Review

On the Keratoconjunctivitis Sicca

Eva Grand, Heather Mossel
Eye Crystal, Inc., Portsmouth, NH 03802, USA
Correspondence to: Ms. Heather Mossel, M.Sc., Email: hmossel@eyecrystal.net
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Keratoconjunctivitis sicca, also known as dry eye disease, is an inflammatory condition of the ocular surface caused by a pathologic reduction in the aqueous component of the tear film. Keratoconjunctivitis sicca usually manifests as dry eyes, foreign bodies, burning, itching, blurred vision, red eyes, and contact lens intolerance. In the reported epidemiological investigations, the global prevalence of keratoconjunctivitis sicca was 5%-50% due to different populations and diagnostic criteria. Wearing contact lenses can aggravate symptoms. This paper reviews the research progress of keratoconjunctivitis sicca.

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Keratoconjunctivitis sicca (KCS) refers to the instability of the tear film and damage to the ocular surface caused by the abnormality of the quality and quantity of the tear fluid or the abnormality of the fluid dynamics of the tear fluid, which leads to a series of uncomfortable symptoms of the eye (1). The symptoms usually include dryness, foreign body, burning, itching, blurred vision, red eyes, and contact lens intolerance (2). KCS is one of the common ocular surface diseases. The etiology of KCS is very complex, such as systemic diseases, drugs, environmental pollution, and inflammatory reactions in the local eye, abnormal eyelid position, and age (3). Using eyes at close range for a long time, the popularity of video terminals is the main reason for aggravating KCS. In recent years, with the widespread use of video terminals in residential and office environments, KCS has become a globally distributed disease.

Epidemiology of Keratoconjunctivitis Sicca

KCS has become a global disease, and its prevalence is gradually increasing. In the reported epidemiological survey, the incidence of KCS ranges from 14.4% to 33% due to different populations and diagnostic criteria. The most recent mata-analysis of the prevalence of KCS showed that the occurrence of KCS was ranged from 5% to 50% (4). Among the people aged 65 to 84 in the United States, 14.6% (4.3 million) suffer from KCS (5). In the screening of 2,127 people in Japan, it was found that 17% had KCS (6). In Taiwan Chinese population, the symptomatic KCS was 33.7% (7). The prevalence of KCS by symptoms and signs were 13.55% and that of KCS by symptoms was 31.40% in Chinese people aged 5-89 years (8). The age-/sex-adjusted Canadian KCS prevalence estimate from this sample was 21.3% (9).

Etiology of Keratoconjunctivitis Sicca

The surface of the normal eye is covered with a tear film. A stable tear film is the foundation for maintaining the health of the eye surface. Any abnormal tear film can cause KCS (10, 11). A vicious cycle will form between tear film instability and ocular surface stress if the balance was broken between meibomian gland and ocular immuno-inflammation modulation (**Figure 1**).

Environmental Factor

Smoke, dust, dryness, wind and sand in the natural environment can affect the stability of the tear film (12). These substances can change the pH value of the tear film and cause dry eyes. Indoor environments such as central air-conditioning or heated rooms and airplanes, the humidity sometimes It can be reduced

