Eye Care Massager Thermal Therapy for Treatment of Meibomian Gland Dysfunction

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I certify that this research work titled "*Eye care massager thermal therapy for treatment of meibomian gland dysfunction"* is my own work. The work has not been presented elsewhere for assessment. The material that has been used from other sources it has been properly acknowledged / referred.

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Abstract

Background

Meibomian gland dysfunction (MGD) is a major etiological factor in the development of evaporative dry eye (EDE), a common manifestation in eye clinics, which can have significant detrimental effects on quality of life. While traditional management strategies often fail to provide alternative solutions, patients and physicians seek alternative options. Thermal therapy is a novel treatment emerging in recent years. Numerous mostly reconsidered or open-label, studies have demonstrated an improvement in the signs and symptoms of EDE after periocular application of thermal therapy.

Purpose

Use contemporary clinical metrics of the mechanism of action (s) to explore the therapeutic efficacy of periocular application of thermal therapy as a treatment for MGD, then to explore the dry eye methods of Pakistani specialists against current evidence-based guidelines.

Methods

Thirty subjects with mild to moderate MGD were enrolled in a prospective and randomized clinical trial. Participants were randomized to receive a course of thermal therapy through eye care eye massage for 3 days, 4 days, and 5 days and evaluated at baseline and after treatment: 1,) certified dry questionnaires, 2) diagnostic techniques, 3) tire breakup time Test and 5) Lid Margin Assessment.

Results

A total of 30 participants were included in the study and 15 participants (mean ± SD age of 32.67 ± 11) were randomized to the control group of the study and 15 participants (mean ± SD age of 31.33 ± 8) were randomized to the treatment group with 3 days, 4 days, and 5 days follow-up. Following participation, dry eye symptom scores in the treatment group significantly improved from baseline relative to control group. Improvements in lid margin appearance, tear film lipid layer stability, tear break-up time, and meibomian gland function also differed significantly between the groups.

Conclusion

Thermal therapy is well tolerated and has proven to be an effective management option for MGD. Cumulative improvement in EDE properties may be related to changes in tear lipid profile rather than tear film lipid layer stability, meibomian gland capping, and meibum expressibility to reduce ocular surface inflammation, thereby broadening the understanding of the current mechanism of action.

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LIST OF ABBREVIATIONS

Acronym / Abbreviation	Definition within Thesis
ºC	Degrees Celsius
ADDE	Aqueous deficient dry eye
AT	Artificial tears
BCVA	Best corrected visual acuity
CL	Contact lens
DED	Dry eye disease
DEWS II	TFOS Dry Eye Workshop II (2017)
EDE	Evaporative dry eye
FML	Fluorometholone
GCP	Good Clinical Practice
IOP	Intraocular pressure
IPL	Intense pulsed light
KCS	Keratoconjunctivitis sicca
Meiboscale	Grading scale for meibography assessment

MG	Meibomian gland
MGD	Meibomian gland dysfunction
NaFl	Sodium fluorescein
OSDI	Ocular surface disease index
PK	Pakistan
SD	Standard deviation
SPEED	Standard patient evaluation of eye dryness
TBUT	Tear Breakup Time
TFLL	Tear film lipid layer
TPA	Therapeutic pharmaceutical agent
TRT	Thermal relaxation time
TTO	Tea tree oil
WE	Wax ester

CHAPTER 1: INTRODUCTION

1.1 Dry Eye Disease

1.1.1 Burden of Dry Eye Disease

Dry eye disease (DED) is a chronic ocular surface pathology that influences countless individuals worldwide, (Stapleton et al., 2017) and is perhaps the most well-known morbidities experienced in ophthalmic practice. (Shanti, Shehada, Bakkar, & Qaddumi, 2020) Symptoms, for example, burning, foreign body sensation, tearing, and ocular fatigue can impede visual performance, (Craig, Nichols, et al., 2017) restricting everyday social and physical functioning. (Rhee & Mah, 2017) Combined with habitually inadequate manifestation of the board, it can prompt depression, anxiety, and psychological stress. (Szakáts, Sebestyén, Tóth, & Purebl, 2017) Placed in setting, the weakness on personal satisfaction in those with moderate to serious DED has been compared to that of extreme angina or dialysis, (Uchino & Schaumberg, 2013) which features the significance of perceiving the connection between dry eye and mental health. (Tounaka et al., 2014) Although the pervasiveness of DED is profoundly connected with age, (Stapleton et al., 2017) (Farrand, Fridman, Stillman, & Schaumberg, 2017) it has gotten more inescapable in more youthful age gatherings, a component ascribed to some extent to expanding dependence on screen devices. (Shanti et al., 2020) Furthermore, the aging populace worldwide (He, Goodkind, & Kowal, n.d.) is demonstrating just to heighten the worry around this developing general health issue. TFOS DEWS II Epidemiology subcommittee looked into enormous accomplice investigations of more than 500 members inside the most recent decade and assessed the pervasiveness pace of DED (with and without side effects) to be somewhere in the range of 5 and 50%. (Stapleton et al., 2017) An absence of standardization in the def and in the classification of

the dry eye represents this variety, which makes deciphering results across various examinations testing. Less easily proven wrong, maybe, is the extensive monetary weight on health care frameworks that DED the board forces as clinical counsels, prescriptions, and surgeries, bringing about the critical financial effects at an individual level for the countless patients affected. (Farrand et al., 2017) Patients cause costs related to ophthalmic consideration because of the chronic idea of the sickness. Moreover, continuous expenses of buying over-the-counter treatments like artificial tears, lid hygiene wipes, and nutritional supplements collect over the long haul. In the USA, the expense of managing DED has been assessed to be around $55.4 billion annually, (Dana, Meunier, Markowitz, Joseph, & Siffel, 2020) anyway the most serious financial effect of DED is accepted to result from roundabout costs identified with diminished profitability in the work environment. Dry eye patients regularly commit huge measures of time to treatment and are affected in their working lives by the apparent need to maintain a strategic distance from specific conditions in the work environment which disturb their indications. From a local area viewpoint, this has been assessed to add up to a yearly profitability deficiency of $11,302 per affirmed DED patient in the USA. (Dana et al., 2020) In the outline, dry eye is the premise of extensive financial weight, both at an individual and cultural level. Projections of longer futures around the globe further increment the strain to look for successful new treatments that could help mitigate this developing general health concern.

1.1.2 Dry Eye Definition

Dry eye was recognized as an illness element in 2017 when the publication of TFOS DEWS II enlarged acknowledgment of the expanding worldwide effect of DED, starting a flood of interest from the scholarly community, clinical practice, and the business. (Craig, Nichols, et al., 2017) Remarkable refinement is in the new stating that moves from posting explicit signs and side effects

to portray an "*loss of homeostasis*", and going with "*ocular indications*", to mirror the horde of signs and manifestations perceived to be related with DED, past explicit individual signs and "*symptoms of discomfort, visual disturbance*". More accentuation has additionally been set on the etiological jobs of tear hyperosmolarity, tear film flimsiness, ocular surface aggravation, and neurosensory irregularities. Figure 1 1 delineates the key drivers which add to the pathogenesis and propagation of the DED Vicious Circle. (Anthony J. Bron et al., 2017)

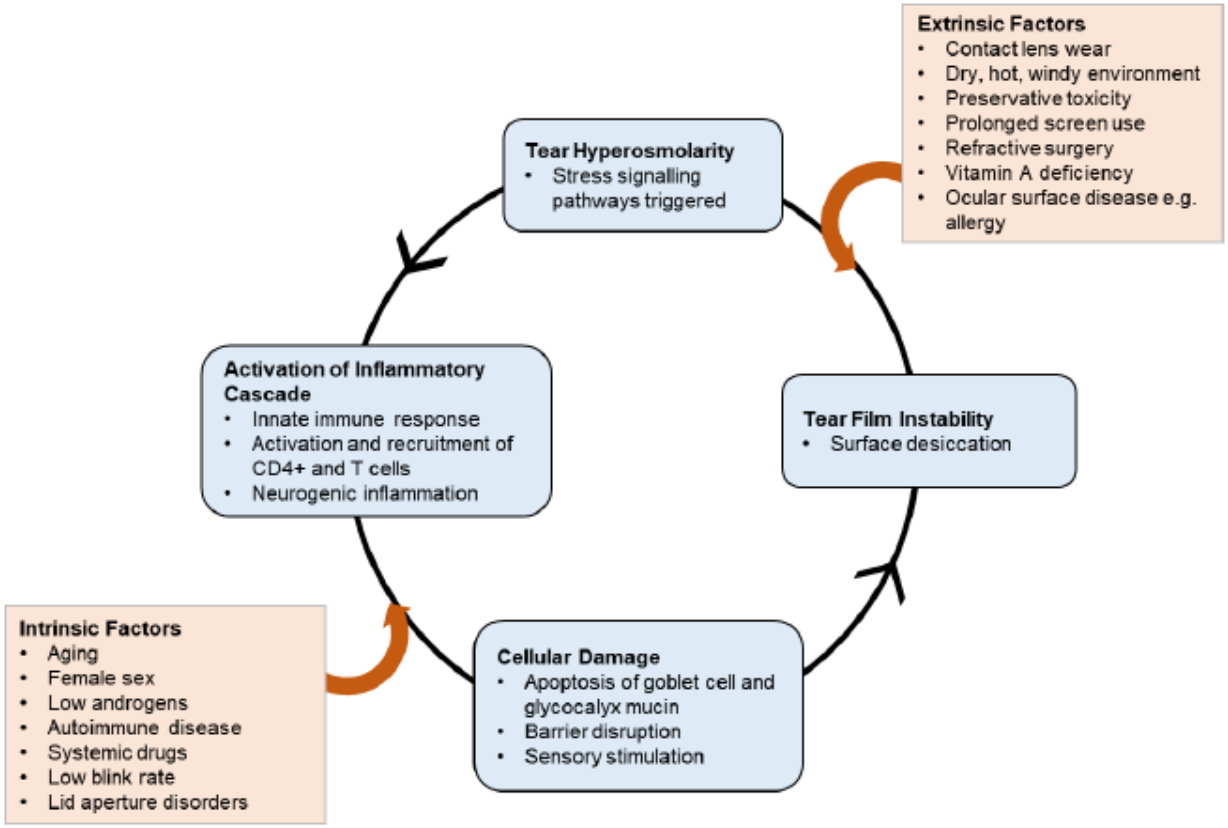

Figure 1 1 key entry points and chain events in the Vicious Circle of DED. (Anthony J. Bron et al., 2017)

1.1.3 Dry Eye Classification

Formalized attempts to classify DED by subtype began with the *(ADES)* on Clinical Trials in Dry Eyes. (Tsubota et al., 2020a) This initial classification of DED has evolved over time, with the

current consensus among dry eye experts being that ADDE and EDE pathophysiology exist on a continuum rather than as discrete entities, (Craig, Nichols, et al., 2017) and thus both subcategories of the dry eye need to be considered during diagnosis (Anthony J. Bron et al., 2017) and management. (Jones et al., 2017) The DED classification system (Craig, Nichols, et al., 2017) proposed by *TFOS DEWS II* Definition and Classification subcommittee further acknowledges the widely recognized mismatch. (Severity et al., 2015) The system allows for categorization of DED according to clinical presentation, based initially on the, and then followed by subdivision according to detectable ocular surface signs. The lower portion of the classification scheme continues to recognize ADDE and EDE as the primary DED subtypes and highlights their possible overlap.

