INTRODUCTION

Dry eye is considered a chronic inflammatory condition of the ocular surface, caused by tear hyperosmolarity and accompanied by ocular surface symptoms. The ocular surface includes the surface of the cornea and of the bulbar and tarsal conjunctiva, extending to the lid margin[1].

Keratoconjunctivitis sicca (KCS), also called dry eye syndrome (DES), is an eye disease caused by eye dryness, which is caused in turn by either decreased tear production or increased tear film evaporation. Any abnormality of any one of the three layers of tears produces an unstable tear film, resulting in symptoms of keratitis sicca.[2]

There is a division of dry eye into evaporative and tear deficiency dry eye. The tear deficiency dry eye is subdivided into Sjogren syndrome tear deficiency and non-Sjogren tear deficiency depending upon whether there are associated systemic symptoms or signs. [3]

Symptoms of keratoconjunctivitissicca include dryness, sandy or gritty eye irritation, itchy, scratchy, burning, and stingy or tired eyes. Other symptoms include redness, pain, foreign body or pulling sensation or pressure behind the eye. The resultant damage to the eye surface increases discomfort and sensitivity to bright light. [4]

Many risk factors of dry eye were identified and discussed. Most common risk factors are: female sex, current contact lens use, allergies, arthritis, thyroid disease, antihistamine and steroid use[5].

Dry eye can be diagnosed by symptoms only. Schirmer's test is done in 5 minutes, with or without anesthesia, using a Whatman 41 filter paper which is 5 mm wide and 35 mm long. If there is < 5 mm wetting with or without anesthesia that's diagnostic for dry eye. Tear breakup time (TBUT) test measures the time taken by tears to break up in the eye. It can be determined by placing a drop of fluorescein in the cul-de-sac.2

Smoking is one of the major lifestyle factors influencing the health of human beings. Smoking causes serious health problems, many of them life-threatening. Tobacco is considered the 2nd cause of death in the world. Tobacco smoking affects multiple organ systems resulting in numerous smoking-related diseases.[6]

Smoking harms different organs in the body including the eyes. Smokers have high risk of developing cataract compared to non-smokers. They also have increased risk of developing (AMD) age-related macular degeneration, compared with non-smokers. There is a link between smoking and uveitis. The development and progression of diabetic retinopathy is also related to smoking.[7]

Smokers are believed to complain of ocular surface symptoms more than non-smokers due to the irritant effect of smoke. Many studies have related smoking with dry eye through reporting and documenting symptoms and signs respectively, and using clinical tests like Schirmer test. Results are still controversial and further studies are required to clarify the topic.[8]Smoking is also considered a risk factor of intraocular and ocular surface inflammation[9, 10, 11, 12].

AIM OF THE WORK

The aim of this study is to compare the incidence of dry eye between smokers and non-smokers of the 3rd and 4th decade, admitted to Ophthalmology Department, Ain Shams University Hospitals.

Chapter One

ANATOMY AND PHYSIOLOGY OF THE TEAR FILM

Tear film overview:

The tear film overlays the ocular surface and provides the interface between the corneal and conjunctival epithelium and the external environment. The tear film is essential for the health and protection of the ocular surface and for clear vision as the tear film is the first refractive surface of the eye[13].

The tear film is a three-layered structure comprising a lipid (oil) layer, an aqueous (water) layer and a mucus layer over the corneal epithelium. The lipid layer is the most outer surface providing a smooth tear surface and retarding the rate of tear evaporation from the cornea. The aqueous layer is comprised of water promoting spreading of the tear film. The inner-most layer of the tear film serves as an anchor for the tear film and helps it adhere to the eye [14].

Some authors described the tear film as a complex mixture of secretions from multiple tissues and epithelia (Fig. 1) and consists of four layers (Fig. 2). The innermost layer is a glycocalyx that extends from the superficial layer of the ocular surface epithelia. The second is a mucous layer that covers the glycocalyx and may mix with the third aqueous layer. The outermost layer contains lipids. Similarly to mucous and

aqueous layers, aqueous and lipid layers may mix. Production and function of tear film layers are distinct and will be presented separately [15].

