Inflamed Obstructive Meibomian Gland Dysfunction Causes Ocular Surface Inflammation

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Meibomian gland dysfunction (MGD) is one of the primary causes of evaporative dry eye. Stagnation of meibum induces an unstable tear film, thus resulting in shortened tear film breakup time and superficial punctate keratopathy (SPK) in the lower cornea and punctate staining of lower bulbar conjunctiva. MGD is sometimes accompanied with inflammation (termed “meibomitis”) via the proliferation of bacteria in the meibomian gland and eyelash area. Meibomitis is strongly related to ocular surface inflammation such as corneal cellular infiltrates and neovascularization, SPK, and conjunctivitis. It is difficult to differentiate SPK caused by dry eye from that caused by meibomitis. When clinicians are unaware of the existence of meibomitis, and only aware of SPK on the cornea, they often try to treat SPK as it is caused by dry eye using dry eye–specific eyedrops or even using punctual plugs when conservative therapy is ineffective. However, even when intensive dry eye therapy is applied, it may be unsuccessful until SPK caused by meibomitis is recognized and treated with systemic antimicrobial agents. Hence, the tear secreting glands, including the meibomian glands, and the ocular surface should be clinically considered as one unit (i.e., the meibomian gland and ocular surface (MOS)) when considering the pathophysiology and treatment of ocular surface inflammatory diseases (i.e., corneal epithelial damage). Following this clinical pathway, a treatment focusing on meibomian gland inflammation may be a more reasonable approach for meibomitis–related or associated keratoconjunctivitis to more effectively treat this ocular surface disease.

Keywords: meibomian gland, meibomitis, meibomian gland dysfunction, superficial punctate keratopathy, ocular surface inflammation, meibomitis–related keratoconjunctivitis (MRKC)
MEIBOMITIS AND OCULAR SURFACE INFLAMMATION

For many years, it has been recognized that the condition of the meibomian gland has an impact on the state of the ocular surface. In 1908, “conjunctivitis meibomiana” was first reported by Elschnig in describing the role of excessive meibomian secretions in chronic conjunctivitis and keratoconjunctivitis. Thygeson and Kimura also believed that abnormal meibomian secretions were the primary cause of conjunctivitis; however, keratitis was not observed in their patients. Keith described a series of patients with meibomian gland abnormalities that were sometimes associated with keratitis.

McCulley and Scallis described a condition of meibomian keratoconjunctivitis (MKC) in a group of adult males and females ranging in age from 20 to 74 years with chronic blepharitis primarily caused by diffuse meibomian gland disease without significant anterior blepharitis. In those patients, no significant age- or sex-related predisposition was observed. Stagnation of meibomian secretion was suggested by inspissated plugs near the meibomian orifices and prominent secretions in the glands viewed through the tarsal conjunctiva. All of their patients exhibited some type of sebaceous gland disorder, such as seborrheic dermatitis or acne rosacea, every patient exhibited bulbar conjunctival injection and papillary tarsal conjunctival inflammation, a reduced fluorescein break-up time of tear film (F-BUT), and punctate staining on the cornea and bulbar conjunctiva. The authors concluded that the SPK was due to unstable tear film rather than to a staphylococcal toxin in which the effect is more typically seen with anterior blepharitis, as the lid cultures were frequently negative or exhibited little bacterial growth, although Staphylococcus epidermidis or S. aureus were the most commonly isolated aerobes. In a later study, the authors reported that bacterial lipolytic enzymes could be important factors in the development of many of the signs associated with meibomitis.

In that study, the authors preferred using the term “meibomian keratoconjunctivitis” to describe this condition, rather than the more general term “blepharokeratoconjunctivitis” used by Keith, to emphasize the role of meibomian gland disease and the lack of inflammatory signs along the lash line.