1.1.3.1 Aqueous-Deficient Dry Eye

In ADDE, the dry eye happens because of diminished gland in the presence of typical tear evaporation rate. (Chan, Chow, Wan, & Yuen, 2019) It can result from a square to the tangible drive of the lacrimal gland or be the symptom of foundational drug use (iatrogenic dry eye) like antihistamines, beta-blockers, and diuretics (Figure 1.1). Not uncommonly, it can be brought about by Sjögren's condition, a chronic immune system issue in which acinar cells and ductal epithelium within the lacrimal and salivary glands are dynamically obliterated by inflammatory infiltration from actuated T-cells. (Craig, Nichols, et al., 2017) (Anthony J. Bron et al., 2017) Historically, it has been partitioned into (SSDE) and (NSDE). It is trusted Sjögren's disorder might be a consequence of unusual insusceptible responses to environmental, viral, and hormonal triggers hereditarily vulnerable. (Anthony J. Bron et al., 2017) (Sullivan et al., 2017) DED victims are often underdiagnosed for Sjögren's syndrome, with a normal chance of finding of around 2.8 years according to the Sjögren's Syndrome Foundation. (Basnet, Basnet, & Karki, 2018) The condition

influences ladies 90% of the time (Yen, Hsu, Li, & Hsu, 2015) and is assessed to have a predominance rate of 0.6 to 1% among the overall grown-up population in the USA. (Helmick et al., 2008) NSDE alludes to the presence of lacrimal dysfunction without the demonstrative highlights of Sjögren's condition. Diminished lacrimal function in NSDE can be congenital or gained yet is most commonly ascribed to aging. (Anthony J. Bron et al., 2017) (Raposo et al., 2018) The Report distinguished a consistent increase from the age of 50 years with a predilection for postmenopausal women. (Stapleton et al., 2017) Such pattern might be explained by decreased androgen levels and collected "mileage" tissue damage. (M. T. M. Wang et al., 2020)

1.1.3.2 Evaporative Dry Eye

The proportion of patients exhibiting highlights of EDE far exceeds that of those exhibiting only ADDE. (Lemp, Crews, Bron, Foulks, & Sullivan, 2012) indeed, the reported pervasiveness of EDE dependent on clinical signs in populations beyond 40 38 years old ranges from 38 to 86%, (Lemp et al., 2012) depending on population partner qualities and the analytic standards employed. (Stapleton et al., 2017) Despite a typical functioning lacrimal gland, EDE happens because of extreme aqueous evaporation when the hindrance function of the tear film is undermined, either because of lid-related or ocular surface-related pathologies. In ocular surface-related EDE, the condition can be driven by extrinsic factors, for example, vitamin An inadequacy, hypersensitive eye sickness, and the additive impacts of skin drugs; (Anthony J. Bron et al., 2017) (Erich Knop, Knop, Millar, Obata, & Sullivan, 2011) while lid-related pathology will, in general, envelop intrinsic components which influence tear elements and lid design. This can include problems of lid opening, congruity, and blinking insufficiency, just as retinoid skin inflammation treatments. Be that as it may, the most common reason for EDE is broadly considered to be meibomian gland dysfunction (MGD).(Teo, Ong, Liu, & Tong, 2020)

1.1.4 Histopathology

Clinical and research middle investigations accomplished in the current few years have determined that dry eye is a continual inflammatory infection that can be initiated by way of diverse extrinsic or intrinsic variables that enhance a flimsy and hyperosmolar tear movie. These adjustments in tear composition, once in a while blended with foundational factors, lead to an inflammatory cycle that causes ocular floor epithelial illness and neural stimulation. Acute desiccation enacts pressure signaling pathways in the ocular surface epithelium and occupant insusceptible cells. This triggers the manufacturing of innate inflammatory center human beings that invigorate the manufacturing of community metalloprotease, inflammatory cell enrollment, and dendritic cell maturation. Those middle human beings, blended with the openness of autoantigens, can spark off a versatile t cell intervened reaction. Cornea boundary disruption creates through protease-interceded lysis of epithelial junctions, leading to increased cellular death; a sporadic, inadequately greased up cornea surface; and openness and of epithelial nociceptors. Conjunctival challis cellular dysfunction and loss of life are superior by way of the t assistant interferon-gamma. Those epithelial adjustments similarly destabilize the tear film, intensify irritation, and make a cycle. (Pflugfelder & de Paiva, 2017. (Rhee & Mah, 2017)

1.1.5 Dry Eye Practice Behaviors

As recently depicted, the publication of TFOS DEWS in 2017, just as resulting workshops in MGD and contact focal point distress set off far-reaching overall recognition of DED as a common and debilitating illness entity. (Pflugfelder & de Paiva, 2017) (Chhadva, Goldhardt, & Galor, 2017) It started freshly discovered excitement in the zone that spread beyond the scholarly world to clinical and industrial areas, and was a critical driver in the publication of a refreshed international outline consensus of the writing of the most recent decade, through TFOS DEWS II, (Nelson et al., 2017)

accordingly providing eye care professionals with an asset of contemporary proof-based procedures to analyze and oversee DED. The adequacy of exploration dissemination into training has been concentrated in numerous nations, and studies that have questioned the utilization of dry eye analytic tests by eye care practitioners have depicted wide variations in self-reported protocols. (Tsubota, 2018) (Yokoi & Georgiev, 2019) (Yokoi & Georgiev, 2018) Studies resulting from the arrival of the initial TFOS DEWS discovered clinicians were adopting a proof-based way to deal with their DED practice conduct, however, there was as yet the potential for improvement. (Xue, Downie, Ormonde, & Craig, 2017) (Geerling et al., 2017) Hence, one of the main TFOS DEWS II Diagnostic Methodology subcommittee was to build up a standardized calculation for diagnosing and classifying DED. By reviewing the writing on the symptomatic precision information of validated symptomology questionnaires, just as ocular surface and tear film boundaries, a consensus battery of tests as described. (Wolffsohn et al., 2017) However, TFOS DEWS II noticed that the convention for sickness on the board was not as basic. The ultimate objective of treatment is to interrupt the "vicious cycle" of DED and reestablish tear film homeostasis. Therefore the initial phase in achieving this point is to recognize the patient's essential wellspring of illness as it is basic in helping to choose the most proper therapeutic strategy. (Jones et al., 2017) However, because of the multi-factorial nature of DED, standardizing the executives' convention that is down to earth in a clinical setting remains a test. The proof-based calculation constructed by the TFOS DEWS II groupings treatments according to infection seriousness, yet in addition cautioned that the administration of DED remains "something of a craftsmanship" and a defined calculation may not oblige all patients. Therefore, optometrists and ophthalmologists should practice their clinical abilities to pass judgment on the underlying illness measures that

show the ocular surface dysfunction so they can shape custom-fitted treatment plans for their patients.

1.2 Meibomian Glands Dysfunction

1.2.1 Meibomian Glands Dysfunction Definition

Meibomian gland dysfunction (MGD) has been described by the TFOS International Workshop on MGD as *"a chronic, abnormality of the meibomian glands, commonly characterized by terminal duct obstruction or qualitative changes in the glandular secretion. This may result in change of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease."*(Erich Knop et al., 2011)

1.2.2 Prevalence and Risk Factors

Albeit the condition gives off an impression of being all the more commonly analyzed in guys and in more seasoned age groups, (Hassanzadeh, Varmaghani, Zarei-Ghanavati, Heravian Shandiz, & Azimi Khorasani, 2020) (Meduri, Frisina, Rechichi, & Oliverio, 2020) (M. T. M. Wang et al., 2020) MGD has a high by and large commonness, affecting up to practically 70% of the population in certain pieces of the world. (Gao, Chen, Tang, & Chen, 2020) Figure 1.2 illustrates the pervasiveness of MGD reported by a few population-based investigations. Albeit these rates contrast depending on components like analytic measures, it has been confirmed by means of meta-investigation that MGD horribleness is seen to be a lot higher in Asian populations (more than 60%) contrasted with Caucasian (3.5 to 19.9%). (Stapleton et al., 2017) (Erich Knop et al., 2011) Risks that may exist together to the pathophysiology of MGD ocular influences, for example, contact focal point wear, (Thulasi & Djalilian, 2017) front blepharitis, (Exp, Arita, & Fukuoka,

2020) and Demodex parasite infestation. (Murphy, O' Dwyer, & Lloyd-Mckernan, 2020) Systemic influences that may exasperate MGD include aging, (M. T. M. Wang et al., 2020) androgen deficiency, menopause, (Kawashima, 2018) Sjögren's syndrome, (Yen et al., 2015) skin inflammation rosacea, psoriases, (Rhee & Mah, 2017) hypercholesterolemia, atopies, (Erich Knop et al., 2011) high blood pressure, and age-related prostate gland amplification (generous prostatic hyperplasia, BPH). (Kawashima, 2018) Medications known to be antagonistically connected with MGD include antiandrogens, (Thulasi & Djalilian, 2017) (Geerling et al., 2017) BPH treatment medications, postmenopausal hormone therapy, antihistamines, (Meduri et al., 2020) (Bu et al., 2019) antidepressants, and retinoid skin inflammation treatments. (Magno, Moschowits, MS, Arita, MD, PhD, Vehof, MD, PhD, & Utheim, MD, PhD, 2021) (Kawashima, 2018) (Kheirkhah et al., 2020) (Rhee & Mah, 2017)

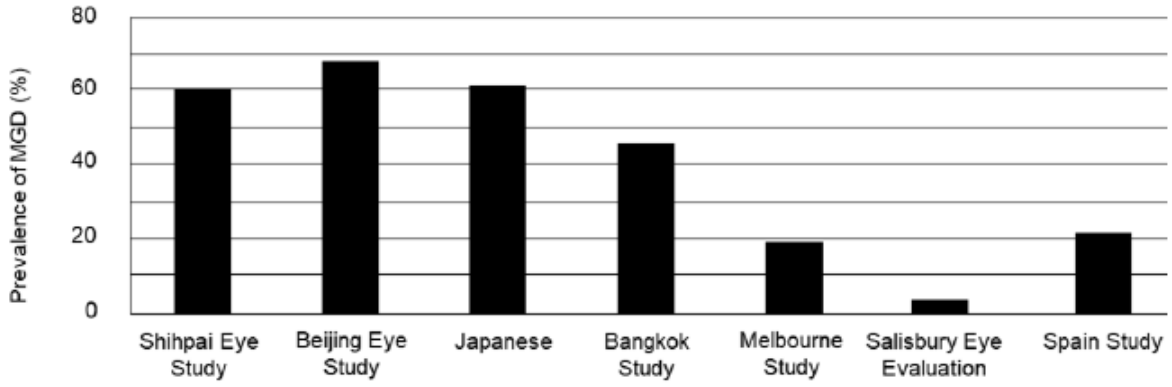

Figure 1 2 Prevalence of MGD reported by epidemiology studies performed in predominantly Asian (Shihpai, (Lin et al., 2003) Beijing, (Jie, Xu, Wu, & Jonas, 2009) Japanese (Uchino et al., 2006), Bangkok (Lekhanont, Rojanaporn, Chuck, & Vongthongsri, 2006)) and Caucasian (Melbourne, (McCarty, Bansal, Livingston, Stanislavsky, & Taylor, 1998) Salisbury, (Schein,

Munuz, Tielsch, Bandeen-Roche, & West, 1997) Spain (Viso, Rodríguez-Ares, Abelenda, Oubiña, & Gude, 2012)) populations.