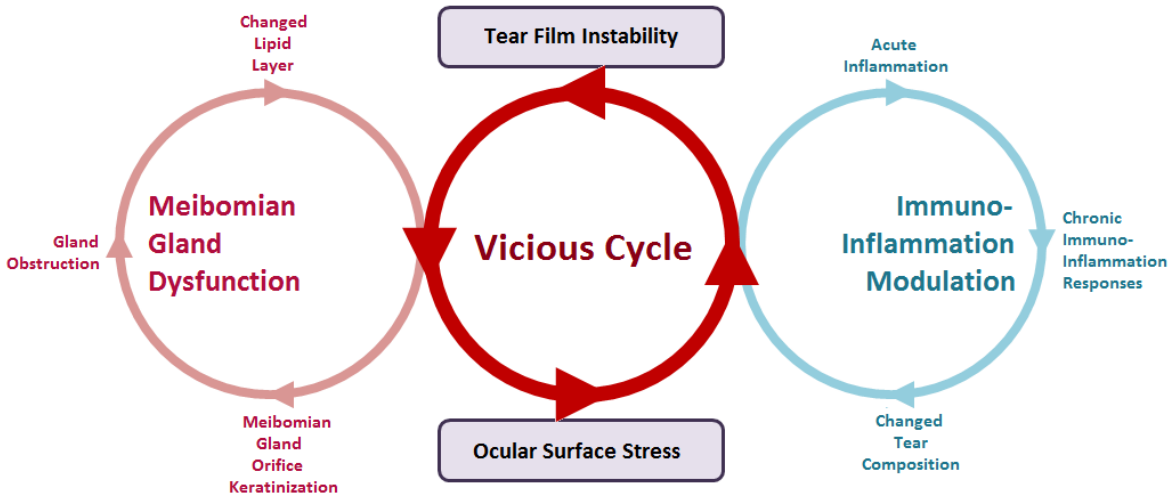

Figure 1. The Vicious Cycle of Keratoconjunctivitis Sicca.

by 50%, which is also an important factor in the production of KCS (13).

Computer

People who look at the screen for a long time, such as computer operators, people who watch TV for a long time, and children who play video game consoles, because the blinking frequency is reduced, the stability of the tear film is reduced, and video display terminal syndrome (VDTS) occurs (14). People who use computers will have at least one symptom of KCS. It takes a long time to use the machine and the symptoms of dry eyes are severe; if you wear contact lenses, the symptoms can be aggravated (15). Frequently engaged in attention-focused work and activities, such as frequent use of a computer, work and reading in front of a fluorescent screen, can cause the eye surface area exposed during the blink interval to increase, and the number of blinks decreases, which leads to accelerated tear evaporation and causes KCS. Under normal circumstances, a person blinks 15 times per minute on average, 5 blinks per minute when operating a computer, and only 3 blinks per minute when playing a game console. The frequency of blinking is reduced, resulting in a decrease in the function of the tear glands of the eyes to secrete tears. Eventually, the eye conjunctiva "tear lubricant" is reduced or insufficient, and the "KCS" symptoms such as dry eyes, itching, burning, and photophobia are prone to occur.

Contact Lens

Wearing contact lenses can aggravate the symptoms of KCS (16). After wearing contact lenses, the tear film on the surface of the cornea is mechanically damaged and dry, and the tear film, especially water, is absorbed by the corneal tissue. Under normal circumstances, each blinking action is to evenly spread tears on the surface of the cornea to supplement the tear film absorbed and evaporated on the surface of the cornea. After wearing contact lenses, the function of eye blinking to replenish the lost part of the tear film is lost or weakened (17). Therefore, the occurrence of KCS is obviously related to the length of wearing contact lenses. Wearing contact lenses can impair the growth and development of sensory nerves in the corners and conjunctiva, resulting in decreased perception of the corners and conjunctiva, reduced blinking, and tear film metabolic dysfunction, which ultimately leads to the occurrence of KCS (18, 19).

Age and Gender

As age increases, hormone levels decrease, causing the function of the lacrimal and meibomian glands to decrease, the secretion of tears decreases, and the stability of the tear film is poor, which can cause KCS (20, 21). Women with KCS are significantly higher than men. This is because androgens have a regulatory effect on the morphology, physiology and immunity of the lacrimal gland and can regulate the meibomian glands to secrete oil into the tear film (22). Under other conditions unchanged, women's corneal sensitivity is lower than that of men of the same age.

Systemic Factors

The prevalence of dry eye in patients with systemic diseases accompanied by certain systemic diseases is high, such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome and some allergic diseases (24, 25). The incidence of KCS in patients with diabetes (26, 27) and cervical spondylosis (28) is also higher than that of normal people. Long-term use of certain systemic drugs can increase the risk of KCS, including thiazide diuretics, antidepressants, β-blockers, anticholinergics, benzenesulfonamides, antiparkinsonian, and antihistamines and antihypertensive drugs (29).