On the other hand, in 2000, Suzuki et al. proposed the concept “meibomitis-related keratopathy” (later re-named “meibomitis-related keratoconjunctivitis” (MRKC)), which is a condition that causes corneal inflammatory cellular infiltration (corneal nodule), superficial corneal neovascularization, SPK, and conjunctival injection associated with meibomitis in young subjects. MRKC is classified into two types: the so-called “phlyctenular type,” which is characterized by nodular cellular infiltration on the cornea with superficial neovascularization (Fig. 1), and the “non-phlyctenular type,” which is characterized by SPK without cellular infiltrates, but with or without superficial neovascularization (Fig. 2). The severity of meibomitis correlates well with the severity of ocular surface epithelial damage in both disease types, and the treatment of meibomitis is considered essential for remission of the ocular surface inflammation. Since 1998, there has been an increased number of reported phlyctenular-type cases, and in addition to characteristic corneal findings, the following clinical features have been reported: (1) a prevalence in young females, (2) a past history of chalazia, (3) a usually bilateral affliction, (4) increased Propionibacterium acnes in the meibum culture, and (5) a characteristic human leukocyte antigen (HLA) predisposition. A systemic review of the literature published after 1980 on pediatric ocular rosacea, phlyctenular keratitis, and childhood BKC reveals similarities in all ocular surface manifestations, including corneal cellular
infiltrates and superficial vascularization in relation to meibomitis and the effectiveness of systemic antimicrobial treatment. Thus, those three categories of diseases might be the same clinical entity as phlyctenular-type MRKC, even though they are designated by different terms.27–29

It should be also noted that for many years Demodex mites have been recognized as a cause of blepharitis28 and corneal change.29 Recently, they have been emphasized as a cause of recurrent chalazia,30–31 as well as for its high prevalence in MGD and ocular surface inflammation.32–34 The corneal features of ocular demodicosis seems to more commonly be a peripheral stromal cellular infiltration with neovascularization than SPK.35

POSSIBLE PATHOGENESIS OF MRKC

Retrospective studies23,25,26 have revealed that more than 80% of phlyctenular-type MRKC patients are young girls or adolescent females, frequently with a history of multiple chalazia. HLA analysis in Japanese patients suggested a possible genetic predisposition (i.e., an association with HLA-A26 and -DR8). Because the corneal manifestation of phlyctenular-type MRKC is very similar to phlyctenular keratitis, the pathogenesis was thought to be a delayed type hypersensitivity (DTH) reaction to foreign microbial pathogens such as Mycobacterium tuberculosis35,36 or S. aureus.37,38 However, in the series of patients who were studied, both aerobic and anaerobic bacterial cultures of meibum disclosed a high probability of P. acnes involvement.23,25,26 These results were surprising, as the lid flora of children normally have a significantly higher proportion of Streptococcus and a lower proportion of P. acnes compared with adults.39

P. acnes, an anaerobic gram-positive Bacillus, normally inhabits human sebaceous follicles and plays a central role in producing the lesions of inflammatory acne.40 In fact, P. acnes has potent inflammatory actions11,42 and is resistant to being killed and degraded by human neutrophils and monocytes.43 This characteristic might underlie the long-standing inflammation or granuloma development that is associated with corneal nodules. Laboratory experiments have been shown that P. acnes can induce a DTH response similar to that of M. tuberculosis, thus confirming a central role for CD4+ T cells and macrophages in disease.44 In fact, following sensitization by heat-killed P. acnes or S. aureus in rats, P. acnes injected into the corneal stroma induced a stronger DTH response than did S. aureus.45 Histological analysis demonstrated massive cellular infiltration, including mononuclear cells and neutrophils and the presence of CD4+ and CD8+ T cells. This finding is compatible with those of immunohistochemical studies of conjunctival phlyctenu-s.46

P. acnes, in concert with coagulase-negative staphylococci, are known to be the most common commensal bacteria of the eyelid and conjunctiva.46 S. aureus is also known to produce previously characterized triglyceride lipases.47 S. epidermidis has been shown to produce not only triglyceride lipases but also cholesteryl esterases.22,48 In chronic blepharitis, significant changes have been reported in some minor free fatty acids (FFAs) of meibum collected from patients in all of the seborrheic groups and MKC, but not the “sebaceous” normal staphylococcal group.49 Dougherty and McCulley46 reported that S. aureus is the etiologic agent in the staphylococcal and mixed groups of blepharitis, but not in the other groups. The greatest amount of bacterial lipolytic activity has been found in patients with meibomian gland abnormality (i.e., chronic blepharitis with meibomian seborrhea, secondary meibomitis, and MKC).50

The pathogenesis of phlyctenular-type MRKC is presumably a DTH reaction to P. acnes proliferating in the meibomian glands.44 It should be noted that phlyctenular-type MRKC is rarely observed in elderly subjects. It is speculated that the subject of the immune reaction changes from Th 1 to Th 2 with age, so it may be difficult to cause a DTH reaction to P. acnes in elderly individuals. P. acnes and S. epidermidis detected from meibum not only in elderly subjects, but also in the non-phlyctenular-type MRKC in young-age subjects, are the most detectable bacteria from the conjunctival sac and lid margin.