1.2.3 Anatomy and Physiology

Meibomian glands (MGs) are tubuloacinar holocrine glands vertically inserted within the upper and lower eyelid tarsal plates, which effectively discharge a slick substance known as meibum the only in front of the mucocutaneous junction, the transition zone between keratinized skin and the palpebral mucosa. (Takahashi et al., 2013) When the meibum spreads onto the foremost surface of the eye, it assists with promoting tear film strength and structures a hindrance against aqueous evaporation. (Brooks & Gupta, 2021) (Yokoi & Georgiev, 2019) Each MG consists of a focal conduit branching horizontally into various ductules that open into acini. (Inaba et al., 2018) (Yokoi & Georgiev, 2018) The focal channels run in equal all through the length of the tarsal plates and their holes open at the back lid margin. (Erich Knop et al., 2011) (Pflugfelder & de Paiva, 2017) The number and volume of MGs are more prominent in the upper eyelid (roughly 25 to 40) than in the lower eyelid (around 20 to 30). (D. N. Wang, Patel, & Luong, 2020) . Sebaceous glands of the skin discovered , MGs have a thick meshwork of tangible, autonomic and peptidergic neural strands surrounding every acinus, which discharge synapses to control MG secretory function. (Georgiev, Eftimov, & Yokoi, 2019) In addition, the presence of androgen and estrogen receptors proposes that MG function is additionally under hormonal regulation, with androgens reportedly increasing meibum outpouring and estrogens inducing the converse effect. (Sullivan et al., 2017) The production of meibum depends on holocrine secretion. (Maruoka et al., 2020) Each acinus is loaded up with secretory cells named melanocytes that migrate toward the focal point of the acinus as meibum-containing vesicles increase within the cytoplasm. (Yoshida et al., 2019) (Ciloglu, Özcan, Incekalan, & Unal, 2020) Ultimately, the phone layer disintegrates when the meibocyte

arrives at the ductule, releasing the contents. In addition to the secretory power from the constant production of new melanocytes in the acini driving the glandular oils toward the opening, a solid "milking action" is generated during the blink by the orbicularis and Riolan's muscles to further contribute to the conveyance of meibum to the lid margin. (Yoshida et al., 2019) Mass spectrometry has been utilized by various examinations to portray meibum lipid profile, and studies, for the most part, concur that meibum consists of different polar and nonpolar lipid classes, particularly wax esters, sterol esters, phospholipids and free cholesterol. (D. N. Wang et al., 2020) (Hwang, Mikula, Xie, Brown, & Jester, 2020) (Olżyńska, Wizert, Štefl, Iskander, & Cwiklik, 2020) Literature has likewise reported an expansive scope of melting points for human meibum (somewhere in the range of 32 and 45°C), (Maki, Braun, & Barron, 2020) (Yokoi & Georgiev, 2018) which is likely owing to various estimation approaches just as varying biochemical composition of meibum among guineas pigs. Once meibum is delivered onto the eyelid margin, it is disseminated over the ocular surface, by blinking, to frame the external layer of the precorneal tear film (TFLL).

The precorneal tear film (Figure 1.3) serves a few functions. It greases up the uncovered ocular surface and shields it from invading microorganisms and environmental insults. Not exclusively does the avascular cornea depends on this thin layer of liquid for supplements and oxygen, (Yoshida et al., 2019) however it likewise gives a smooth refractive surface at the air-liquid interface by compensating for any inconsistencies on the corneal surface. (Tsubota et al., 2020b) (Uchino & Schaumberg, 2013) The original trilaminar model of the tear film included an innerlayer, an overlyin, and an external lipid layer. Since then, the consensus among scientists is towards a bilaminar model. (Rathnakumar et al., 2018) (Kumari, 2017) In the contemporary two-layer structure are considered a single much aqueous gel stage, where the mucin concentration

continuously diminishes from the epithelium towards the external lipid shell. The aqueous period of the much aqueous gel is predominantly emitted by the lacrimal gland. It contains electrolytes, vitamins, hormones, development factors, dissolvable proteins, immunoglobulins, and mucins. (Olżyńska et al., 2020) (Raposo et al., 2018) Mucins are profoundly glycosylated glycoproteins that are arranged as either transmembrane (MUC1, MUC4, MUC16) or secretory (MUC5AC, MUC5B). (Georgiev et al., 2019) They are communicated by epithelial tissues of mucosal surfaces, like the conjunctiva. Mucins lessen the hydrophobicity of the epithelial cell surfaces to improve the wettability of the cornea. The challis cells of the conjunctiva are the essential wellspring of gel-forming mucins, with MUC5AC being the most plentifully expressed. (B. Li, Fu, Liu, & Xu, 2020) (Yokoi & Georgiev, 2019) The tear film lipid layer (TFLL) is gotten principally from the lipid-rich meibum discharged from the MGs. As depicted before, the slick substance goes through an arrangement of ductules connected to a focal pipe that terminates with an opening at the back lid margin. The communicated meibum is then determined by surface tension powers to spread across the tear film with each blink. Polar lipids in the TFLL interact with tear lipophilic proteins (lipocalin), which help to advance thermodynamic dependability between the hydrophobic highest layer of nonpolar lipids and hydrophilic much aqueous stage underneath. An intact TFLL is integral to counteracting aqueous fume loss90 by maintaining a steady tear film, and in ordinary patients the tear separation time (TBUT) is around 10-20 seconds. (Raposo et al., 2018) (Olżyńska et al., 2020) In MGD patients, in any case, diminished meibum conveyance and/or alteration of the lipid organic chemistry can fundamentally abbreviate the TBUT. (Erich Knop et al., 2011) Disruption of tear film integrity causes the underlying much aqueous gel to evaporate rapidly, which can at last prompt desiccation, irritation, and inflammation of the ocular surface.(Nelson et al., 2017) (Rhee & Mah, 2017)

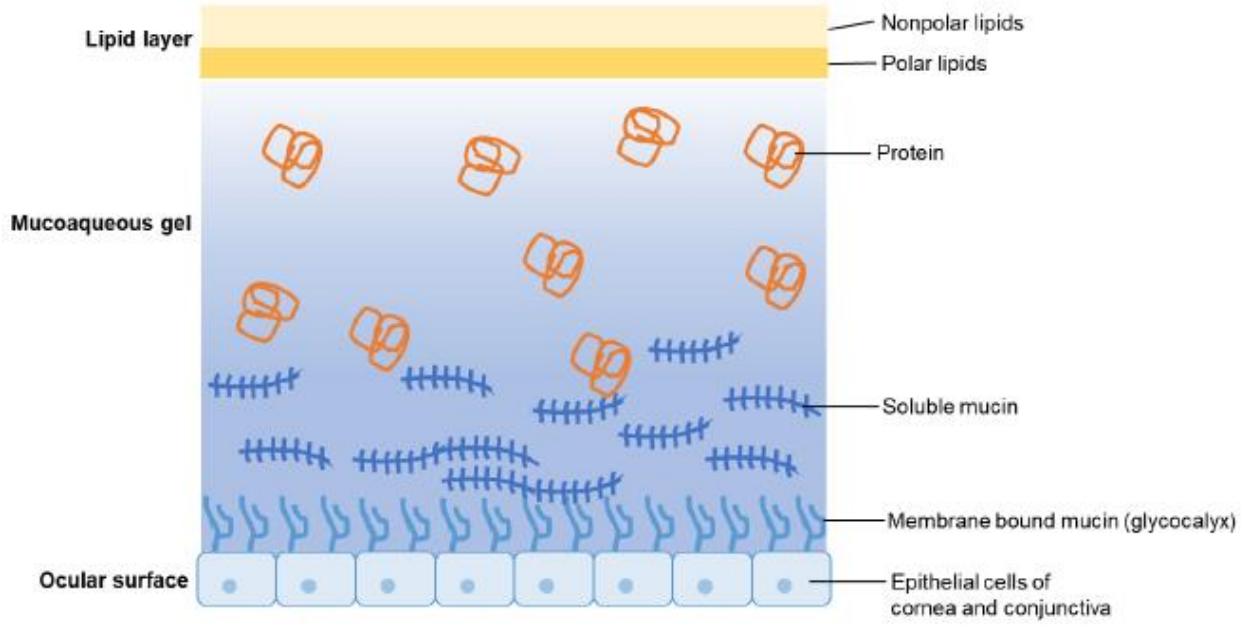

Figure 1 3 Schematic representation of the structure of the precorneal tear film.

1.2.4 MGD Pathogenesis

The TFOS International Workshop on Meibomian Gland Dysfunction (MGD) built up a classification plot that distinguishes MGD subtypes based on glandular secretary function. The framework further isolates those groupings according to expected clinical results and aetiologies. (Tsubota et al., 2020a) (Craig, Nichols, et al., 2017) The Definition and Classification Subcommittee underscored that obstructive MGD seems, by all accounts, to be the most unavoidable amongst all the infection subdivisions. Figure 1.4 demonstrates the center components involved and how they identify with the inflammatory occasions of EDE.

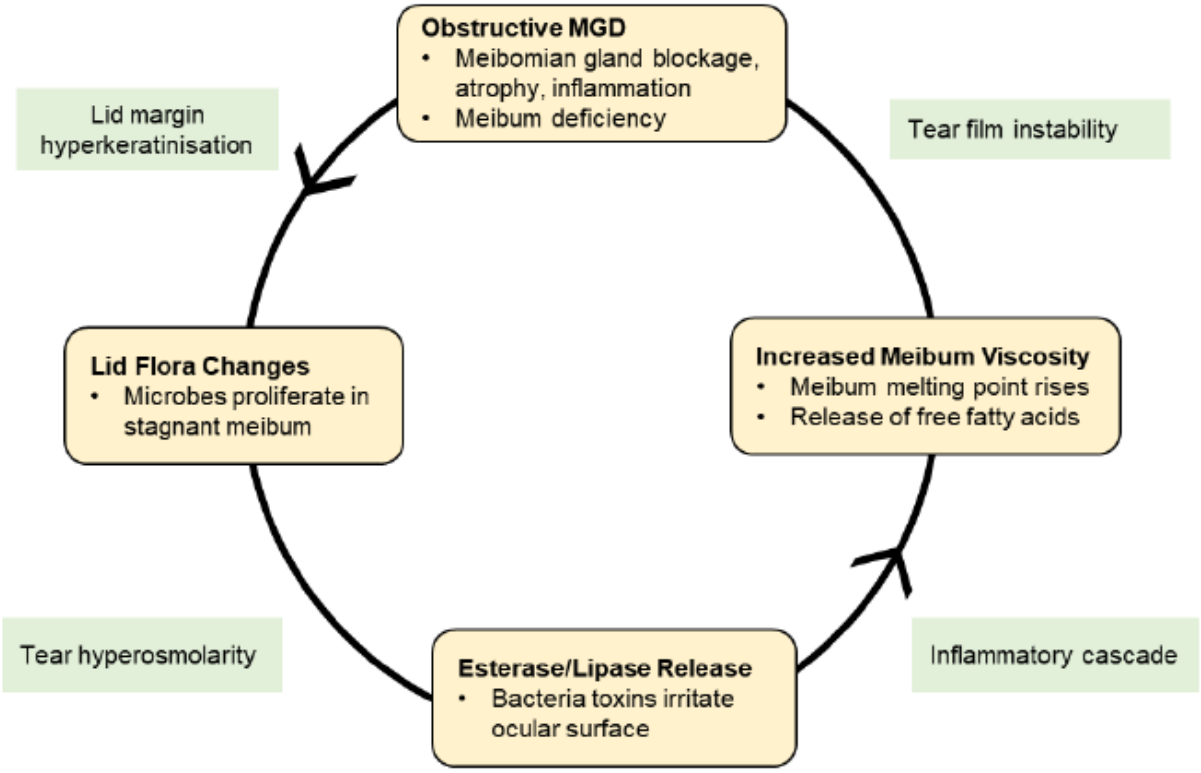

Figure 1 4 The entry points and chain events in the Circle of obstructive MGD. (Anthony J. Bron et al., 2017)