Diagnosis of Keratoconjunctivitis Sicca

In the past, the diagnostic criteria of KCS followed Sjogren's comprehensive diagnostic criteria, but there are still no unified diagnostic criteria internationally. The criteria for diagnosing KCS vary from country to country, and the inspection indicators are not uniform. Commonly used are the diagnostic criteria of Japan, Copenhagen, Greece and California. A kind of KCS diagnostic criteria, namely rb staining, But and Slt three tests, if there are two positive (rb++, But ≤ 10 s, Slt ≤ 10 mm) or one strong positive (rb++, But ≤ 5 s, Slt ≤ 5 mm) can be diagnosed as KCS (30). If only one item is positive or suspicious, increase the measurement of lactoferrin, and the diagnosis can be confirmed by < 100 mg. After clinical application, the accuracy rate is 98% (31).

Other diagnostic criteria are: (i) Subjective symptoms: dry eyes, foreign bodies, burning, photophobia, asthenopia or blurred vision, jealous, etc., of which one or more items are positive. (ii) The tear film rupture time < 10 s is abnormal (32). (iii) Lacrimal fluid decreases, Schirmer test tear secretion test < 10 mm/5 min (33). (iv) Ocular surface damage, fluorescein staining > 3 (34). While excluding other reasons, KCS can be diagnosed with the above 1+2 (< 5 s) or 1+2 (< 10 s) +3. Among them, those with reduced tears were diagnosed as aqueous tear deficient (ATD) eyes; those with tear secretion> 10 mm/5 min were diagnosed as lipid tear deficiency (LTD) eyes. 5-10 mm/5 min diagnosed as suspicious dry eyes.

Therefore, asking about medical history and symptoms is extremely important for diagnosing KCS. By asking the medical history, you can understand the severity and duration of the illness, as well as the presence or absence of diseases such as rheumatoid arthritis, systemic medications, eye trauma and surgery history, working environment, nature and living conditions. Merali believed that patients who have only KCS signs but no complaints of eye discomfort rarely occur (35). Symptoms are an important basis and necessary condition for diagnosing KCS. The most common symptoms of KCS are dryness, foreign bodies, burning, itching, photophobia, jealous, blurred vision, and fluctuations in vision; in addition, most people have symptoms of visual fatigue (36).

Therapy of Keratoconjunctivitis Sicca

For the treatment of KCS, we should first understand its etiology and classification, and treat different causes and clinical classifications. Since KCS is the result of the combined effects of various factors inside the body and external environmental factors, its pathological mechanism is very complicated, so the cause of the disease should be searched for and the inducement removed during the treatment process.

Replenish Tears

Artificial tears are still the main treatment method. Artificial tear replacement therapy can relatively improve ocular surface lubrication and increase ocular surface moisture, and even help improve vision (37). According to the length of time the artificial tears keep the ocular surface moisturized after instillation, the artificial tears are divided into 5 generations. At present, there are more than ten kinds of artificial tears available for clinicians, including dextran-70 eye drops, polyethylene glycol 400 eye drops, carboxymethyl cellulose Sodium eye drops 0.3, sodium carboxymethyl cellulose eye drops 0.1, vitamin A palmitate eye drops, carbomer sorbic acid eye drops, Sodium Hyaluronate 0.1 Eye Drops, Sodium Hyaluronate 0.3 Eye Drops, Polyvinyl Alcohol Eye Drops, Polyvinyl alcohol eye drops (38). Although there are many types of artificial tears, each type of artificial tears has its indications. In the clinical selection of artificial tears, the corresponding choice should be made according to the type and degree of KCS and the patient's response to treatment (39).

Preserve the Patient's Original Tears

The hydrophilic soft lens combined with artificial tears can have a certain effect on mild and moderate KCS, which cannot be tolerated by severe patients (40). Seal the lacrimal punctum and prevent the discharge of tear fluid (41). Use 50 mA current to burn the punctum for 5 to 10 s or use a red pin to burn the punctum to destroy the punctum, so that the patient's extremely precious trace of tears can be preserved until the evaporation is complete. For sealing punctum, in the past, the punctum was closed. Recently, a lack of local tears has been found, and the upper bulbar conjunctiva is more common than the lower, which is considered to be a cause of the superior limbic keratoconjunctivitis (SLK) (42). Sealing the upper lacrimal dot can effectively reduce the damage caused by blinking, thereby improving the condition of the non-exposed ocular surface.