**FIGURE 2.** Non–phlyctenular-type MRKC of various severities observed in young-age patients. Varying degrees of severity of MRKC, increasing from left to right. The severity of the corneal inflammation correlates well with that of the meibomitis. (A, D) A 15-year-old female with mild MRKC showing a few inflamed orifices (A, D) and SPK in the lower cornea. (B, E) A 9-year-old female with moderate MRKC showing that the number of inflamed orifices (B, E, dotted line) increases according to the area of corneal SPK. (C, F) A 27-year-old male with severe MRKC showing that all of the orifices are inflamed (C) and diffuse dense SPK with superficial corneal neovascularization (F).
Both of these bacteria have a lipase that degrades lipids contained in meibum.\textsuperscript{22} In particular, \textit{S. epidermidis} and \textit{S. aureus} have lipase that degrades cholesterol ester not found in \textit{P. acnes}, and FFA itself, produced by lipase, reportedly has cytotoxicity.\textsuperscript{25} When the FFA increases to a certain concentration in the tear fluid, the TFLL breaks down in a concentration-dependent manner.\textsuperscript{50} That increase of FFA might be one of the causes of SPK of non–phlyctenular-type MRKC, or of “MKC.”

\textit{Demodex} mites are also regarded as a causative factor of blepharitis\textsuperscript{28,51} and are commonly found in the skin of elderly humans and humans surpassing middle age (e.g., in 84\% of human subjects at 60 years of age and in 100\% of those older than 70 years).\textsuperscript{28,51} Even though \textit{Demodex} infestation is more common in rosacea patients,\textsuperscript{52–55} it remains unclear as to whether it plays an etiological role in rosacea or whether it may act as a cofactor in the disease.\textsuperscript{56} Two \textit{Demodex} species have been identified in humans: \textit{Demodex folliculorum} and \textit{Demodex brevis}.\textsuperscript{57,58} \textit{D. folliculorum} is found within hair and eyelash follicles, and reportedly can induce hyperkeratinization around the lash base with the characteristic formation of cylindrical dandruff.\textsuperscript{58,59} On the other hand, \textit{D. brevis} is able to enter and obstruct the meibomian gland.\textsuperscript{60} As stated above, \textit{Demodex}, especially \textit{D. brevis}, has recently been reported as a cause of recurrent chalazia, as well as for its high prevalence in MGD and ocular surface inflammation.\textsuperscript{30–35} Moreover, \textit{Demodex} reportedly acts as a vector for bacteria, such as \textit{Streptococcus} and \textit{Staphylococci} species,\textsuperscript{61} and \textit{Demodex} itself contains \textit{Bacillus oleronius}.\textsuperscript{62} Li et al.\textsuperscript{63} demonstrated that there is a close correlation between positive serum immunoreactivity to the \textit{Bacillus} proteins, ocular \textit{Demodex} infestation, facial rosacea, and blepharitis. Although ocular demodicosis is common in adults (most rosacea patients being older than 30 years), Liang et al.\textsuperscript{55} reported \textit{Demodex} infestation in pediatric blepharoconjunctivitis cases that were not successfully treated with conventional therapies such as eyelid hygiene with Cliradex (Bio-Tissue, Inc., Miami, FL, USA), topical steroids/antibiotics, and systemic erythromycin/doxycycline (EM/DOXY).\textsuperscript{52,54} As described in the TFOŚ DWES II pathophysiology report,\textsuperscript{64} \textit{Demodex} appears to be one of the causes of lid margin inflammation or blepharoconjunctivitis; however, their causative role in MGD and evaporative dry eye have yet to be fully elucidated. In our series study of phlyctenular-type MRKC patients, \textit{Demodex} mites were not observed or detected. Thus, \textit{Demodex} infestation in humans might be highly influenced by both region and environmental condition. The reported effective treatment for \textit{Demodex} blepharitis is eyelid scrubs with 50\% tea tree oil.\textsuperscript{60,65} \n
\textbf{Non–Phlyctenular-Type MRKC}

