

Introduction

Dry eye is the most frequent disorder in ophthalmology. It is the commonest cause of chronically red, itchy, irritated eyes (**Boyd, 2001**).

Despite this prevalence, dry eye is worldwide an Under-diagnosed problem (**Kaercher, 2001**).

When dry eye develops as a result of autoimmune mechanism causing lacrimal gland dysfunction, the condition is called keratoconjunctivitis sicca (KCS). Patients with KCS and dry mouth (xerostomia) have Sjögren's syndrome or sicca syndrome (**Christopher et al., 1999**).

The traditional concept of a three-layered precorneal tear film is still considered to be correct .However, some modifications have been proposed with regards to the structure and thickness of the tear film (**Yokoi and Komuro, 2004**).

The main aims of treatment are to relieve discomfort, provide a smooth optical surface, and prevent structural corneal damage (**Kanski, 2003**).

This entails recent lines of medical and surgical management of dry eye. Medically, the availability of preservative-free tear substitutes is an important advance in management in addition to other topical medication as autologous

Introduction and Aim of the Work

serum, anti-inflammatories, cyclosporine A, dextran, epidermal growth factor, etc (*Lubniewski and Nelson, 1990*).

Variable methods of punctual occlusion are an alternative line for treatment of dry eye (*Gillbard, 2000*).

Surgical treatment of dry eye has many advances including punctal patch technique, amniotic membrane transplantation and submandibular gland transfer (*Boyd, 2001*).

As the aetiology and pathogenesis of dry eye is increasingly understood, management of dry eye expects promising days (*Boyd, 2001*).

Aim of the Work

Is to discuss the efficacy and safety of recent lines in treating dry eye disease.

Anatomy

I. Anatomy of the Lacrimal Secretory System

The lacrimal secretory system includes:

- The main lacrimal gland.
- Accessory lacrimal glands which are: Krause and Wolfring's glands in addition to Henel and Manz glands (*Wolff, 1997*).

A-Main lacrimal gland:

The Lacrimal gland lies above and anterolateral to the eye ball. It appears in all vertebrates except fish, it is divided by the levator aponeurosis into large orbital (superior) part and a small palpebral (inferior) part. The two parts continue with each other, secrete tear through a series of ducts into superior fornix (*Snell and Lemp, 1998*).

Histologically it is a tubulo-acinar gland with short branched tubules. Larger intra-lobular ducts have a two – layered epithelial lining. The smallest intra-ocular ducts are lined with a layer of low columnar or cuboidal cells have myoepithelial cells at the periphery (*Bron et al., 1997*).

A-Accessory lacrimal glands:

The glands of krause: They are resembling in structure the main lacrimal gland. They are present deeply in the subconjunctival connective tissue mainly in the upper fornix. Their number is about 42 in the superior fornix and 6-8 in the lower fornix. Their ducts have been united into another long ducts which open into the fornix (*Snell and Lemp, 1998*).

Glands of Wolfring:

They are larger than glands of Krause. They are 2-5 glands in the upper lid situated in the upper border of the tarsus and two in the lower edge of the lower tarsus. Their ducts are short, wined and lined by epithelium made of two layers: deep cubical and superficial cylindrical cells (*Snell and Lemp, 1998*).

II. Anatomy of the Ocular Surface

A- Cornea:

The transparent cornea forms the anterior one sixth of the outer coat of the eye ball. It is the main structure responsible for refraction of the light entering the eye (*Wolff, 1997*).

Structure:

Microscopically, the cornea is formed of five layers as shown in Fig. (1).