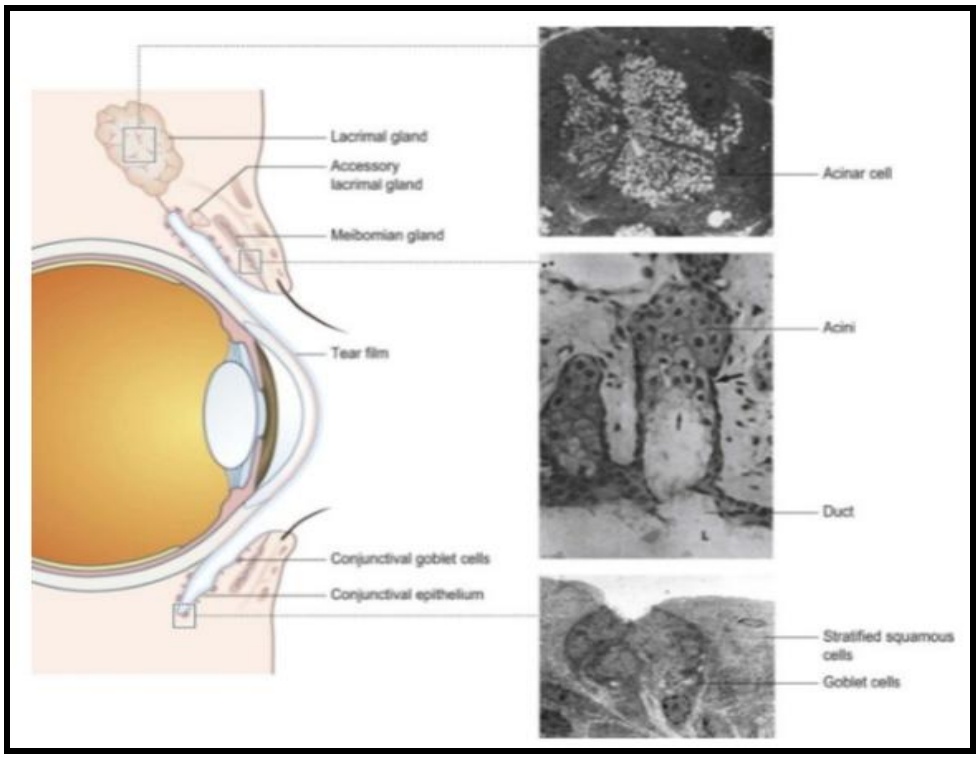

Fig. (1): Schematic of the glands and epithelia that secrete tears. The ocular surface epithelia are in beige and lacrimal glands in pink and their contribution to the tear film is in blue. An electron micrograph of conjunctival goblet cells is in the bottom inset. An electron micrograph of a lacrimal gland acinus, is shown in the top inset. An electron micrograph of a meibomian gland acinus with its attached duct is shown in the middle inset **(Dartt)** [25]