1.2.4.1 Hyperkeratinisation

Hyperkeratinisation of the terminal ductal epithelium is believed to be key to the beginning phases of MGD (Figure 1.5). Keratinized cells swamp into pipes and in combination with increased meibum consistency, advances obstruction of MG orifice. (E. Knop & Knop, 2009) (Jester, Parfitt, & Brown, 2015) The development of continuous secretory pressing factor, accumulation of meibum and cell garbage, in the end, brings about cystic dilation of the ductules. "Neglect" decay may follow, (Jester et al., 2015) leading to a deficiency of melanocytes, which is obvious as MG dropout during meibography imaging. (Pult & Riede-Pult, 2012) Overall, the result of MGD is diminished meibum secretion. The consequences of this may include diminished tear film

solidness, and enhanced bacterial burden on the lid margins because of the reduction in antimicrobial movement from decreased meibomian lipids. (Mudgil, 2014)

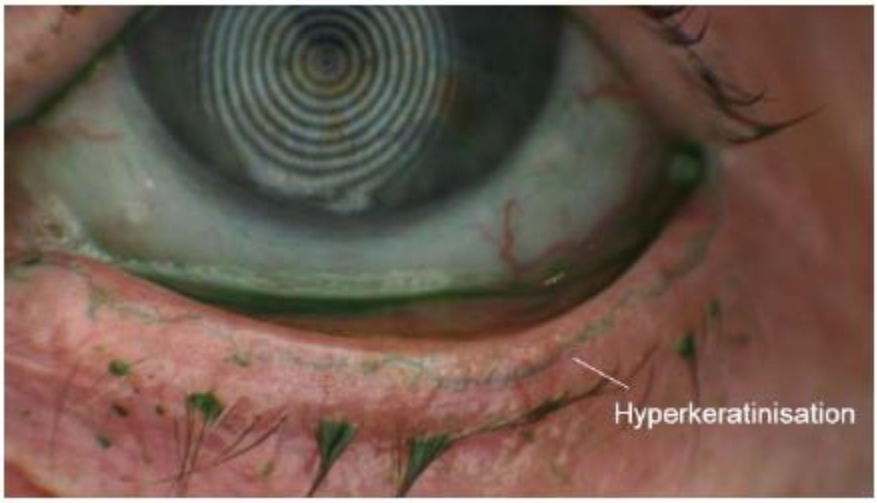

Figure 1 5 Hyperkeratinisation of the lower eyelid margin epithelium.

1.2.4.2 Acinar Atrophy

Following hyperkeratotic obstruction of the gland opening, the MG may go through degenerative atrophy. (Jester et al., 2015) (E. Knop & Knop, 2009) In addition, ensuing intraglandular pressure from the balance of continuously emitted meibum can likewise contribute to this interaction. Consistent with other organs of the body, reformist loss of MGs may likewise be influenced by aging. (E. Knop & Knop, 2009) The aging cycle adjusts the back lid margin morphology with unfavorable changes like increased vascularity, cutaneous hyper keratinization, and hole narrowing. (Jester et al., 2015) It additionally diminishes the quantity of dynamic MGs, lessens meibum expressibility, and causes noticeable gland tissue misfortune, noticed clinically as MG dropout, (Lemp et al., 2012) (Anthony J. Bron et al., 2017) in spite of the fact that proof to confirm whether gland dropout reflects the actual loss of MG tissue or basically a deficiency of gland contents that bring about it assuming the qualities of the surrounding tissues, is lacking. Given

atrophic occasions happen in other glands, decay in gland, the chance ought to be considered that there is an essential, age-subordinate type of MGD that prompts a slow loss of MG function. (Jester et al., 2015)

1.2.4.3 Inflammation

Inflammation, in the etiopathogenesis of MGD, might be intertwined of the eyelid margin, (Erich Knop et al., 2011) (Rhee & Mah, 2017) anyway specialists have to a great extent neglected to recognize an immediate link between meibum stagnation and inflammation. (Rhee & Mah, 2017) (Fu et al., 2019) Thus, it remains uncertain whether inflammation has a causative job or is just a sequela of strange MG function. (Erich Knop et al., 2011) This absence of lucidity in writing may likewise be credited to how inflammation is defined. In the event that interpreted in the traditional sense, clear inflammation is the presence of inflammatory cell infiltration, first demonstrated in MGD in histopathology investigations of tarsal plate tissues obtained at post-mortem. Leukocyte migration was missing in many instances of obstructive MGD, which raises uncertainty about whether these progressions address pathologic highlights of MGD. (Erich Knop et al., 2011) To date, there is no proof to confirm inflammation within the glands themselves in MGD. (Anthony J. Bron et al., 2017) (Craig, Nelson, et al., 2017) From the current atomic science point of view, quantifiable stress responses from the deficiency of homeostasis at the ocular surface because of MGD would demonstrate a "favorable to inflammatory state", (Rhee & Mah, 2017) (Anthony J. Bron et al., 2017) which presents clinically as indications of ocular irritation. (Pflugfelder & de Paiva, 2017) on the side of inflammation representing a downstream impact of MGD, it is proposed that increased intraglandular pressure causes cell stress within ductal and acinar epithelia, which triggers the action of cell proteins in the MGs with consequent arrival of inflammatory middle

people, and at last the foundation of nearby inflammation.(Rhee & Mah, 2017) (Pflugfelder & de Paiva, 2017)

1.2.4.4 Role of Bacteria

Inflammation can likewise be grouped according to the presence or otherwise of an underlying infectious state. Rather than immediate and dynamic bacterial infection being implicated, it is accepted that overpopulation of commensal microorganisms on the eyelid margins and within the glands, is all the more pathogenically relevant. Gram-positive organic entities (Staphylococci, Corynebacterium, Streptococcus, and Propionibacterium species) are common commensals of the mucosal tissues and eyelid margins of healthy individuals, and more uncommon gram-negative (Haemophiles, Neisseria, and Pseudomonas species) and contagious confines have likewise been refined from the ocular surface, anyway in low numbers these are related with minimal to no indications of inflammation or infection. Compared to typical subjects, a few bacteriological investigations have noticed increased microbial burden on the eyelids of MGD patients.(Ciloglu et al., 2020) (Rhee & Mah, 2017). The pathogenic job of microorganisms is accepted to emerge from discharged esterases and lipases, causing the breakdown of typical meibum complex lipids into conceivably inflammatory-free unsaturated fat sections and glycerides.(Anthony J. Bron et al., 2017) These atoms disturb the ocular surface, which in turn advances inflammation and hyper-keratinization, subsequently completing oneself perpetuating Vicious Circle of MGD (Figure 1.4). (Jester et al., 2015) (Anthony J. Bron et al., 2017) Enzymatic action additionally changes the meibum lipid profile by raising the degree of esterified cholesterol and increasing its melting point, making the secretion harder to communicate from the glands. Shine et al. demonstrated in vitro that cholesterol can invigorate S. aureus development, which recommends that the hydrolysis of cholesteryl esters in vivo might be a factor in propagating Staphylococcus colonization at times of

chronic blepharitis. Ultimately, the balance of meibum within the MGs takes care of back to further advance the propagation of commensal bacteria. (E. Knop & Knop, 2009) (Pflugfelder & de Paiva, 2017)

1.2.4.5 Role of Demodex

Demodex bugs that appeared in Figure 1.6 are tiny ectoparasites considered a piece of the ordinary skin fauna. They commonly live within s (*Demodex folliculorum*) within the MGs (*Demodex brevis*). The presence of Demodex is perceived to worsen foremost blepharitis and MGD and is often incriminated in the etiology of blepharitis that is hard-headed to conventional treatment. High densities of Demodex have been demonstrated to connect emphatically with the seriousness of ocular signs and side effects of DED, just as increasing age.(M. T. M. Wang et al., 2020) (Murphy et al., 2020) The specific components of Demodex pathogenicity are yet to be completely explained, however, proposed pathways include direct harm to the tissue by truly blocking the MG opening, just as their consumption of epithelial cells and miniature abrasions brought about by the vermin's paws, which are accepted to contribute to epithelial hyperplasia and receptive hyper keratinization. Demodex may likewise be a vector for microbes with their antigens, which can trigger a course of host inflammatory responses. In conclusion, the chitinous exoskeleton of Demodex, and their garbage or breakdown items may get the host's inflammatory reactions by means of a postponed touchiness reaction.(Murphy et al., 2020) (Anthony J. Bron et al., 2017)

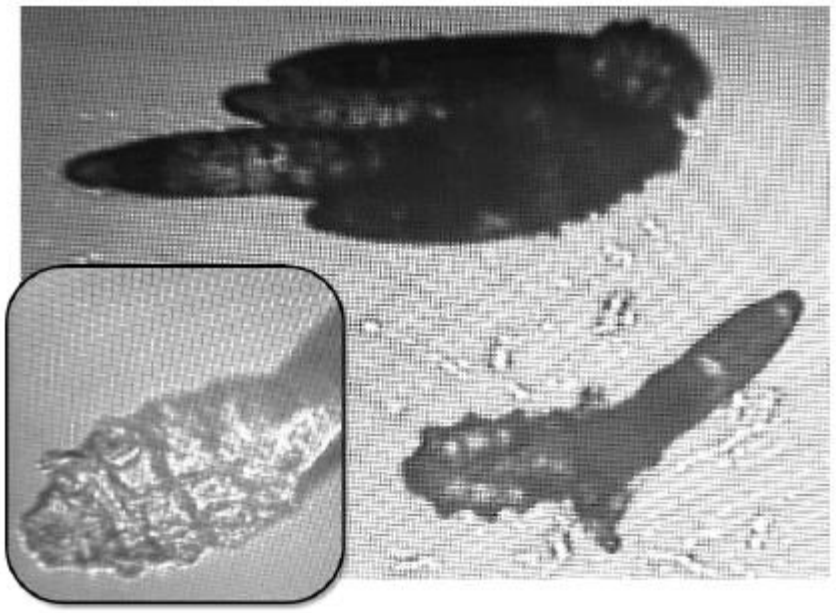

Figure 1 6 Microscope view of multiple and single Demodex folliculorum.

