Role of Matrix Metalloproteinase-9 in Diagnosis of Dry Eye

Thesis

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List of Contents

Title	Page No.
List of Abbreviations	4
List of Tables	6
List of Figures	7
Introduction	- 1 -
Aim of the Work	11
Review of Literature	
▪ Anatomy of Secretory Part	12
▪ Physiology of Lacrimal System	19
▪ Dry Eye Syndrome	27
▪ Matrix Metalloproteinase-9	51
Patients and Methods	57
Results	62
Discussion	74
Summary	79
Conclusion	81
References	82
Arabic Summary	

List of Abbreviations

Abb.	Full term
AP-1	*Activated Protein-1*
ATF	*Activating Transcription Factor*
BAFF	*B cell Activating Factor*
GVHD	*Graft Versus Host Disease*
HIV	*Human Immunodeficiency Virus*
HLADR	*Human Leukocyte Antigen Π*
ICAM-1	*Inter Cellular Adhesion Molecule-1*
IgG	*Immunoglobulin G*
IL-1β	*Interlukin-1beta*
IL-6	*Interlukin-6*
IL-8	*Interlukin-8*
INF-α	*Interferon- α*
LASIK	*Laser Assisted in Situ Keratomileusis*
LIPCOFs	*Lid Parallel Conjunctival Folds*
MAPK	*Mitogen Activated Protein Kinase*
MCT	*Medial Canthal Tendon*
MMP	*Matrix Metalloproteinase*
MUC	*Mucins*
NF-KB	*Nuclear Factor Kappa light enhancer*
NGF	*Nerve Growth Factor*
NSAID	*Non- Steroidal Anti Inflammatory Drugs*
NTR	*Neurotrophin Receptor*
OCT	*Optical Coherence Tomography*
OSDI	*Ocular Surface Disease Index*
PRG4	*Proteoglycan-4*
ROS	*Reactive Oxygen Species*
SAPK	*Stress Activated Protein Kinase*
SIgA	*Secretory Immunoglobulin A*

List of Abbreviations cont...

Abb.	Full term

SP .....*Surfactant Protein*
TBUT .....*Tear BreakupTime*
TFF .....*Tre Foil Factor*
TIMPs .....*Tissue Inhibitors of Metalloproteinases*
TNF-α .....*Tumor Necrosis Factor-α*
TrKA .....*Tyrosine Kinase receptor A*
ZO-1 .....*Zonula Occludence-1*

List of Tables

Table No.	Title	Page No.
Table 1:	Component of lipid layer	22
Table 2:	Component of aqueous layer	23
Table 3:	Ocular Surface Disease Index	32
Table 4:	Demographic data of the study group	62
Table 5:	Data of different dry eye diagnostic tests.	63
Table 6:	Distribution and percentage of clinical examinations	64
Table 7:	Correlation between InflammaDry® test results and demographic distribution of study population	66
Table 8:	Relations between results of InflammaDry ® and other diagnostic tests for dry eye disease.	68
Table 9:	Relation between Meibomian gland function and InflammaDry® test results	72

List of Figures

Fig. No.	Title	Page No.
Figure 1:	Schematic drawings of tubuloalveolar structure of lacrimal gland	12
Figure 2:	Superior view of lacrimal gland	13
Figure 3:	Reflected orbital lobe of lacrimal gland with levator horn partially excised to show secretory ducts and palpebral lobe	14
Figure 4:	Approximate dimensions of the lacrimal excretory system	15
Figure 5:	Bony anatomy of lacrimal sac fossa	17
Figure 6:	Tear Film Layers	21
Figure 7:	Meibomian gland dysfunction	34
Figure 8:	Lid-parallel conjunctival folds grade 1	35
Figure 9:	**A.** Rose Bengal staining in severe dry eye, **B.** Lissamine green in moderate dry eye	37
Figure 10:	Examination with fluorescein 1 % at the slip lamp with cobalt blue light	37
Figure 11:	Vital staining of the ocular surface in a patient with dry eye disease	38
Figure 12:	Oxford grading of corneal and conjunctival staining	39
Figure 13:	Measuring tear film break-up time to assess tear film stability	41
Figure 14:	The Schirmer test	42
Figure 15:	MMP-9 expression and synthesis	53
Figure 16:	Hyperosmolar stress causes the release of MMP	54
Figure 17:	Inflammatory kit	59
Figure 18:	Gender of the study group	62
Figure 19:	Results of InflammaDry® test	64
Figure 20:	Meibomian glands assessment	65
Figure 21:	Relation between InflammaDry® results and different sex	67

List of Figures cont...