Since the “abnormality of the meibomian glands without inflammation of the eyelid margin” reported as “MGD”\textsuperscript{1} does not seem to exist in apparent inflammatory reactions in obstructive MGD\textsuperscript{66} based on histological examination in obstructive MGD samples, the presence of inflammation in obstructive MGD found in the elderly subjects is questionable. Thus, SPK associated with obstructive MGD without inflammation is thought to be due to evaporative dry eye (EDE) (Fig. 3). Although there may not be clinically evident inflammation on the ocular surface, evidence suggests that tear hyperosmolarity and/or compositional changes may stimulate production of inflammatory mediators by the ocular surface epithelium and resident immune cells in EDE.\textsuperscript{64} It is possible to control SPK due to EDE with tear-film–oriented therapy proposed by Yokoi et al.\textsuperscript{67} For example, eyedrops developed specifically for the treatment of dry eye, such as hyaluronan, diquafosol sodium, and rebamipide, are generally effective to treat SPK in EDE cases, yet not in all cases. The SPKs seen in the patients not effectively treated with dry eye–specific eye drops sometimes obtain remission with systemic antimicrobial therapy, most of which are non–phlyctenular-type MRKC cases (i.e., meibomitis with SPK). The concept of non–phlyctenular-type MRKC started as one of the two types of MRKC, originally seen in young-age women.\textsuperscript{23} A survey of MRKC in elderly subjects revealed that the corneal epithelial damage was mainly SPK, not accompanied by cellular infiltration, which is typical non–phlyctenular-type MRKC.\textsuperscript{68} In that survey, the percentage of female patients was less than that of young-age non–phlyctenular-type MRKC cases (i.e., 57.1\% and 83.3\%, respectively). MRKC in young-age subjects is likely to develop in those who tend to have MGD due to repeated chalazion from childhood. In addition, in the female menstrual cycle, the meibomian gland function periodically decreases as a result of the influence of sex hormones such as estradiol and progesterone.\textsuperscript{69} Thus, MRKC tends to easily develop in adolescence and/or young-age women. On the other hand, because sex hormone concentration decreases in elderly subjects of both genders, it is considered that the age-related decrease in meibomian gland function may affect the onset of MRKC in both males and females.\textsuperscript{70} Thus, non–phlyctenular-type MRKC is less prevalent in elderly females.

\textbf{Treatment of MRKC}

For the treatment of phlyctenular-type MRKC cases, cephalosporins, such as cefmenoxime and cefcapene pivoxil, have proved to be effective.\textsuperscript{25,26} Those antibiotics are bactericidal
and are effective in reducing the number of targeted bacteria such as *P. acnes* proliferating in the inflamed meibomian glands. In addition, it has been theorized that switching to bacteriostatic macrolides such as clarithromycin (CAM) may then be useful to restore a normal inhabitant to the meibomian glands. At sub-antimicrobial doses, tetracyclines (i.e., tetracycline [TC], minocycline [MINO], and DOXY) and macrolides (i.e., EM and azithromycin [AZM]) reportedly have important anti-inflammatory properties and are able to inhibit inflammation\(^1,72\) and the production of bacterial lipases.\(^73-74\) Moreover, TCs are regularly used at sub-antimicrobial doses in the management of rosacea.\(^75-77\) Possibly, this may be sufficient to manage a certain proportion of the adult cases of MGD-related disease.\(^74,78,79\) However, the contribution of FFAs produced by bacterial lipases to corneal infiltration or corneal neovascularization in MRKC is unknown, and clinical observation suggests that in phlyctenular-type MRKC cases, suppression of the inflammatory response alone may be insufficient to break the cycle of disease. Thus, the strategy is to use antimicrobial agents, such as cephalosporins, macrolides, and TCs, at doses achieving a good minimal inhibitory concentration against *P. acnes* in order to eliminate *P. acnes* from the meibomian gland. This concept is similar to that used in the elimination of *Helicobacter pylori* in cases of gastritis. These antimicrobial agents have been found to be clinically effective in treating meibomitis in patients with ocular rosacea, phlyctenular keratitis, and childhood BKC, and it could be hypothesized that the meibomitis is caused by the same bacteria that is observed in MRKC (i.e., *P. acnes*). Foukls et al.\(^80\) recently reported that both topical AZM and oral DOXY improved the signs and symptoms of MGD, and that treatment with the two drugs changed the characteristics and composition of meibum differently. They speculated that these agents have different mechanisms of action and that it is possible that the treatment of MGD could lead to reduction of bacterial-induced inflammation, as both drugs have antibiotic properties. Greene et al.\(^81\) reported the effectiveness of pulsed oral AZM treatment (1 g per day) for meibomitis in adults. These reports further support the hypothesis that elimination or reduction of the bacteria in the meibomian glands is effective for the treatment of meibomitis.