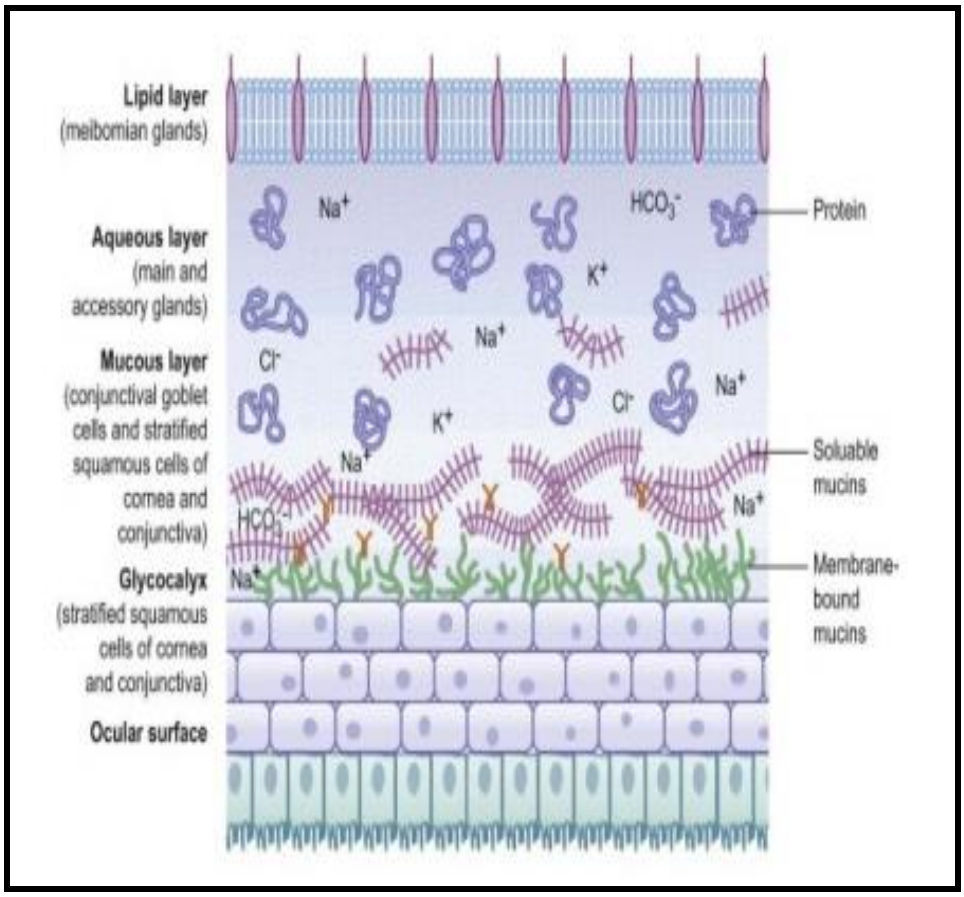

Fig. (2): Schematic of the tear film **(Hodges and Dartt, 2003)**[15].

Tear secretion by all ocular adnexa and ocular surface epithelia must be coordinated. Mucous and aqueous layers secretion is regulated by neural reflexes. Sensory nerves in cornea and conjunctiva are activated by mechanical, chemical, and thermal stimuli that in turn activate the efferent parasympathetic and sympathetic nerves, which innervate the lacrimal gland and the conjunctival goblet cells, and cause mucous and fluid secretion. For the lipid layer, the blink itself regulates release of pre-secreted meibomian gland lipids stored

in the meibomian gland duct. When the eyelids retract a thin film of lipid overspreads the underlying aqueous and mucous layers[13].

Aqueous tear secretion appears to have 2 modes, basal and stimulated. A major portion of tear production is reflexive via stimulation of the ocular surface and nasal mucosa. This reflexive secretion is thought to arise primarily from the main lacrimal gland and its palpebral lobe. Basal secretion (i.e. occurring in the absence of neural stimulation) is believed to come from the accessory lacrimal glands.[16]

However, some experts have questioned whether basal tear secretion exists. It has been proposed that so-called basal tearing may result from continuous corneal stimulation that is below the threshold of perception. On the other hand, some laboratory experiments suggest that basal tearing may be non-glandular, arising from active transport of fluid and chloride across the conjunctival epithelium16.

Tear secretion is balanced by drainage and evaporation. Tears on the ocular surface are drained through lacrimal puncta into the lacrimal drainage system. Drainage of tears can be regulated by neural reflexes from the ocular surface that cause vasodilation and vasoconstriction of the cavernous sinus blood supply of the drainage duct (Fig. 3). Both vasoconstriction and vasodilation cause a change in geometry of the lumen that decreases drainage. Evaporation depends on the amount of time

the tear film is exposed between blinks and temperature, humidity, and wind speed[17].