1.2.4.6 Meibum Composition

Different insightful strategies have demonstrated that blepharitis and MGD can adjust ordinary meibum lipid composition, disturbing the proportion, altering the levels, and inducing conformational changes of polar and non-polar lipids. (Olżyńska et al., 2020) At a sub-atomic level, this influences the interaction between lipid-lipid and lipid-protein, which in the long run prompts bargained tear film composition and function that bring about EDE. Changes to meibum lipid types varied depending on the subtype of lid disease. Compared to typical controls, the overall measures of cholesterol esters in meibum by and large diminished with MGD. (Raposo et al., 2018) (Tsubota et al., 2017) Furthermore, patients suffering from hypersecretory MGD seem to hold more coagulase negative Staphylococcus microorganisms contrasted with healthy individuals. These are equipped for hydrolyzing cholesteryl oleate to increase the general measures of oleic corrosive in the meibum, which clinically reported by burdened patients. For obstructive MGD (the most common type of MG infection), portrayed changes to the meibum lipid composition

have included lessening in fatty substances and cholesterol levels, yet a higher concentration of wax esters (WE), short-chain Wes, and monounsaturated greasy acids.(Rhee & Mah, 2017) (B. Li et al., 2020) Together, these alterations contribute to raising the meibum melting point, promoting inspissation within the focal duct. Modifications to meibum lipid profile may likewise vary according to illness severity. Compared to gentle DED cases, Moderate DED showed lower levels of fatty substances, more significant levels of cholesterol esters (C18:0, 20:0, and 21:0), and a decreasing relative proportion of a few O-acyl-ω-hydroxy unsaturated fat classes was seen as infection seriousness worsened. (Teo et al., 2020) (Magno et al., 2021) Given the MG is an androgen target organ, androgen inadequacy has likewise been appeared to adjust the general proportion of polar and nonpolar lipids present in MG secretion. (Olżyńska et al., 2020) Overall, lipidomic research recommends it could be conceivable to utilize lipid species recognized in meibum and tear liquid as expected biomarkers of DED. (Yoshida et al., 2019) (Maki et al., 2020)

1.2.5 Clinical Characteristics of MGD

A few key qualities are considered significant in the clinical conclusion of MGD.

1.2.5.1 Eyelid Morphology

Morphological changes, for example, plugging or pouting of the holes are common clinical indications of MGD, secondary to accumulation of meibum and gland obstruction. As expressed before, "neglect" decay of the glandular acini secondary to dilation of the conduits can be seen as gland drop out by transillumination, however is all the more promptly obvious through infrared meibography imaging strategy. Alterations to the morphology of the eyelid margin might be linked with increasing age and long-term contact focal point wear. (Alghamdi, Markoulli, Holden, & Papas, 2016) However, research likewise indicates that foremost or back translocation of the

mucocutaneous junction, where the mucous film of the palpebral conjunctiva and keratinized skin meet (otherwise called Marx's line), is related with more noteworthy loss of MG function. (Jester et al., 2015) Other lid margin highlights normal for MGD include dimpling, notching, surface telangiectasia, and formation of cystic concretions within the acini. (Erich Knop et al., 2011)

1.2.5.2 Meibomian Gland Expression and Quality

The ordinary meibum occupant in the MG conduits is a reasonable oil, which can be communicated by applying light computerized strain to the tarsal plates. In MGD, the meibum gets shady, gooey, and increasingly hard to express. (Butovich, 2017) Consequent low secretion and helpless conveyance of produce a deficient tear film (TFLL), a trademark indication of EDE. (Anthony J. Bron et al., 2017) (Pflugfelder & de Paiva, 2017) In research, a standardized instrument to guarantee the application of a consistent pressing factor is utilized to review meibum expressibility and quality. (Magno et al., 2021)

1.2.5.3 Tear Film Lipid Layer

The TFLL spreads over the mucoaqueous period of the tear film and plays out a significant job in reducing water fume misfortune from the ocular surface. Obstructive MGD, related with decreased TFLL thickness, is perceived as the most common reason for EDE. (Tsubota et al., 2020a) (Craig, Nichols, et al., 2017) (Erich Knop et al., 2011) MGD treatments pointed toward improving meibum outpouring into the tear film have been appeared to increase the and general security. The thickness of the TFLL can be assessed using the principle of thin-film interferometry, whereby the predominant shading fringe design saw under white light is illustrative of the thickness of the layer. (Georgiev et al., 2019) The mucoaqueous stage and TFLL are considered to ward elements in DED with critical cover in the pathophysiology of EDE and ADDE noted with advancing disease.

(Craig, Nichols, et al., 2017) (Tsubota et al., 2020b) Mucoaqueous layer seems to assume a correlative part in providing a satisfactory base upon which the meibum can spread to shape the defensive TFLL. (Olżyńska et al., 2020) (Georgiev et al., 2019)

1.2.5.4 Ocular Surface Quality

Ocular surface epitheliopathy might be experienced secondary to MGD. Etiological components that have been presented in writing include evaporative water misfortune resulting in a deficiency of lubrication that causes frictional harm that in transform advances the arrival of inflammatory arbiters into the hyperosmolar tear film Exacerbating the situation are proinflammatory side-effects of lipid hydrolysis that emerge through the enzymatic action of microbial commensals. (A. J. Bron, Argüeso, Irkec, & Bright, 2015) (Chhadva et al., 2017) In clinical settings, ocular surface harm might be evaluated and conjunctiva, including the marginal conjunctiva, (Wolffsohn et al., 2017) using ocular colors like sodium fluorescein (NaFl, Figure 1.7). For research purposes, direct estimation of inflammatory go-betweens in the tear liquid can be made with biochemical procedures, for example, multiplex immunobead assay. (Raposo et al., 2018) Alternatively, the inflammatory status of ocular surface cells might be surveyed from tests gathered by impression cytology, using stream cytometry, or through quantitative polymerase chain reaction method (qPCR). (Inaba et al., 2018)

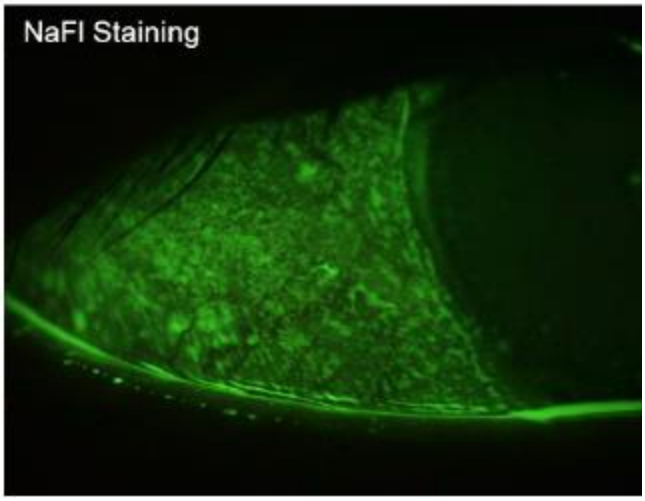

Figure 1 7 Ocular surface staining on the temporal conjunctiva with sodium fluorescein highlighted with blue excitation filter and yellow barrier filter.

1.2.5.6 Meibography

Loss of acinar tissue resulting in MG dropout can be identified by meibography, which is an imaging method created numerous many years prior to notice the gland morphology in vivo. While different strategies and advancements exist, non-contact infrared meibography is considered the current gold standard. (Erich Knop et al., 2011) This strategy records a picture (Figure 1.8) of the everted upper and lower eyelids illuminated with an infrared source, using an infrared channel and charge-coupled camera. Patients with obstructive MGD ordinarily show highlights, for example, gland shortening, distortion, dilation, and convolution on meibography. Like LWE, scientists have created scoring frameworks to standardize the documentation of MG drop out. (Pult & Riede-Pult, 2012) (Hwang et al., 2020) Overall, meibography is a fast, agreeable test for the patient, hence becoming increasingly well known in ophthalmic practices that focus on diagnosing and managing ocular surface sickness.

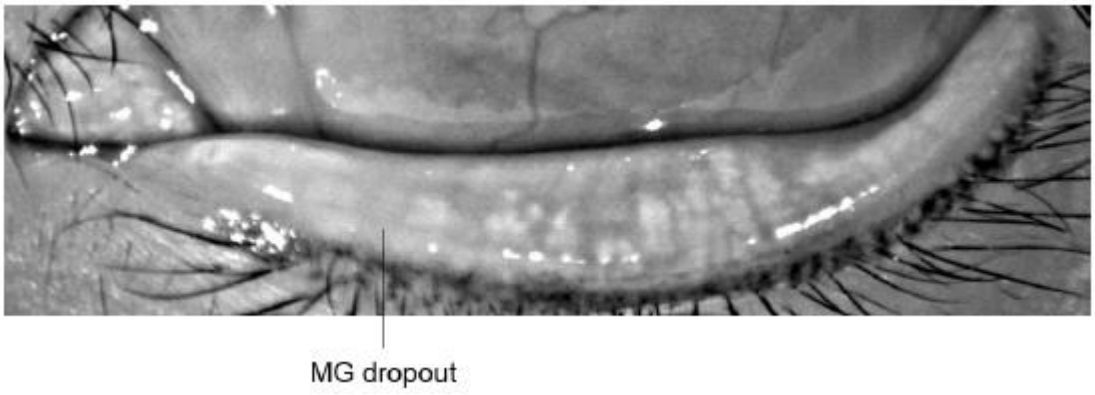

Figure 1 8 Non-contact meibography of lower eyelid showing meibomian gland dropout captured on the Oculus Keratograph 5M.

1.2.6 Current MGD Management

Notwithstanding expected contributions from helper factors, for example, lid margin vegetation, tear hyperosmolarity, and ocular surface inflammation, hyper keratinization of the terminal pipes assumes a significant part in obstructive MGD. (Jones et al., 2017) It follows, then, that the accomplishment of any obstructive MGD treatment will be dependent on optimizing hole patency, and secondarily upon the administration of coexisting sequelae. (Ngo, Srinivasan, & Jones, 2019) Summarized beneath are a few current treatment options.