Suppress Ocular Surface Inflammation and Immunosuppressive Therapy

Anti-inflammatory and immunosuppressive treatments are only suitable for moderate to severe KCS patients with ocular surface inflammation, and mild patients do not need to use it (43). (i) Cyclosporine A (CsA): Its mechanism of action is to inhibit the apoptosis of lacrimal gland cells and conjunctival goblet cells, promote the apoptosis of lymphocytes, and reduce the inflammatory reaction on the ocular surface (44). (ii) Glucocorticoids: Topical use of glucocorticoids can significantly relieve eye irritation. Long-term use of glucocorticoids may cause increased intraocular pressure and cataracts (45). It is generally suitable for short-term treatment of severe dry eye. After the inflammatory reaction is controlled, it should be stopped in time.

Promoting Tear Secretion Medicine

There are many drugs that stimulate the lacrimal glands to secrete tears. At present, these drugs mainly include: (i) M cholinergic receptor agonists, such as pilocarpine hydrochloride, can stimulate the parasympathetic nerves to increase tear secretion (46). (ii) Respiratory mucus decomposer, benzyl cyclohexylamine has achieved good results in many studies (47). (iii) Phosphodiesterase inhibitor: This drug is currently in the clinical trial phase, and the osmotic pressure of tears in patients with sicca can be significantly reduced (48). (iv) Vitamin A can stimulate mucus secretion; on the one hand, it can inhibit the infiltration of lymphocytes in the lacrimal gland and reduce the inflammatory response; on the other hand, it can inhibit the scarring of the lacrimal gland tissue (49).

Treatment of Video Terminal Operators

This type of dry eye is clinically classified as evaporative dry

eye. The treatment of excessively evaporative dry eye should emphasize the improvement of the environment, such as the use of indoor humidifiers and wet room glasses to reduce tear evaporation, and even the use of ski goggles and swimming goggles are also cheap and practical treatments (50). Try to avoid eye contact with chemical irritants, smoke, etc. The treatment of VDTS should focus on improving eye hygiene habits (51). It is recommended that the patient's eyes keep a distance of 50-60 cm from the screen, the geometric center of the fluorescent screen is below the visual plane, within 15 °, and the duration of using the computer is about 1 hr. It is best to rest for 10 min every 50 min. Use artificial tears for severe symptoms. If you need to instill artificial tears two or more times a day for a period of time, lacrimal embolism is the first choice (52).

Strengthen the Management of the Wearing of Contact Lenses

According to the mechanism of KCS and surface punctate corneal epithelial lesions related to the wearing of contact lenses, strengthen the medical management of soft contact lens fitting, whether it is pre-fitting inspection, trial-wear evaluation and post-fitting review (53). The corneal condition and tear function must be checked in detail under the slit lamp (54). Those who wear contact lenses should pay attention to the method of wearing them, properly control the time of wearing them, standardize scientific care, and go to the ophthalmology department for health checkups on a regular basis. If abnormalities are found, stop wearing glasses or update lenses.

Autologous Serum

Autologous serum is a physiological tear supplement, containing some necessary components of tears, such as epidermal growth factor (EGF), vitamin A and other biologically active substances, which can improve eye nutrition and accelerate tissue recovery (55). It is the best tear substitute, but its source has great limitations and it is inconvenient to prepare and preserve, so it is not widely used in clinical practice.

Surgery

For severe KCS, if medical treatment is ineffective, submandibular gland transplantation is feasible (56-58). (i) The secretion of the transplanted submandibular gland is not directly innervated by the parasympathetic nerve, and saliva secretion generally does not cause severe tears due to eating; (ii) The submandibular gland secretes mucus in tears, while the parotid secretion is pure serous, the former is closer to tears ingredient. (iii) As long as the indications are selected appropriately, the removal of one submandibular gland will not cause dry mouth and no obvious damage to the body.

Concluding Remarks

With the continuous in-depth research on the etiology and pathogenesis of KCS, the drug treatment of KCS will continue to have new breakthroughs. Because the cause of KCS is more complicated, it is not only necessary to improve the ocular surface symptoms of KCS patients, but also to carry out individualized treatment for the cause. Individualized treatment is the best way to treat KCS. Therefore, seek a safe, reliable, and satisfactory KCS treatment method to achieve the goal of treating both the symptoms and the root causes.

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