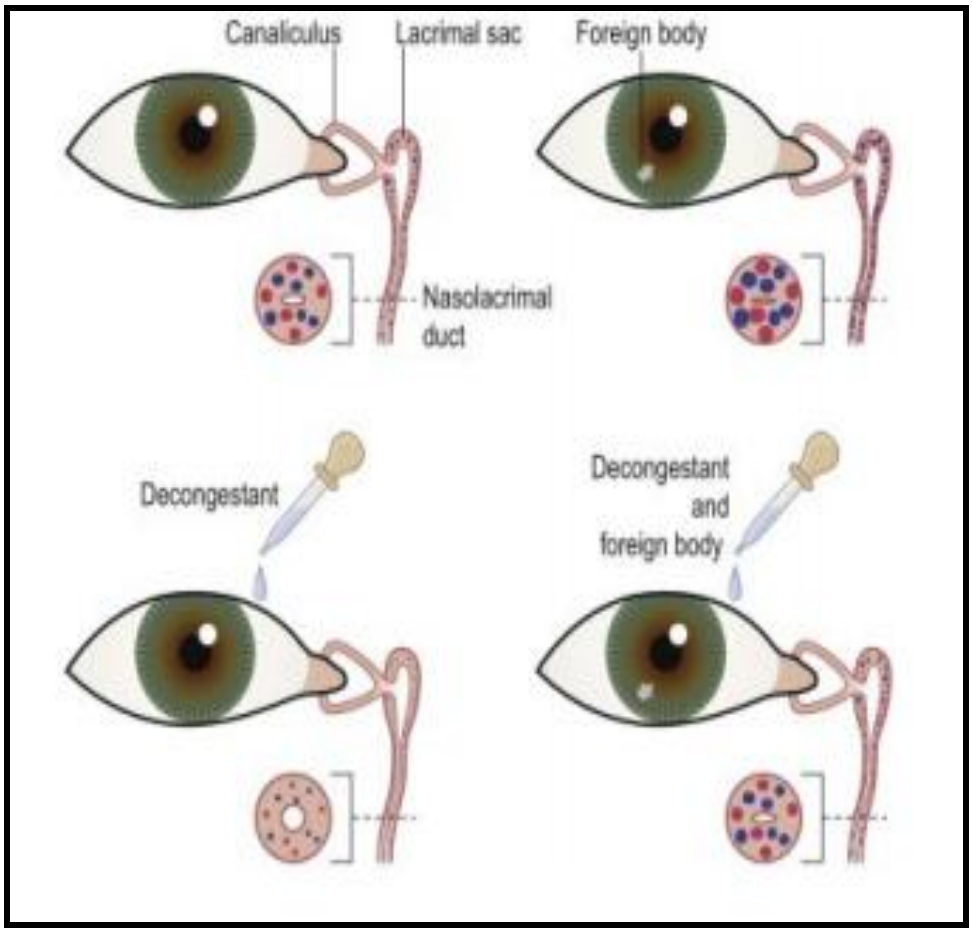

Fig. (3): Schematic anatomic model of the state of the cavernous body and lacrimal passage. The top left illustration shows the lumen of the nasolacrimal duct under resting conditions. A foreign body in the eye causes activation of nerves in the cavernous body causing vasodilation of the blood vessels and a narrowing of the lumen that results in decreased tear drainage. The third panel shows the placement of decongestant of the ocular surface causes vasoconstriction of the blood vessels of the cavernous body, and opening of the lumen of the nasolacrimal duct, and surprisingly a decrease in drainage. The final panel shows that the vasoconstriction caused by the foreign body and vasodilation by the topical congestant prevent a change in the shape of the lumen and in the drainage of tears **(Ayub et al., 2003).**[17]

Glycocalyx:

A- Structure:

The glycocalyx is a network of polysaccharides that project from cellular surfaces. In corneal and conjunctival epithelia, the glycocalyx can be found on the apical portion of the microvilli that project from the apical plasma membrane of the superficial cell layer (Fig. 2). Mucins are a critical component of the glycocalyx. Mucins are classified by the nomenclature MUC1–21 and are divided into secreted and membrane- spanning categories (Fig. 4). Membrane-spanning mucins consist of a short intracellular tail, membrane-spanning domain, and large, extended extracellular domain that forms the glycocalyx[13].

The ocular surface contains the membrane-spanning mucins, MUC1, MUC4, and MUC16. These mucins are produced by stratified squamous cells of the cornea and conjunctiva and are stored in small clear secretory vesicles in the cytoplasm (Fig. 1). Fusion of secretory vesicles with plasma membrane inserts these molecules into the plasma membrane. Mucin molecules are localized to the tips of the squamous cell microplicae[18, 19].