1.2.6.1 Lid Hygiene, Warm Compresses and Massage

The mainstay treatments for MGD have traditionally been: 1) mechanical expulsion of microbes and/or flotsam and jetsam from eyelid margins with weakened child cleanser or business lid cleansers) heat application (commonly accomplished by warm packs) pointed toward improving meibum expressibility by melting the thickened meibum within gland ductules and solidified attachments at gland orifice) advanced back rub to precisely communicate the softened meibum from orifices. The result of these three stages, whenever performed effectively and tenaciously, is

to oust unusual secretions from discouraged glands in request to encourage typical MG function. (Takahashi et al., 2013) (Butovich, 2017) However, it remains obscure whether this essential conventional treatment for MGD animates atomic pathways that support ordinary MG function. In-office therapeutic expression of the MGs may give better prognostic results in unmanageable MGD cases; this method involves powerfully squeezing the eyelid against an inflexible surface (for example Mastrota paddle) inserted between the inner lid surface and the eyeball. (Butovich, 2017) Patients are prescribed to then enhancement this with self-expression at home, yet rehashed instruction to the patient on appropriately and routinely applying lid hygiene and warm pack therapies, is necessary, otherwise the suggested self-administration strategies might be seen as ineffective, and result in decreased treatment consistence. Another obstacle for this home therapy is that hot washcloths that were prescribed in the past will in general lose heat rapidly. Therefore industry has created contemporary options for MGD patients, for example, microwaveable wheat bags and inert warmth devices that give better thermal energy retention and conveyance. Where huge eyelid margin keratinization of the mucosal tissue is distinguished, debridement of the phone trash is often proposed as a subordinate treatment to help unblock the stopped hole, in this way enhancing the viability of resulting warming therapy. (Ngo et al., 2019) (Borchman, 2019) During debridement, skin anesthesia is applied to numb the ocular surface for patient solace, and to soften the keratinized lid margin tissue, then cell flotsam and jetsam is painstakingly taken out with a golf club spud. According to eye care suppliers, there is considerable cover in patients presenting with front blepharitis and MGD. Hence another commonly noticed co-grimness is Demodex infestation, particularly in the older population, (Murphy et al., 2020) and cylindrical collarettes around the base of the lashes are considered exceptionally reminiscent of ocular demodicosis. (Basnet et al., 2018) Current examination reports lid hygiene treatment with a tea tree oil-based cleaning agent,

enhanced by a week-by-week half tea tree oil lid scour in-office with an eye care professional for one month, as a successful eradication method. (Thulasi & Djalilian, 2017) (Jones et al., 2017)

1.2.6.2 Artificial Lubricants

Artificial lubricants are a further mainstay treatment of ocular surface illness. Whether brought about or diminished, DED raises the tear osmolarity, a focal component of dry eye pathophysiology. Instilling artificial oils weakens the hyperosmolar tear liquid and can diminish during blinking. It can likewise improve tear layer spreading to frame a more intact defensive barrier. (Xue et al., 2017) Furthermore, the successful utilization of artificial oils flushes the ocular surface of toxins and weakens proinflammatory stimuli. Factors to consider in the selection of artificial greases include additive harmfulness, formulation thickness, and lipid content. DED that requires more incessant drop installation may profit from additive-free and grease formulations with longer retention times on the ocular surface, and patients with lipid insufficiency, as seen in MGD, may get additional profit by lipid-containing eye drops or liposomal sprays. (Liu et al., 2020) (Yokoi & Georgiev, 2019)

1.2.6.3 Topical Therapies

Antibiotics

Inflammatory sequelae from the production of inflammatory go-betweens are accepted to contribute to the pathogenesis of MGD therefore effective anti-microbial therapy can be utilized in MGD with concurrent front blepharitis to decrease the bacterial burden on the ocular adnexa and minimize the antagonistic impacts of bacterial exotoxins. (Jones et al., 2017) (Liu et al., 2020) As recently depicted, the most common commensal microorganisms of the eyelid are

Staphylococcal species, therefore, an anti-microbial powerful against Gram-positive microscopic organisms, for example, fusidic corrosive is regularly prescribed. (Ciloglu et al., 2020)

Corticosteroids

Topical corticosteroids with restricted corneal penetration, for example, fluorometholone, are an intense therapy option and might be indicated for transient administration of inflammation related with extreme MGD. Corticosteroids hose the safe response by binding to glucocorticoid receptors, which eventually inhibits T-cell interceded invulnerability and quality transcription of cytokines, for example, interleukin-6. (Jones et al., 2017) (Inaba et al., 2018) The chronic idea of dry eye related with MGD doesn't fit long term utilization of corticosteroids because of the dangers of genuine results like waterfall formation and intraocular pressure elevation. (Yokoi & Georgiev, 2018)

1.2.6.4 Systemic Therapies

Tetracyclines

Tetracyclines (like doxycycline and minocycline) are bacteriostatic anti-infection agents utilized in the administration of MGD for their calming more than their antimicrobial properties. Doxycycline recommended at a low portion (around 50 mg/day for 6-12 weeks) smothers bacterial lipase production, reducing the arrival of pro-inflammatory free unsaturated fats and diglycerides at the ocular surface. Tetracyclines are by and large very much tolerated, however, their utilization is contraindicated in pregnancy, nursing mothers, infancy and adolescence (<12 years) because of the danger of tooth discoloration. Foundational azithromycin for MGD therapy has likewise been demonstrated to be advantageous in managing MGD and can demonstrate helpful especially in situations where doxycycline can't be prescribed. (Xue et al., 2017) While the ideal system remains under banter, Kashkouli et al. showed better viability and clinical response relative than

fundamental doxycycline in MGD patients following an (500 mg on day 1 and then 250 mg/day). (Geerling et al., 2017) Azithromycin tweaks the expression of proinflammatory cytokines and has more noteworthy power against Gram-negative miniature life forms than the other individuals from the macrolide family. (Thulasi & Djalilian, 2017) (Ciloglu et al., 2020)

Essential Fatty Acids

Omega-6 fundamental unsaturated fats (EFAs) and omega-3 EFAs can't be synthesized by the body and therefore should be ingested through food. EFAs are the forerunners of locally acting hormones known as eicosanoids, which control numerous parts of the inflammatory process. Omega-6 EFAs give rise essentially to proinflammatory eicosanoids, while omega-3 EFAs lead predominantly to calming eicosanoids. (Fukuoka et al., 2021) Both EFAs go after similar compounds (delta 5 and delta 6 desaturases) during this interaction of conversion. The inflammatory physiologic condition of the body relies upon the equilibrium of these circulating biomolecules and this equilibrium can be adjusted by the general intake of EFAs. Dietary examples in the created world often lead to overconsumption of omega-6 EFAs which advances inflammation. Increasing foundational omega-3 EFA levels through dietary intervention can possibly improve DED status by inhibiting the production of omega-6 inferred favorable to inflammatory middle people and enhancing production mitigating mediators. (Inaba et al., 2018) Several clinical and epidemiological examinations portray upgrades in tear film lipid layer quality with omega-3 dietary intervention. However late explorations has questioned whether clinical advantage exists over placebo. (Butovich, 2017) Of note, all wellsprings of omega-3 EFAs are not naturally the same, to such an extent that creature oils are more powerful in their breakdown and conveyance than plant sources. Even within marine sources, contrasts in bioavailability exist,

with krill oil proposed to confer additional advantages over fish oil supplementation in the treatment of DED. (Yoshida et al., 2019)

1.2.6.5 Heat Application Technology

Thermal Pulsation

The reported melting point for discouraged MGD secretions goes from 32 to 45°C. Traditional warm pack and advanced back rub treatment are restricted in its viability because of the distance of the glands from the front lid surface and likely dissipation of warmth prior to reaching the glands, to such an extent that it can only accomplish a most extreme temperature of around 40°C when the pack is warmed to 45°C. (Borchman, 2019)To beat this constraint, a thermal pulsation gadget was created with heating components contained within haptics inserted underneath the patient's upper and lower eyelids that permit direct warmth application to the palpebral surfaces while protecting the cornea from thermal damage. (B. Li et al., 2020) As the MGs are warmed from the back part of the eyelid, air bladders on the foremost lid surface throb to communicate the warmed secretions from the glands. Enhancements inpatient manifestations and MG functionality have been confirmed as long as 12 months after a single treatment. (Tauber, Owen, Bloomenstein, Hovanesian, & Bullimore, 2020)

Latent Moist Heat Therapy

Blephasteam and Eye care eye massager can be utilized to convey warmth to the eyelids in a repeatable way, without direct contact with the eyelids. The gadget permits the client utilization of their vision during treatment to do typical assignment exercises like reading and watching television. (Valencia-Nieto, Novo-Diez, Blanco-Vázquez, & López-Miguel, 2020) Studies have shown that ordinary use improves dry eye symptomology and signs and seems to give more viable warming than traditional pack therapy in a gathering of healthy volunteers. However, a later report

showed tantamount advantage, following single application, of Blephasteam, warm packs, and liposomal splash in MGD. (Jones et al., 2017) (Ngo et al., 2019)

Intense Pulsed Light

Intense beat light (IPL) therapy utilizes an expansive range, a non-lucid, polychromatic light source with a frequency range ranging somewhere in the range of 500 and 1200 nm, to treat MGD. (Wei, Ren, Wang, Chou, & Li, 2020) Demonstration of therapeutic adequacy in managing dry eye because of MGD from various clinical trials has arisen only within the most recent five years, yet contrasts in the member qualities, study plan, therapy conventions, gadget boundaries and result estimations among clinical trials have hindered direct comparison of results between the studies. (Vigo, Giannaccare, Sebastiani, Pellegrini, & Carones, 2019) Many of the reported results have emerged reflectively from patients treated in a clinical setting. Furthermore, forthcoming investigations have to a great extent been performed exposed, without fake treatment control, and often in combination with therapeutic MG expression, which is a confounding element in interpreting the aftereffects of IPL treatment viability. (Xue, Wang, Ormonde, & Craig, 2020)

1.2.7 Aims and Hypothesis.

The Aims and hypotheses related to this thesis are as per the following:

1.2.7.1 Aims

1) To assess the analytic and therapeutic DED practices of eye care professionals in relation to current proof-based guidelines.
2) To survey the therapeutic viability of Device in reducing the signs and indications of MGD in a planned, randomized, fake treatment controlled, non-matched eye preliminary.

3) To investigate the potential physiological mechanism(s) by which this device may contribute to the executives of MGD.

1.2.7.2 Hypothesis

1) To improve the translation of DED research proof into the act of PK eye care professionals.
2) Thermal Pulsation therapy has potential in MGD, by improving tear film quality and reducing DED indications.

CHAPTER 2. CLINICAL MATERIALS AND METHODS

2.1 Background

Extreme evaporation is a component in 80% of indicative dry eye sickness (DED), (Nelson et al., 2017) and meibomian gland dysfunction (MGD) has been reported to be the leading cause. Uninhibited progression of the slick meibum, created by the (MGs) onto the ocular surface is fundamental in supporting tear liquid retention and stability. (Anthony J. Bron et al., 2017) When this cycle is undermined, evaporative dry eye (EDE) can follow. (Jones et al., 2017) In that capacity, the justifications for undertaking this current Device's clinical preliminary were recently outlined. Section 1 summed up the current writing on EDE, the information hole in Eye Massager's mechanism(s) of action for MGD alleviation, including the scarcity of excellent logical proof that unequivocally demonstrates the viability of this Device as a successful standalone therapy.

2.3 Proposed Mechanisms of Action

Proposed mechanisms of action that may contribute to improving tear film quality and reducing DED indications include:

- Eye Massager, through the conveyance of thermal energy, condenses congealed lipids, promoting stream from the glands and supplementing the tear film lipid layer.
- Delivery of thermal energy to the lower eyelid region inhibits the arrival of inflammatory middle people in the vicinity of MGs correlating with improved ocular solace.
- Delivery of thermal energy in trained heartbeats to the lower eyelid region increases neuropeptide discharge, which impacts an improvement in gland function through neural stimulation.

2.4 Components of Eye Massager

The freshest intelligent eye massager, with complete function and exquisite appearance, the remote electric eye massager can assist you with relieving EDE manifestations. Furnished with a clear

LCD show, it's not difficult to switch various modes with one tick button circle. Programmed 15 minutes timing is set to save force and protection of eyes. It has a convenient Bluetooth Connection. The Bluetooth connection empowers to make the most of #1 music while massaging in the wake of connecting the eye massager with advanced cell. It is compact and battery powered. The eye massager is 180° foldable, making it little to place in your pack and convey in movement. The lash is movable to fit various appearances. Implicit 1200mAh battery-powered battery, it is not difficult to accuse of our including USB charging link.

