baudouin (France), Eiki Goto (Japan), Yukihiro Matsumoto (Japan), Terrence O'Brien (USA), Maurizio Rolando (Italy), and Joseph Tauber (USA)

Design and Conduct of Clinical Trials

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eye that may be related to the pathophysiology of the meibomian glands?

Terminology and Definitions

It became clear very early in the MGD workshop process that previously reported terminology had been used interchangeably, with lack of agreement regarding preferred terminology. The term *meibomian gland dysfunction* and its description first came to our attention in the mid-1980s. Since that time, terms such as posterior blepharitis, meibomian gland disease, meibomitis, meibomianitis, meibomian gland dysfunction, MGD (with no reference to disease or dysfunction), and meibomian keratoconjunctivitis have been used by clinicians and researchers to describe clinical conditions involving meibomian gland and/or lid disease. This report provides a new definition for MGD and clearly defines additional terminology, to allow the field to move forward.

Clinical Outcomes and Design of Clinical Trials

Central to both issues (relation to dry eye and terminology) is an appropriate clinical diagnosis and diagnostic technology. Definitions are only as good as the ability to appropriately classify disease, and like dry eye, there is no agreed upon gold standard diagnostic test for MGD. Emerging technology, biochemical (lipidomic and proteomic) analyses, and improved clinical grading schemes for individual lid and meibomian gland parameters, as well as for the co-morbid dry eye/MGD clinical condition, should be further explored and validated. The key questions include:

1. Can a gold standard diagnostic test for MGD be developed? Could a single clinical subjective parameter (e.g., meibomian gland expressibility or meibum quality) or objective parameter (e.g., tear osmolarity) differentiate subcategories of ocular surface disease?
2. Can any eyelid or meibomian gland parameter demonstrate appropriate change over time or with treatment? Can a biochemical or physical measure (biomarker) demonstrate change?
3. Will a battery of tests be required to adequately diagnose MGD for clinical trials? What tests should be included to determine entry/exclusion criteria as well as clinical outcomes?
4. Can standardized testing protocols be developed, validated, and adopted for individual tests or batteries of tests in MGD?

Furthermore, without a known natural history of MGD, including progression, it remains a challenge to determine which clinical findings constitute the natural aging process and which findings indicate disease. Importantly, natural history studies were recommended by nearly every subcommittee to better elucidate methods to define, detect, manage, and monitor MGD, including the design of clinical trials for MGD. Standardizing of clinical outcomes for MGD, dry eye, and other ocular surface conditions has been determined to be a major need within the community.

Specific Subcommittee Controversies

Within each subcommittee, debate about controversial issues, or lack of group consensus, often was a subtle indicator of areas in which further research or knowledge was needed to bring about agreement or resolution. External (to the committee) review of the reports by workshop participants also provided an indication of discord, and while agreement, for the most part, is indicated in the reports, it is important to recognize areas in which the committees struggled. Several of these issues are highlighted by subcommittee in the following section.

Definition and Classification. As mentioned, the lack of consensus regarding terminology and the need for a working definition and classification scheme provided the backdrop for this committee. The committee acknowledged the significant contributions in the past while creating a reference point with a new definition and classification scheme for future clinical and basic studies in the field of MGD.

Anatomy and Pathophysiology. Although MGD has been described as a condition for more than 100 years, its etiology remains in dispute. Significant evidence regarding the etiology of MGD is reported by this committee, yet systemic and ocular contributions have yet to be fully understood. In addition, it is unclear whether changes in meibomian gland structure result in alterations to the meibomian lipid and whether this process can be halted or reversed. The presence or absence of inflammation and infection in the meibomian gland was considerably debated relative to the etiology and pathogenesis of MGD and requires further exploration.

Lipids. Lipid production and subsequent delivery onto the lid margin as meibum, as well as the interaction of meibum with the tear film, are generally understood on a clinical level; however, specific chemical and biochemical interactions in the lipid production process, as well as in the tear film, are poorly understood. Newer techniques allow for determination of the molecular and physical structure of lipids, and the most controversial issue related to lipid measurement is the phospholipid content, once thought to be critical to the maintenance of tear film stability. Given the holocrine nature of lipid production, phospholipid detection in meibum is expected, although the mass spectrometry techniques currently used to assess meibum have demonstrated relatively low levels of phospholipids in the meibum. In addition, methods of comparing lipid profiles statistically are needed to determine the differences between health and disease.

Epidemiology. The natural history of MGD and of dry eye disease in general has not been established; therefore, a fundamental understanding of disease etiology, clinical presentation across severities, and disease progression have yet to be determined. Population-based studies are needed, to better assess prevalence and determine incidence, as well as to assess differences in subtypes of dry eye disease. The impact of potential causative factors, including contact lens wear, medication use, and hormone status should be explored further. In addition, survey instruments specific to MGD should be developed, as well as methods of classifying and analyzing clinical data for which the validity and repeatability are unknown.

Diagnosis and Management. Historically, MGD has been evaluated primarily in clinical and basic research settings, although it has often been overlooked or underdiagnosed in clinical care. In writing this report, the diagnosis and management committees struggled to create algorithms for both research and clinical applications. Each committee approached the task from opposing points of view, and their work, while harmonized as much as possible, reveals some of the controversy within the profession regarding the grading of clinical findings and the appropriate paired clinical management approaches. In both scenarios, the evidence supporting therapies across severity levels must be studied to achieve a consensus.

Clinical Trials. The clinical trials report highlights 26 clinical trials in MGD, most of which were small and were not randomized, controlled, and/or masked. Additional studies are needed in which diagnostic criteria are established for MGD, with terminology that is widely accepted, such that new or existing treatments can be assessed and compared across studies. New methods to assess MGD, both clinically and biologically, are needed to further the field, alone and in conjunction with dry eye disease.

This process has been an incredible experience for everyone involved. The countless hours spent by committee members reading the literature, writing, and reviewing the reports could easily go unnoticed. Therefore, it is with gratitude that I would

like to thank everyone who played a role in the creation of this report, for giving encouragement, knowledge, and insight into the process. It is my hope that this report will provide the framework needed to move to the next level of achievement in this field and will inspire research that will ultimately benefit clinical care of patients with MGD across the world for years to come.

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Dedication

This workshop report is dedicated to our colleague, Jeffrey P. Gilbard, MD, and all past, current, and future researchers in the field of meibomian gland dysfunction.

APPENDIX

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