Fig. No.	Title	Page No.
Figure 22:	Relation between inflammaDry® results and mean of age	67
Figure 23:	Relation between Ocular Surface Disease Index (OSDI) and InflammaDry® test results	69
Figure 24:	Relation between corneal staining and InflammaDry® results	70
Figure 25:	Relation between Schirmer test, Tear breakup time and InflammaDry® results.	71
Figure 26:	Relation between Meibomian glands assessment and InflammaDry® results.	73

INTRODUCTION

Dry eye is a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface" ***(Foulks et al., 2007).***

Symptoms of dry eye, which include visual disturbances and pain, have been found to negatively impact quality of life ***(Pouyeh et al., 2012).***

Due to the multifactorial etiology of dry eye and its varied pathophysiologic mechanisms, it has been difficult to identify specific biomarkers that can aid in the diagnosis of dry eye. Inflammation is known to play an important role in the initiation and propagation of dry eye ***(Sambursky et al., 2014).***

Matrix Metalloproteinase-9 (MMP-9) is a 23 zinc and calcium ion-dependent enzyme important for tissue remodeling in normal physiological processes like wound healing and bone development. It plays a pathogenic role in inflammatory disease, arthritis, cardiovascular diseases, pulmonary diseases, and cancer ***(Lanza et al., 2016).***

MMP-9 activity is regulated by epigenetic processes, cell-cell interactions, and cytokine-mediated pathways. On the corneal surface, the hyperosmolarity of the tear fluid seen in dry eye has been shown to trigger the stress-activated protein kinase (SAPK) signaling cascade. SAPK signaling leads to the

release of MMP-9 from corneal epithelial cells themselves, thus initiating a cycle of progressive inflammation. Tight junction proteins; occludin and zonula occludens-1 (ZO-1) are cleaved by MMP-9, thereby disrupting epithelial layers ***(Aragona et al., 2015).***

T-cell recruitment, the proteolytic activity of the MMP-9 molecule itself, and activation of secretion of additional cytokines initiate a self-perpetuating cycle of inflammation, secretory dysfunction, and worsening eye dryness ***(Hessen and Akpek, 2014).***

In this study, we will use InflammaDry (RPS, Sarasota, FL), a novel test to measure level of MMP-9. It measures the presence of MMP-9. The test provides a qualitative (yes/no) response. The lower detection limit of the test is 40 ng/ml. If the collected sample is less than 5 µL, the test may falsely give a negative result ***(Sambursky et al., 2013).***

AIM OF THE WORK

To assess the presence of ocular surface matrix metalloproteinase-9 (MMP-9) in dry eye by InflammaDry® test.

Chapter 1

ANATOMY OF LACRIMAL SYSTEM

Anatomy of secretory part

1- Main lacrimal gland

The main lacrimal gland is located in the superotemporal part of orbit in a shallow lacrimal fossa of the frontal bone. The gland is composed of numerous acini which drain into larger tubules and ducts. The acini are made up of a basal contractile myoepithelial cell layer with inner columnar secretory cells (figure 1) ***(Lemke and Lucarelli, 2012).***

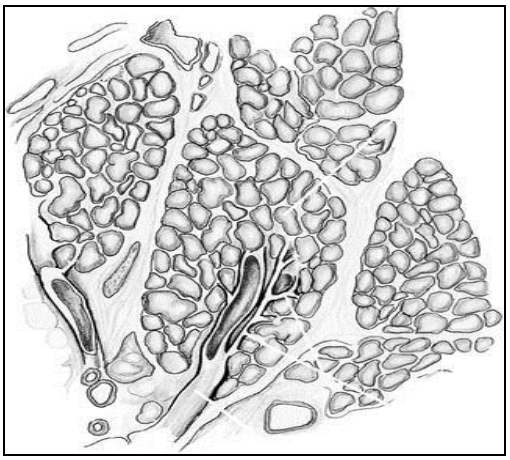

Figure 1: Schematic drawings of tubuloalveolar structure of lacrimal gland ***(Lemke and Lucarelli, 2012).***

The gland measures $20 \times 12 \times 5$ mm and the lateral horn of the levator aponeurosis divides it into a larger orbital lobe, and a lesser palpebral lobe below (figure 2). The orbital lobe

lies posterior to the orbital septum and preaponeurotic fat and anterior to the levator aponeurosis ***(Dutton, 1994).***

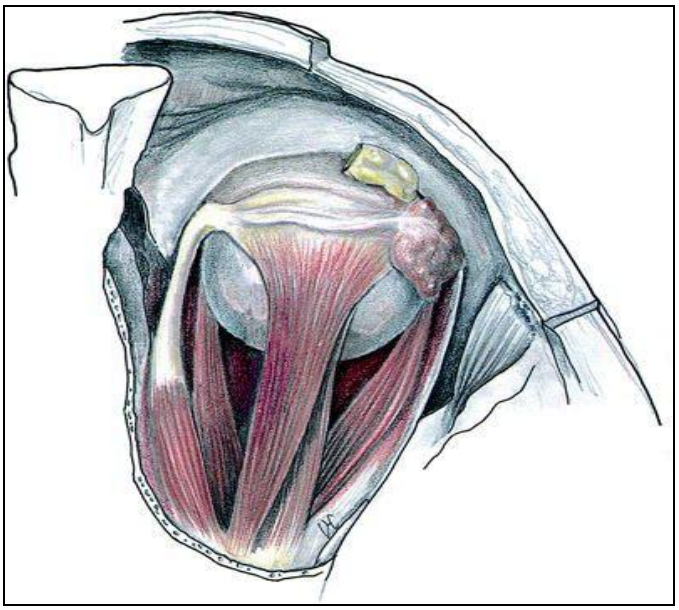

Figure 2: Superior view of lacrimal gland ***(Lemke and Lucarelli, 2012).***

Two to six secretory ducts from the orbital lobe of the lacrimal gland pass through the palpebral lobe or along its fibrous capsule (figure 3), joining with ducts from the palpebral lobe to form 6–12 tubules that empty into the superolateral conjunctival fornix 4–5 mm above the tarsus ***(Lemke and Lucarelli, 2012).***