- Massage Principle: Hot Compresses (40-degree centigrade)
- Material: ABS + PU
- Battery: 1200mAh battery-powered lithium battery
- Rated voltage: DC 5V.
- Power:3.4W
- Power adapter: AC100-240V
- Bluetooth: yes
- Mode:5

Figure 2 1 Eye Care eye massager

2.5 Participants

An aggregate of 30 subjects was enlisted from the Eye OPD of District Headquarter Hospital, Bahawalnagar. All members were matured somewhere in the range of 18 and 60 years at the hour of enrolment. No unfriendly occasions happened. Tear film soundness was picked as a worldwide index of tear film quality in diagnosing dry eye illness, its association with comfort, (Yokoi & Georgiev, 2018) and as a key result measure dependent on reports in the writing of its positive association with an increased lipid layer thickness (LLT) and decreased aqueous evaporation. (Booranapong et al., 2020)

2.5.1 Inclusion Criteria

- Males and females
- Age above and equal18 years
- Normal lid, and closure
- Clinically critical indications of MGD and manifestations of EDE (scored >12 on Ocular Surface Disease Index and/or <11 SPEED questionnaire)

2.5.2 Exclusion Criteria

- Wearers of contact lens unwilling to do away with lenses at any price multi-week previous to the initiation of, and in the course of the research.
- Ocular scientific process (like refractive or waterfall clinical manner) in either eye within three months of the screening go to.
- A foundational circumstance or infection taken into consideration unsteady or decided by using the exam (as an instance ebb and go with the flow essential contamination, uncontrolled immune machine illness, uncontrolled immunodeficiency sickness, records of myocardial infarction and so forth).
- The set of experience, turmoil, or utilization of medications that may interfere with the investigation results, or are contraindicated for Hot Compresses treatment (for example doxycycline, or other photosensitive medications).
- The set of reports or presence of any skin situation, turmoil, or usage of medicines that may interfere with the investigation effects, or are contraindicated for warm compresses treatment (for instance doxycycline, or other photosensitive medications).
- Dynamic or uncontrolled severe essential sensitivity, persistent seasonal hypersensitivities, rhinitis requiring remedy (for instance antihistamines, decongestants, oral or vaporized steroids) at the hour of screening.
- Utilization of drugs regarded to cause ocular drying (for instance cyclosporine, antihistamines, beta-blockading specialists, diuretics, steroids, and so on) within 30 days of the screening visit.
- Punctal connects situ.

- Participation in initial with every other dynamic substance or another device all through the preceding 30 days or earlier warm compresses remedy for MGD at any time.
- Females who self-report to be pregnant, planning a pregnancy, or nursing at observing phase.

2.5.3 Ethical Considerations

The trail was completed in understanding the moral principles that have their origin in the Declaration of Helsinki, ISO 14155:2011, (GCP), and (ICH) guidelines. Only the systems portrayed in the convention and affirmed by Ethics Committee were performed. All recorded information and study observations were entered on the suitable case report structures (CRFs).

2.6 Research Methodology

2.6.1 Clinical Study Design

This was a prospective and randomized clinical trial. Highlights of the tear film were portrayed by the essential investigator using the following standard clinical strategies:

- Grading of DED manifestations using Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness (SPEED)
- Examination of the foremost eye with biomicroscope
- Evaluation of the tear film (solidness), and bulbar hyperemia.
- Schirmer's test

2.6.2 Device Application

Participants went for their first visit (Day 1) of roughly 1.5 hours, at the Eye OPD situated in the District Headquarters, Bahawalnagar. Clinical appraisals were performed successively, from least to generally invasive in the request. Follow-up surveys to evaluate most of the result measures

were performed by the essential investigator toward the finish of 3 days, 4 days, and 5 days. Full ocular health status was surveyed on examination passage and reconfirmed at the leave test.

2.6.3 Clinical Visits

Participants attended for their first visit (Day 1) of approximately 1.5 hours, at the Eye OPD located in the District Headquarters, Bahawalnagar. Clinical assessments were performed sequentially, invasive in order. Follow-up reviews to assess the majority of outcome measures were performed by the primary investigator at the end of 3 days, 4 days and 5 days. Full ocular health status was assessed on study entry and reconfirmed at the exit exam.

2.6.4 Clinical Techniques

2.6.4.1 Dry Eye Symptoms

Patient history is commonly utilized by eye care professionals to analyze and grade the seriousness of DED. (Uchino & Schaumberg, 2013) In request to standardize the interaction, TFOS DEWS, and DEWS II suggest the administration of validated side effect questionnaire(s). (Jones et al., 2017) This guarantees consistent characterization and permits monitoring of infection progression, just as a response to therapy. At present accessible self-administered DEQs assess components of visual aggravation or ocular distress related to dry eye and their effect on the nature of life. (OSDI), and the (SPEED) (Asiedu et al., 2016) questionnaires were administered to score DED indications at baseline. The OSDI (favored result measure), and SPEED DEQs were chosen as the questionnaires to be administered all through the investigation to think about patient indications longitudinally among treatment and fake treatment bunches toward the beginning of each clinical visit, based on their application and validation, as portrayed in the literature.

Standard Patient Evaluation of Eye Dryness: SPEED (Appendix A) is validated, and repeatable questionnaire created to evaluate and monitor the recurrence and seriousness of patient symptoms. The eight things of the questionnaire use a four-point Likert scale, and the outline of the scores (alluded to as the SPEED score) can go from 0 to 28. Strengthening questions in the SPEED study gather information on member's present history of artificial ointment use, just as their diurnal and long-term indication changes throughout the past three months. In this examination, DED was defined as indicative if the SPEED score was ≥11. (Asiedu et al., 2016)

Ocular Surface Disease Index: OSDI (Appendix B) is broadly utilized questionnaires for assessing and monitoring DED status in clinical and epidemiological research. The OSDI is made from 12 questions that measure recurrence of visual aggravation (obscured or helpless vision), visual related personal satisfaction (issues reading, driving around evening time), and environmental triggers that may worsen DED manifestations. The questionnaire utilizes a five-point Likert scale, and the determined scores can go from 0 (no incapacity) to 100 (complete inability). Mill operator et al. defined scores in the scope of 13-22 as gentle DED, as moderate DED, and 33-100 as extreme DED. For the motivations behind this investigation, members who scored over 12 on OSDI were considered qualified to take part. (Dougherty, Nichols, & Nichols, 2011) (Asiedu et al., 2016)

2.6.4.2 Slit Lamp Biomicroscopy

Traditional indications of blepharitis including lid margin edema and erythema, just as lash trash, were distinguished and reviewed by slit light biomicroscopy. The following ocular designs were assessed for pathology: eyelids, meibomian glands, conjunctiva, cornea, anterior chamber, and lens. On the off chance that the test uncovered issues recorded in the exclusion rules (for example corneal dystrophies or scarring), the evaluation was not continued further now. An ocular health check, which involved measuring intraocular pressures (IOP) and an expanded fundal test, was

performed following exploration information had been gathered as a security measure, to confirm no alteration happened because of study participation, toward the beginning and at the conclusion of the investigation.

2.6.4.3 Tear Breakup Time

Placed 1 to 2 micro-l (maintain consistency for every trial) of additive-unfastened 1% fluorescein approach to using a micropipette or the favored strategy. The affected person must initially blink in some instances. Then train the affected person the maintain their eyes open. Degree the c programming language among the remaining general blink and the predominant look of any aggravation, repeating it 3 instances, and take the ordinary of the measurements. (Tsubota, 2018)

2.6.4.4 Schirmer's Test

Schirmer's take a look at with (basal discharge/sch-2) turned into accomplished after the installation of effective 4% xylocaine. The cloth utilized was industrially handy Whatman no. 41 channel paper strips estimating 35 × five mm known as Schirmer's tear test channel strips and is collapsed 5mm from one cease. The patient was made to take a seat in a faintly lit room; collapsed at the rating was set tenderly over the decrease conjunctiva on the intersection of horizontal 1.3 and average 2.3. The patient turned into taught to hold his eyes open and gaze directly ahead moreover, flicker generally. After 5 min, the strips were taken out furthermore, the degree in millimeters changed into recorded. The Schirmer's-2 take a look at becoming viewed as unusual if the length of the wetting was <6 mm toward the finish of 5 min. (kumari, 2017)

2.6.4.5 Quality of expressed meibum

The nature of meibum was evaluated as grade 0, clear liquid; grade 1, marginally turbid; grade 2, thick hazy; grade 3, toothpaste-like; grade 4, complete opening blockage. (Butovich, 2017)

CHAPTER 3: RESULTS AND CONCLUSION

3.1 Results

A total of 60 eyes of 30 participants (22 women and 8 men) were enrolled in this study. There were two groups controlled and treatment groups in this study each of them consisting of 15 participants. The mean age for the control group was (32.67± 11) years and (31.33 ± 8) years for the treatment group. The mean Tear Break Up time for the control group was 7s±0, 8s±0.71 and 8.4s±0.49 at baseline visit and 9.5s±0.5, 11.12s±0.78, and 12.4s±0.49 after follow-up of 3 days, 4 days, and 5 days, respectively. The mean Schirmer's test results for the control group were 8mm±0, 9.87mm±1.35 and 8.8mm±1.67 at baseline visit and 10.5mm±0.5, 13mm±0.87, and 11.8mm±1.67 after follow-up of 3 days, 4 days, and 5 days, respectively. The mean OSDI score for the control group was 41.5±4, 35.24±6.53 and 36.3±7.47 at baseline visit and 34.4±3.1, 25.12±7.11, and 25.76±4.58 after follow-up of 3 days, 4 days, and 5 days, respectively. The mean SPEED score for the control group was 20±0, 17.5±2.6, and 19.8±0.75 at baseline visit and 14.5±0.5, 11.75±3.15, and 11±0.9 after follow-up of 3 days, 4 days, and 5 days, respectively. (Table no. 3.1) Similarly, the mean Tear Break Up time for the treatment group was 7.2s±0.44, 7.8s±0.75 and 8.5s±0.96 at baseline visit and 13.75s±0.9, 15s±1.48, and 16.17s±1.86 after follow-up of 3 days, 4 days, and 5 days, respectively. The mean Schirmer's test results for the treatment group were 9.25mm±1.09, 8mm±0.63 and 10.8mm±2.29 at baseline visit and 13.75mm±0.83, 13.6mm±1.02, and 14.33mm±0.75 after follow-up of 3 days, 4 days, and 5 days, respectively. The mean OSDI score for the treatment group was 33.52±5.11, 33.24±5.38 and 30.82±5.34 at baseline visit and 17.12±4.67, 17.26±4.36, and 12.53±1.75 after follow-up of 3 days, 4 days, and 5 days, respectively. The mean SPEED score for the treatment group was respectively 19.5±1.12,

17.6±2.25, and 17±2.08 at baseline visit and 7.75±0.83, 7.8±1.17, and 7±0.82 after follow-up of 3 days, 4 days, and 5 days. (Table no.3.2)

Table 3 1 Clinical measurements of the eyes of subjects in the control group at baseline, 3 days, 4 days, and 5 days post follow up. Data is presented as mean values.