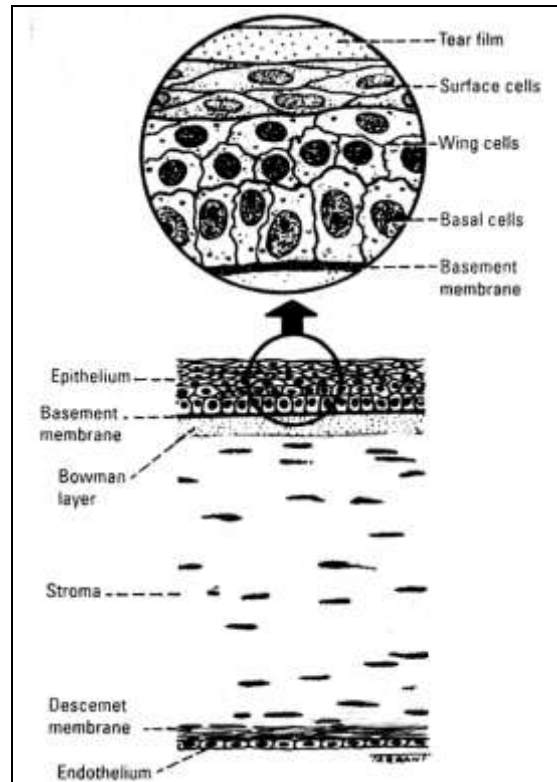


Fig. (1): Anatomy of the cornea (Kanski, 2003).

The cornea is avascular and devoid of lymphatic drainage. It derives nourishment by diffusion from the aqueous humour and from the capillaries at the limbus. The central part receives oxygen indirectly from the air via the tear film. The peripheral part receives oxygen by diffusion from the anterior ciliary blood vessels (**Bron et al., 1997**).

B- Conjunctiva:

Conjunctiva can be divided into regions, palpebral conjunctival, fornices conjunctiva and bulber conjunctiva. Lacrimal caruncle and plica semi-lunaries. Histologically it has an epithelium and submucosal lamina propria, conjunctival structure varies from region to region and this may affect on the pathological process. Conjunctiva has an epithelial covering of stratified columnar cells consisting of two to five layers resting on a lamina propria of loose connective tissue (**Snell and Lemp, 1998**).

Cells present in between conjunctiva is melanocyte, Langerhans cells and Goblet cells. Goblet cells are present through conjunctiva especially the plica semilunaris singly or in associated with epithelial crypts. There are regional variation in conjunctival goblet cell distribution and density. They are most dense nasally in lower conjunctival fornix, least dense in upper temporal fornix and absent at the palpebral muco-cutaneous junction and the limbus. Goblet cell density doesn't decrease with aging, and no significant difference in goblet cell density between men and woman was established (**Vujkovic et al., 2002**).

Electron microscopy of goblet cells demonstrate, It is true unicellular mucous gland, round or oval in shape as they

approach the surface where they develop stoma and discharge their mucin content, they are finally shed. It is 10 : 20 μm wide with flat basal nuclei dense cytoplasm in which rough endoplasmic reticulum, mitochondria and a well developed Golgi apparatus are embedded they are attached by desmosomes to neighboring epithelial cells. Goblet cells have abundant secretory granules 0.4: 10 μm in diameter with the largest granules close to apical membrane sometimes referred as subsurface vesicles (*Diebold et al., 2001*).

The Pre-ocular Tear Film

The pre-ocular tear film is a complex liquid structure covering the exposed corneal and conjunctival surfaces of the eye.

Structure and composition

The tear film consists of three layers: a thin superficial lipid layer, a thicker aqueous layer and a very thin mucoid layer covering the corneal epithelium from anterior to posterior (*Kanski, 2007*).