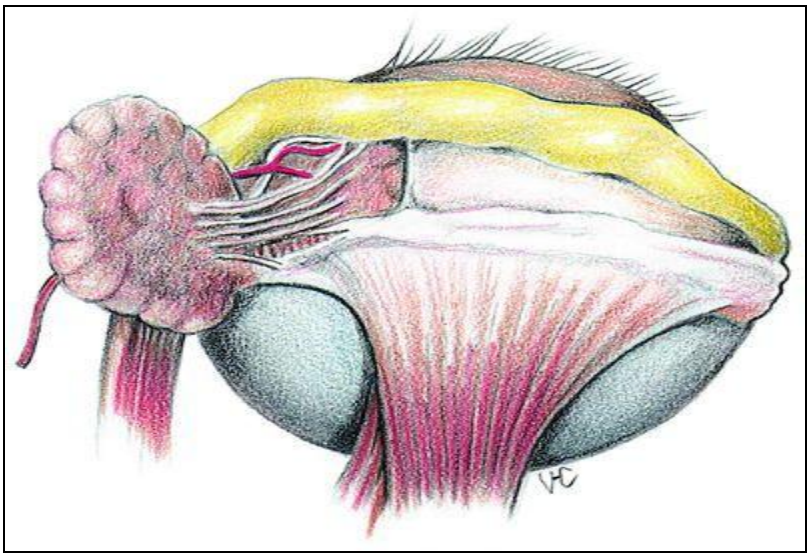

Figure 3: Reflected orbital lobe of lacrimal gland with levator horn partially excised to show secretory ducts and palpebral lobe ***(Lemke and Lucarelli, 2012).***

2- Accessory Lacrimal Glands

Accessory lacrimal glands are located in the conjunctival fornices and along the superior tarsal border. There are approximately 20–40 accessory glands of Krause in the superior conjunctival fornix, and half that number present in the lower eyelid. Accessory glands of Wolfring are located along the superior tarsal border in the upper eyelid ***(Seifert et al., 1994).***

Anatomy of excretory part

1- Lacrimal punctum

The lacrimal punctum lies on lacrimal papilla a small fibrous mound (figure 4). It measures 0.2–0.3 mm in diameter and directs posteriorly toward the ocular surface. The inferior

punctum lies 0.5– 1.0 mm more temporally than the superior one. The inner epithelium is nonkeratinized stratified squamous epithelium**.** No Meibomian glands exist medial to the papillae, and most medial Meibomian orifices are situated at 0.5–1.0 mm lateral to the puncta ***(Kakizaki and Valenzuela, 2011).***

2- Lacrimal canaliculus

The lacrimal canaliculus is divided into vertical and horizontal portions. The vertical portion length is 2 mm and the horizontal part is 10 mm (figure 4), the punctum and vertical canaliculus are encircled by hard fibrous tissue. This fibrous tissue contains the muscle of Riolan. The epithelium of the canaliculus is a nonkeratinized stratified squamous epithelium. The temporal 4/5 part is surrounded by the Horner's muscle ***(Kakizaki et al., 2012).***

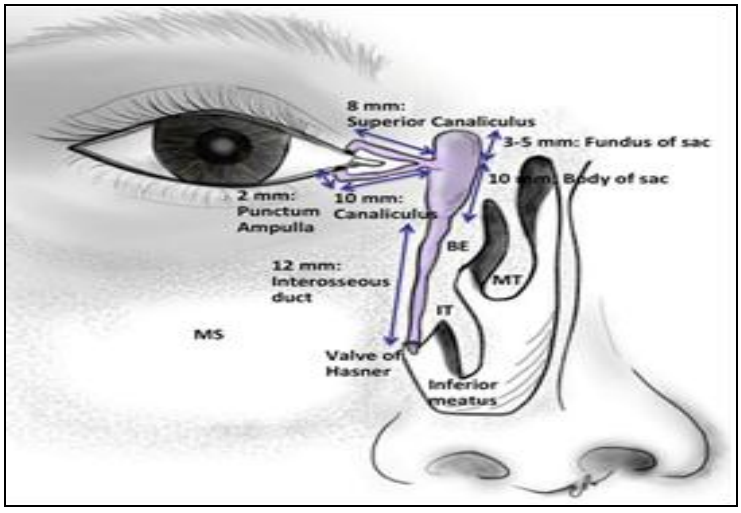

Figure 4: Approximate dimensions of the lacrimal excretory system (BE bulla ethmoidalis, IT inferior turbinate, MS maxillary sinus, MT middle turbinate) ***(Lemke and Lucarelli, 2012).***