It has been reported that suppression of the decomposition of meibum lipids by bacterial lipase is effective for treating ocular surface inflammation via the oral administration of TCs such as MINO.\(^78,82\) MINO therapy eradicates *S. aureus* as well as significantly reduces the bacterial count of coagulase-negative staphylococci and *P. acnes*. It seems reasonable that with a decrease of responsible bacteria in the ocular flora, there would be a significant decrease in the quantity of bacterial lipases present. In fact, we have experienced that systemic administration of macrolides such as CAM was also effective for non–phlyctenular-type MRKC, thus suggesting the importance of reducing the quantity of bacteria as an effective treatment for meibomitis and ocular surface inflammation (Fig. 4). It is thought that this is because bacterial minimum inhibitory concentration is low in both antimicrobial drugs and a decrease of bacteria in the meibomian glands will result in the reduction of FFA in the meibum, thus leading to improvement of the ocular surface epithelial disorder. In non–phlyctenular-type MRKC cases, meibomitis and SPK are observed simultaneously, unless meibomitis is controlled using antimicrobial agents systemically, and SPK does not disappear with dry eye treatment only. Conversely, in approximately 50% of the elderly patients, even if the remission of meibomitis almost occurs, SPK does not disappear completely. This is considered to be a state in which SPK due to EDE accompanies obstructive MGD remains due to long-term meibomitis. Switching to treatment using dry eye–specific eye drops at the stage when meibomitis is controlled, SPK can successfully be eliminated. Thus, especially in elderly patients with SPK, it is important to confirm the presence of inflammation around the eyelid margin, especially the meibo-
mian gland orifices, and start appropriate treatment; that is, in young-age subjects it is possible to obtain complete remission of the ocular surface epithelial disorder only by treatment of meibomitis, but in elderly subjects, it is necessary to treat SPK associated with noninflammatory obstructive MGD after treatment of meibomitis.

**FUTURE DIRECTIONS**

Due to the importance of the “meibomian glands and the ocular surface” (MOS) concept (Fig. 5)\(^2\) that meibomian glands and the ocular surface are considered as one unit, a detailed clinical observation of meibomian glands is a key to managing ocular surface abnormalities, such as those seen in MRKC. Further investigation of meibum alteration, such as meibogenesis\(^8\) microbiome, and lipid hydroperoxides in the meibomian glands, will help verify the critical cause of meibomitis and possibly lead to the development of the new therapeutic agents.

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**FIGURE 5.** Flow chart of MGD. Obstructive MGD is divided into mainly two types: (1) inflamed/obvious and (2) noninflamed/nonobvious. Although it is focal, but not diffuse, a chalazion is also categorized in inflamed obstructive MGD. Inflamed obstructive MGD (meibomitis) is specifically related to the cell-mediated ocular surface inflammation (MRKC, phlyctenular type) as well as SPK (MRKC, non-phlyctenular-type). On the other hand, noninflamed/nonobvious obstructive MGD is a leading cause of EDE. Furthermore, hypersecretory MGD is sometimes inflamed and associated with corneal epithelial damage ("MKC").\(^9\) The meibomian gland and the ocular surface have a close relationship. Modified from the figure in Reference 27.