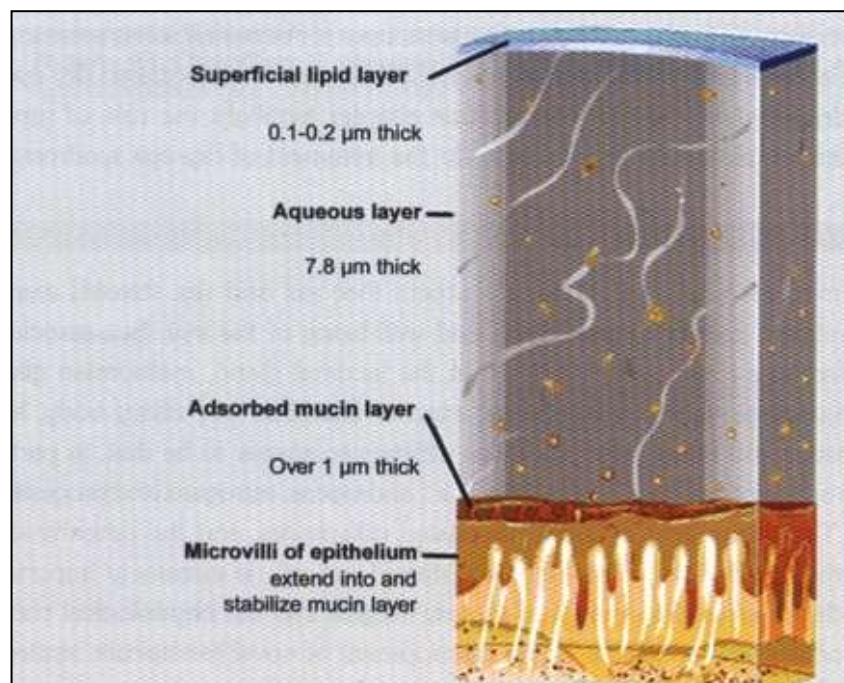


Fig. (2): Structure and composition of tear film (*Snell and Lemp, 1998*).

1) The lipid layer:

The lipid layer is approximately 0.1 micron thick. This superficial layer is secreted by Zeis and Meibomian glands of the lid (*Gracher, 2001*).

Meibomian glands are located within tarsal plate of eye lids, they are arranged vertically about twenty five in the upper lid and twenty in the lower lid. The small orifice of the canal opens on the lid margin just in front of the mucocutaneous junction. Histologically they are belonging to the category of Holocrine glands. Delivery of meibomian oil onto the lid margin as the result of secretion supplemented by the muscular action of each blink. It was found that these glands are under neuro-hormonal control (*Esmaeli et al., 2000*).

Glands of Zeis are modified sebaceous glands which are attached directly to the follicle of eye lash. There are two for each lash; each gland consists of one to three acini (*Bron et al., 1997*).

2) The aqueous layer:

The aqueous layer is about 8 μm thick. It represents the innermost layer of the precomeal tear film. It is composed of 98% water but also contains water-soluble gases, electrolytes, hormones,

organic molecules, live and dead desquamated cells and proteins (5-8 g/L). 99% of these proteins are synthesized in the main lacrimal gland (*Gracher, 2001*).

The traditional concept is that the accessory lacrimal glands of Krause and Wolfring are the source of basal tears, whereas reflex secretion may include contributions from the main and accessory lacrimal glands. This concept has been challenged. Recently, it has been suggested that all aqueous tear secretion is the result of stimulation, beginning with activation of the sensory nerves in the cornea (*Gracher, 2001*).

3) The mucous layer:

Inner mucous layer rest on the underlying corneal and conjunctival epithelium, its thickness is about 0.02 to 0.05 μm . Mucin component of the tear film has two-layer structure. The inner (mucin-like glycoprotein) most tightly bound component associated with epithelial cell surface, that is thought to be a product of the secretion of the cells themselves (non-goblet mucin cells), these called secondary mucus secretory system. Just above this layer there is a much thicker, looser layer referred to as mucous blanket (hydrated glycoproteins), this thought to be the product of the goblet cells of the conjunctiva (*Gendler and Spicer, 1995*).

Physiology of the Pre-Ocular Tear Film

Understanding the dry eye could be a great deal easier if thoroughly understood normal tear function and this also important in treatment of tear abnormalities and ocular surface disease. The ocular surface, tear film, and eye lids act as a functional unit to preserve the quality of the refractive surface of the eye (**Smith, 2001**).

The total volume of the tear film is 7-9 μl . about 1.1 μl of this lies in the precocular film within the palpebral fissure, 2.9 μl within the marginal tear strip, and about 4.5 μl within the fornices (**Gracher, 2001**).

The basal secretion rate has been estimated by means of uorophotometry to be 1.2 μl /min. and ranges between 0.5-2.2 μl /min. It is lowest during sleep and other conditions of low-level consciousness such as general anesthesia, and highest during stimulation by emotional stimuli or, irritants such as foreign bodies (**Christopher and Gillbard, 1997**).

Until recently, the tear film was believed to be tripartite, with a lipid superficial layer of 0.1 μm thickness, an aqueous mid-phase 7 μm thick, and a mucin basal layer 20-50 nm thick .

