Keratoconjunctivitis Sicca Associated With Meibomian Secretion Polar Lipid Abnormality

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Objective: To determine whether an association between keratoconjunctivitis sicca (KCS) and meibomian gland lipids exists in patients with chronic blepharitis.

Methods: Meibomian gland lipids were collected from normal patients and those with chronic blepharitis. Some of the chronic blepharitis patients had an ocular surface abnormality with apparent aqueous deficiency similar to KCS. Lipids were separated by thin-layer chromatography and polar lipids were further separated by high-pressure liquid chromatography with detection by UV absorbance. Lipids were identified by retention time with comparison with standards and by gas chromatography and mass spectroscopy.

Results: A strong association between specific lipids and KCS signs was observed only with the polar lipids. Low levels of 2 phospholipids, identified as phosphatidylethanolamine and sphingomyelin, were significantly (P<.05) associated with ocular surface abnormalities that were consistent with KCS.

Conclusions: Evaporative KCS syndrome (rather than tear insufficiency) in many individuals may be the result of polar lipid abnormalities. We believe that the 2 associated phospholipids identified in the patients with chronic blepharitis act as important structural components in the polar phase of the tear film lipid layer. We suggest that a deficiency in these lipids results in a poorly structured polar phase that in turn affects the nonpolar phase. Ultimately water transmission through the tear film lipid layer increases, thus resulting in evaporative KCS. These results should aid in development of tear film substitutes directed toward specific abnormalities.


C H R O N I C B L E P H A R I T I S (CB) is an ocular disorder commonly seen by ophthalmologists. Among the many ocular symptoms described by patients are foreign body sensation, itching, and dryness. We have observed that CB often has an associated ocular surface abnormality similar to that seen in keratoconjunctivitis sicca (KCS), but an understanding of how it was related to abnormal meibomian gland secretions (meibum) was lacking. In earlier studies we observed that 45% of patients with CB (n = 21), evenly distributed as to sex, had an associated KCS; the patients with KCS were also distinguished by significantly (P<.01) lower tear lysozyme levels than other patients with CB. In a classic sense, KCS is defined by aqueous insufficiency as determined by the Schirmer test, as well as other tests. However, sicca syndromes have been associated not only with CB, but also with Sjogren’s syndrome and ocular rosacea. More recently it has been determined that signs of KCS associated with CB can result not only from low tear production but also from insufficient secretion from the meibomian gland. Subsequent research determined that high rates of tear film evaporation were correlated with this KCS condition. Thus, KCS conditions can result not only from insufficient production of tears but also from high rates of tear film evaporation.

Our investigations of CB have included numerous microbial and lipid assays. Microbial analysis included extracellular and meibomian gland secretions; lipid assays included the nonpolar lipids in meibomian gland secretions and the effects of tetracycline on ocular flora and lipids. In these investigations, we have observed associations with a picture of KCS-like ocular surface abnormalities with polar lipid changes in meibum that may represent the mechanism behind this association. These findings also provide insight into the fact that the lipid layer is most likely highly structured with the thin po-

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PATIENTS AND METHODS

Informed consent was obtained from all patients and the study was conducted according to the tenets of the Declaration of Helsinki. Patients who had any form of CB in our classification system (thus all types were included) for at least 6 months were carefully evaluated. The patient population was 56% male (n = 61); of this male population, CB-KCS was present in 39% (n = 24) and CB-KCS was present in 50% (n = 23) of the female population. If the patients with a staphylococcal infection were omitted, the occurrence of CB-KCS in the female population was 38% (n = 11) and 41% (n = 23) in the male population. In a previous study, we published an analysis of the various lipid classes of the lipid layer of the tear film and proposed that the lipid layer is highly structured. The polar lipid layer may be only 1 to 3 molecules thick20 but serves a very critical function, ie, that of a surfactant creating a transition from a hydrophilic aqueous-mucin tear interface but with a reverse polarity, ie, converting a hydrophilic environment to one of hydrophobicity.