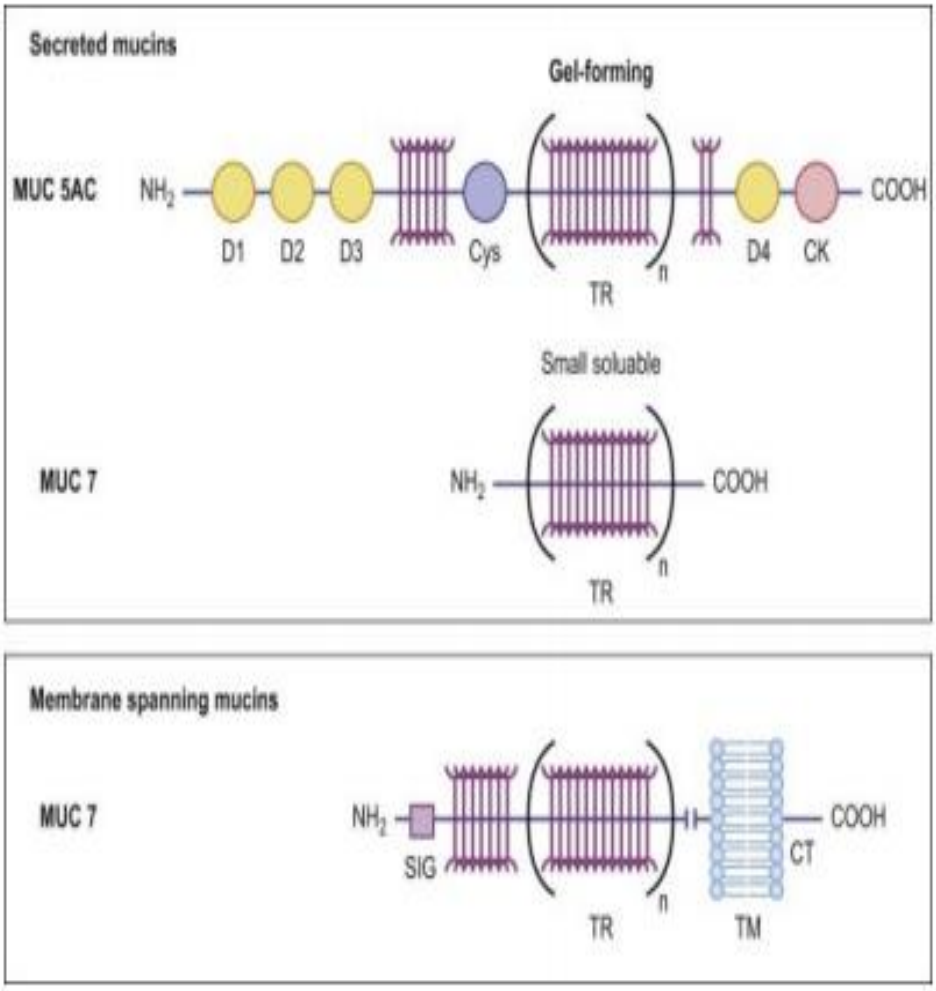

Fig. (4): Structural motifs of the secreted and membrane-spanning mucins. MUC5AC consists of four cysteine-rich D domains for disulfide cross-linking and flank a region of variable number tandem repeats (TR). MUC7 is monomeric, has a variable number of tandem repeats. The membrane spanning mucins have an SIG domain, a variable number of tandem repeats, a site for cleavage of the extracellular domain, a transmembrane domain (TM) for insertion of the molecule into membranes, and a carboxy terminus (CT) that is the intracellular domain. SIG: peptide signal sequence; CK: cysteine knot **(Gipson and Argueso, 2003).** [18]

B- Function:

The membrane-spanning mucins function is to hydrate the ocular surface and serve as a barrier to pathogens. Membrane-spanning mucins are considered to be dis-adhesive, allowing the mucous layer to move over the ocular surface. The carbohydrate side chains hold water at the surface of the apical cell membranes. The function of individual membrane-spanning mucins remains unclear[20].