However, it is now clear that there is no clear-cut barrier between the three components by they are intricately (*Gracher, 2001*).

I- Outer Lipid Layer of the Tear Film

The lipid layer is the most superficial layer of the tear film, produced by the tarsal meibomian glands (*Warwick, 1981*).

The thickness of this layer is only 0.1 μm varying during the day, attaining its maximum thickness on awakening. It is composed of triglycerides, free fatty acids, waxes, and esterified cholesterols, a small amount of polar lipid and free fatty acids. Androgens regulate Meibomian gland function, enhance the quality and/or quantity of lipids produced by this tissue. Abnormalities of the lipid layer has provides to be one of the mostly important causes of dry eye syndrome (*Sullivan et al., 2002*).

The major role of the lipid layer is to retard evaporation of aqueous layer from the tear film. It also decreases the surface tension of the tear film holding it tight to the ocular surface. Adherence to the ocular surface is ensured by lipids known as lipocalins, this layer serves to lubricate the action of lids over the cornea and conjunctiva surface and prevent contamination of tear film by polar lipid of the skin of the lids (*McCully and Shine, 2001*).

II. Middle Aqueous Layer of the Tear Film

This layer account for 90% of tear film 95% of this layer is formed by the main lacimal gland. The rest is formed by the accessory glands of Krause and Wolfing (**Gracher, 2001**).

Aqueous tear secretion is largely a reflex mechanism cranial nerve V is the afferent pathway in the reflex tear arc. Stimulation of receptors in the fifth nerve distribution in the cornea or nasal mucosa induces tear secretion from the lacrimal gland. Parasympathetic fibers leave cranial nerve VII in the greater superficial petrosal nerve and pass to sphenopalatine ganglion. From there the lacrimal secretory nerve fibers travel with the zygomatico temporal nerve of the maxillary division (V₂) and join the cranial nerve V brfore entering the lacrimal gland (**Gracher, 2001**).

Aqueous tears now out of the ductal opening of the lacrimal glands and are either isotonic or slightly hypotonic. It contains the water-soluble contents such as inorganic salts, glucose, urea, proteins and trace elements (**Sullivan, 1998**).

Aqueous layer of the tear film has a unique electrolyte composition that differs from both aqueous humor and serum > he reported the normal values of the electrolyte concentration

in tear samples collected rapidly from the inferior marginal strips of normal subjects to be as follows:

Table (1): Electrolyte composition of tear film (*Gillbard, 1994*).

Na ⁺	132.8 mmol/L
K ⁺	23.8 mmol/L
HCO ₃ ⁻	32.7 mmol/L
Ca ⁺	0.80 mmol/L
Mg ⁺	0.61 mmol/L

The pH of tears varies not only among different persons but also at different times in the same person usually tears are slightly alkaline, The average pH is about 7.5 but may range from above pH (8) to below pH. Tear pH is lowest on awakening due to acid by products associated with the relative anaerobic condition in prolonged lid closure and increases due to loss of CO₂ as the eyes are opens (*Milder, 1987*).

Oxygen in the tear film is the major source for cornea metabolism. So a partial pressure of 155 mmHg is maintained, with the eye closed an oxygen partial pressure of about 55 mmHg is obtained from diffusion of O₂ through the conjunctival capillary bed into the tear film (*Lambert, 1990*).

Lysozyme content of the tears destroys the bacterial cell membranes. Its concentration in tears is much higher than that of serum. Lactoferrin, β-lysin, .albumin and immunoglobulins

are known to be present in normal tearfilm. IgG is present in significant quantity. Components of the entire complement system are present. Specific antibodies for herpes, influenza, and trachoma have been also isolated from tears. Other proteins can be synthesized by connective tissue, mainly during inflammatory conditions (**Gracher, 2001**).

III. Inner Mucin Layer of the Tear Film

The mucous layer is the deepest tear film layer and adheres firmly to the underlying epithelial cells and partly mixed with the overlying aqueous layer (**Gracher, 2001**).

The mucous layer is 0.02 to 0.05 micron thick (less than 0.5% of the tear film thickness). It is secreted by the goblet cells of the conjunctiva and also by the crypts of Henle and glands of Manz. Some of it may be derived from the main lacrimal gland.