Meibomian lipids are quite varied and more complex than previously understood. In our investigation of CB, we find that meibum polar lipids of normal individuals were not notably different from those of patients with CB without a KCS-like picture, composition of which is given in the Table. The most striking observation was that in patients with CB with a KCS-like picture; phosphatidylethanolamine (PE) and sphingomyelin (SM) were significantly lower (P<.05) than in the patients with CB without associated KCS (Table, Figure 1). It was also observed that the significance (P<.02) of low PE was much more important than low SM in male patients (Table). When the sum of PE and SM was compared for all patients, the sum for the CB-KCS group was significantly lower (P<.005) than that for the CB group (Figure 2). We have presented elsewhere an analysis of the various lipid classes of the lipid layer of the tear film and proposed that the lipid layer is highly structured. The polar lipid layer may be only 1 to 3 molecules thick but serves a very critical function, ie, that of a surfactant creating a transition from a hydrophilic aqueous-mucin phase to a hydrophobic nonpolar lipid phase. Phosphatidylethanolamine and SM are most likely to be the key molecules in establishing the integrity and function of the polar layer. These 2 phospholipids are...
prominent in lung surfactant phospholipids and are much more effective than phosphatidylcholine in maintaining in vitro lipid layer integrity and in lowering surface tension (surfactant properties). These polar lipids have also been observed to be dominant in rabbit meibomian glands. Although evidence has accumulated suggesting that meibomian disease and KCS syndrome may be related, this is the first evidence that specific lipids could be involved. Low levels of both PE and SM are significantly related to an ocular surface abnormality similar to KCS (Table), but PE appears to be more important, at least in men. Although we believe that it is the nonpolar lipid phase of the tear film that ultimately determines the tear film evaporation rate, the importance of the supporting structure of the polar lipid phase should not be ignored; as suggested by model systems both are important. We believe that it is both the structural and water transmission (activity) characteristics of the polar lipid phase that are compromised by low levels of PE and SM. The results presented in Figure 2 suggest that when PE and SM are at low levels, KCS is much more likely to occur.

The functionality of PE and SM in the polar lipid phase can be altered by associated conditions. The uniqueness of PE and its role in promoting a functional polar lipid phase can be understood in terms of the structure of PE. Thus, because of the molecular shape of the PE molecule, it has been proposed that the presence of PE reduces curvature stress, as would occur at the tear film surface. Also because of its molecular structure, and unlike phosphatidylcholine and SM, the amino (NH3+) group of PE which lacks the trimethylation (N[CH3]3+) of the choline group in phosphatidylcholine and SM is not sterically hindered. Therefore, PE is the only lipid present in meibum that contains an NH3+ group and thus can form ionic bonds and multiple hydrogen bonds (eg, to other lipids in the polar lipid phase). Finally, the amino group of PE (with a dissociation constant of about a pH of 7.5 in a membrane environment) can readily lose hydrogen-bonding ability at higher pHs, but especially...
when calcium levels are high. These characteristics of PE enhance both its structure-forming and surfactant properties, but under abnormal conditions these properties can be diminished. Finally, the hydroxyl groups present in SM but not phosphatidylcholine also increase its hydrogen-bonding ability and therefore its structure-forming properties. On the basis of these reports and our results, we believe that the functional polar lipid layer of the tear film can be compromised by abnormal conditions such as low levels of key polar lipids such as PE and SM.

Our results in no way suggest that all KCS conditions, whether due to high rates of aqueous evaporation, aqueous hyposecretion, or other lipid or mucin abnormalities, are the result of low levels of these 2 phospholipids. For example, we have reported an association of one type of CB, ie, rosacea, with meibomian keratoconjunctivitis and apparent nonpolar and polar lipid abnormalities; more recently, there has been another report of an abnormal tear film associated with ocular rosacea. As a point of future interest, we would also like to point out that in Sjögren’s syndrome, the tear film is a parsimony of aqueous production, the presence of serum antiphospholipid antibodies (primarily IgA) are a commonly associated condition. In general high levels of IgA and lower levels of IgM are found in human tears in individuals with evaporative KCS condition. In many patients with aqueous deficiency and especially those with an evaporative KCS condition, the functional polar lipid layer of the tear film can be compromised by increased rates of aqueous evaporation. With these insights it may be possible to devise a tear replacement to correct the defect in many patients with aqueous deficiency and especially those with an evaporative KCS condition.

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