Membrane-spanning mucins appear to be altered in dry eye. MUC16 protein levels decreased in conjunctival epithelium and increased in tears of patients with Sjogren's syndrome [8]. MUC1 splice variants also play a role in dry eye[21]. Human cornea and conjunctiva contain five previously identified MUC1 splice variants and a new splice variant. These splice variants have unique changes that could affect their ectodomain shedding, signaling properties of the intracellular domain, and water retention, lubrication, and barrier properties of the extracellular domains. When the type of MUC1 splice variant was determined in dry eye patients (both evaporative dry eye and Sjogren's syndrome) compared to control patients there was a reduced frequency of MUC1/Avariant and an increase in MUC1/B variant in dry eye patients[22].

Mucous layer:

A- Structure:

The mucous layer backbone is the gel-forming mucin MUC5AC, synthesized and secreted by conjunctival goblet cells. MUC5AC is encoded by one of the largest genes known, producing a protein of about 600 kDa. [13].

Measurements using laser interferometry suggests that the full thickness of the mucous layer was not recognized using conventional methods. Some have estimated tear layer thickness in the range of 34 to 45 um, with the mucous layer the thickest [11]. The mucous and aqueous portions are not static and may not remain as separate and distinct layers but may form a sort of gradient hampering accurate measurements [24].

B- Conjunctival goblet cells:

Goblet cells are identified by the large accumulation of mucin granules in the apex (Fig. 1). MUC5AC is synthesized in the endoplasmic reticulum and carbohydrate side chains added in the Golgi apparatus. The mature proteins are stored in secretory granules. Upon stimulation secretory granules fuse with each other and apical membrane releasing secretory product into the tear film. Upon cell stimulation the entire complement of granules is released, known as apocrine secretion. The amount of secretion is controlled by regulating the number of cells that are activated by a given stimulus [25].

C- Mucous layer function:

The major roles of the conjunctiva are to contribute to tear production by secreting electrolytes and water, modify composition of the tear film by secreting mucins, absorb various organic compounds found in tears (including ophthalmic therapeutics), and contribute to resistance of the eye to infection by providing protection against microorganisms. ucins serve as wetting agents that keep the apical epithelia hydrated. Finally, conjunctival cells release paracrine signaling agents such as growth factors that affect ocular surface properties [26].

Aqueous layer:

A- Overview:

The main lacrimal gland is the major producer of the aqueous layer. Other ocular surface epithelia also contribute to the aqueous layer, most notably the conjunctiva, accessory lacrimal glands, and to a small extent corneal epithelium. Accessory lacrimal glands, which are similar to the main gland, are embedded in the conjunctiva[13].

B- Lacrimal gland structure:

The secretory system includes the main lacrimal gland, the accessory lacrimal glands, meibomian glands and the conjuctival goblet cells. The main lacrimal gland is located in a fossa on the temporal side of the orbital plate of the frontal bone, just posterior to the superior orbital margin. The lacrimal

gland is divided into two portions, palpebral and orbital, by the aponeurosis of the levator muscle. The superior orbital portion is larger and almond shaped. The superior surface lies against the periorbita of the lacrimal fossa, the inferior surface rests against the aponeurosis, the medial edge lies against the levator, and the lateral edge lies on the lateral rectus muscle.[27]

The palpebral lobe is one third to one half the size of the orbital lobe and is subdivided into two or three sections. If the upper lid is everted, the lacrimal gland can be seen above the edge of the upper tarsal plate. Ducts from both portions of the gland exit through the palpebral lobe[27].

The lacrimal gland consists of lobules made up of numerous acini. Each acinus is an irregular arrangement of secretory cells around a central lumen surrounded by an incomplete layer of myoepithelial cells[28]. (Histologically the main lacrimal gland is identical to the accessory lacrimal glands). A network of ducts connects the acini and drains into one of the main excretory ducts. There are approximately 12 of these ducts, which empty into the conjunctival sac in the superior fornix. The secretion is composed of water, electrolytes, and antibacterial agents including lysozyme, lactoferrin, and immunoglobulins[27].