Serial No.	**No. of patients**	**Follow-Up days**	**Tear Break Up Time (s)**		**Schirmer's Test (mm)**		**OSDI Score[*1]**		**SPEED Score[*2]**	
			Pre-follow up	Post-follow up	Pre-follow up	Post-follow up	Pre-follow up	Post-follow up	Pre-follow up	Post-follow up
1	2	3	7±0	9.5± 0.5	8± 0	10.5± 0.5	41.5± 4	34.4± 3.1	20± 0	14.5± 0.5
2	8	4	8± 0.71	11.12 ± 0.78	9.87± 1.35	13± 0.87	35.24 ±6.53	25.12 ± 7.11	17.5± 2.6	11.75 ± 3.15
3	5	5	8.4± 0.49	12.4± 0.49	8.8± 1.67	11.8± 1.67	36.3± 7.47	25.76 ± 4.58	19.8± 0.75	11± 0.9

OSDI Score[*1] = Ocular Surface Disease Index and SPEED Score[*2] = Standard Patient Evaluation of Eye Dryness

Table 3 2 Clinical measurements of the eyes of subjects in the treatment group at baseline, 3 days, 4 days, and 5 days post follow up. Data is presented as mean values.

Serial No.	**No. of patients**	**Follow-Up days**	**Tear Break Up Time (s)**		**Schirmer's Test (mm)**		**OSDI Score**		**SPEED Score**	
			Pre-follow up	Post-follow up	Pre-follow up	Post-follow up	Pre-follow up	Post-follow up	Pre-follow up	Post-follow up
1	4	3	7.25± 0.44	13.5± 0.9	9.25± 1.09	13.75 ± 0.83	33.52 ±5.11	17.12 ±4.67	19.5 ±1.12	7.75 ±0.83
2	5	4	7.8± 0.75	15± 1.48	8± 0.63	13.6± 1.02	33.24 ±5.38	17.26 ±4.36	17.6 ±2.25	7.8 ± 1.17
3	6	5	8.5± 0.96	16.17 ± 1.86	10.8± 2.29	14.33 ± 0.75	30.82 ±5.34	12.53 ±1.75	17 ± 2.08	7 ± 0.82

OSDI Score[*1] = Ocular Surface Disease Index and SPEED Score[*2] = Standard Patient Evaluation of Eye Dryness

The difference in the post-follow up results of Tear Break Up Time and Schirmer's Test in the control and treatment groups is clearly shown in a line graph. (Figure 3.1). Similarly, the difference

in the post-follow up results of OSDI Score and SPEED Score in the control and treatment groups is also clearly shown in a line graph. (Figure 3.2)

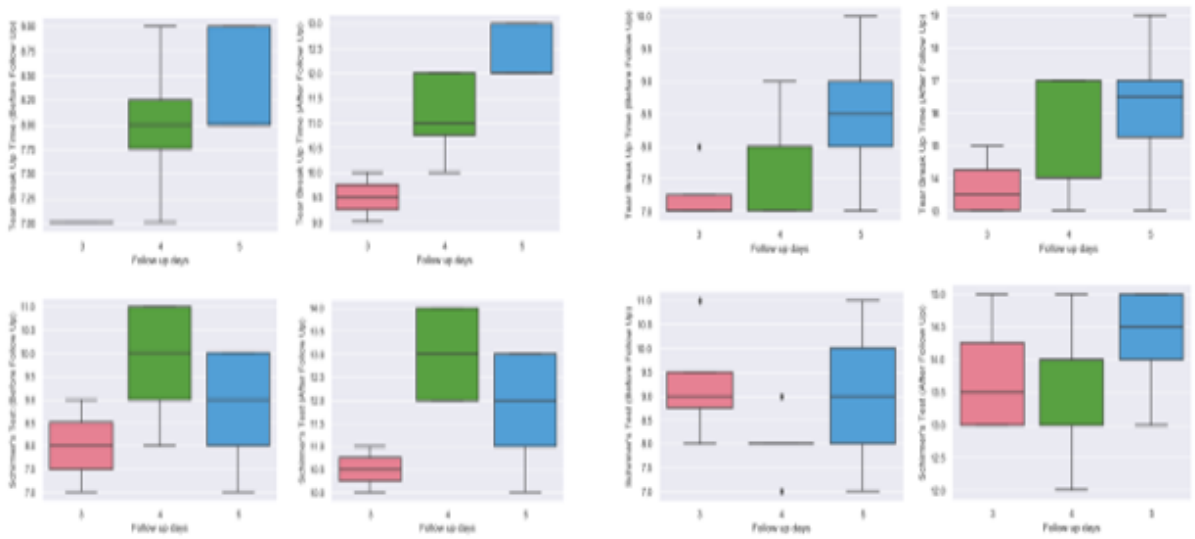

Figure 3. 1 Comparison of changes in Tear Break Up Time and Schirmer's Test results in the control and treatment groups before and after follow-up. Left side (Control group), Right side (Treatment group). Tear Break-up Time (Above), Schirmer's Test (Below)

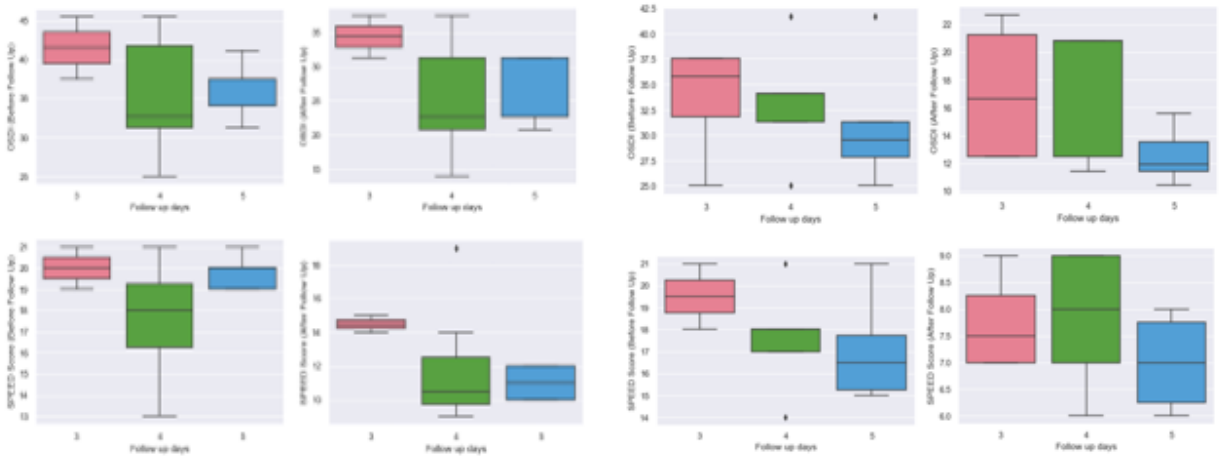

Figure 3. 2 Comparison of changes in OSDI and SPEED Scores in the control and treatment groups before and after follow-up. Left side (Control group), Right side (Treatment group). OSDI score (Above), SPEED score (Below).

3.2 Discussion

Subjective results uphold the hypothesis that Eye massager hot compresses therapy is a compelling treatment for MGD. The examination gives convincing proof that Eye massager hot compresses therapy, independent of other secondary administration strategies, and in a genuinely unprejudiced fashion, is affecting level-headed and abstract upgrades in ocular surface health. Interestingly, clinical indicative procedures hitherto propose the suggestive help is the consequence of Eye massager hot compresses therapy facilitating MG function, as demonstrated by the critical reduction in MG capping, meibum expressibility, and quality evaluated by means of cut light examination and meibum quality reviewed. While the most ebb and flow Hot Compresses therapy concentrates in writing have likewise discovered these progressions to varying degrees, most scientists have put accentuation on detecting improvement in the inflammatory status of the ocular surface because of tradition of Eye massager hot compresses therapy's instrument of action when applied in the field of dermatology. (M. T. M. Wang, Feng, Wong, Turnbull, & Craig, 2019) It could be that in a gathering of MGD patients with more extreme indications of EDE, Eye massager hot compresses therapy would improve their condition to a clinically and genuinely critical level. When planning a clinical preliminary, the mean seriousness of infection of members ought to be adequately extraordinary to permit 25% improvement upon therapy, and by restricting the examination population to one seriousness level, it would help tight the generalizability of conclusions. (Geerling et al., 2017) Additionally, the current cut-off estimations of OSDI (>12) are set for gentle moderate dry eye. In the event that the OSDI cut-off was set up for more extreme dry eye (>22), a more prominent demonstrable contrast in results may have been recognized. (Dougherty et al., 2011)

Further supporting this recommendation is the critical improvement in meibum expressibility and quality accomplished when the examination was performed on this arrangement of patients. One of the hypotheses expressed that periocular Eye massager Hot compresses therapy application may lessen the spillage of inflammatory middle people, and along these lines improve tear film quality to reestablish ocular surface homeostasis. Notwithstanding, results from this preliminary were not genuinely critical for clinical results of homeostasis marker tests, for example, ocular surface staining. An explanation for this could be that clinical visits at every information collection point didn't begin simultaneously of the day because of scheduling conflicts, and baseline levels were at that point low in instances of gentle moderate MGD members so that there was no "room" to enhance with therapy. Furthermore, the Eye massager Hot compresses therapy preliminary traversed across seasonal changes that influenced temperature and relative stickiness of the environment. Because of the exploratory idea of the current Eye massager Hot compresses therapy preliminary into the gadget's potential mechanism(s) of action in the treatment of MGD, need was given to patient manifestations as the essential result measure.

Therefore, in future investigations, biomarkers of inflammatory infection state, for example, tear hyperosmolarity could be utilized as an inclusion criterion to limit the investigation members to a conceivably responsive example in which treatment is bound to demonstrate viability.

3.3 Conclusion

This thesis has depicted, through a progression of experiments and a randomized, clinical preliminary that Eye massager Hot compresses therapy is a powerful and safe treatment for gentle moderate MGD in Pakistan's population. In addition, more clear advantages are experienced by patients who endure moderate to serious DED side effects and have generally patent MG holes. Therefore, the recommendation of Eye massager Hot compresses therapy as another road of

treatment for patients with MGD is justified. The examination exploring oneself reported dry eye infection the executives' practices of Pakistan eyecare suppliers indicate the dependence of practitioners on the conveyance of the most recent logical proof, disseminated through continuing education programs, to offer the best proof-based consideration for patients. The logical proof introduced in this thesis, confirming indication help and clinical signs in MGD Eye massager Hot compresses therapy treatments, is wanted to profit patients, eventually by providing affirmation to eye care professionals that Eye massager Hot compresses therapy offers a protected and compelling treatment option for managing MGD.

APPENDEX

APPENDEX A: SPEED Dry Eye Questionnaire

Dry Eye Questionnaire - SPEED

Name: _____ **Date:** _____ ☐ **Right eye** ☐ **Left eye**

Please answer the following questions by ticking the box ☑ that best represents your answer. Select only one answer per question. Please complete one questionnaire for the **Right eye** and the other questionnaire for the **Left eye** (and tick the **Right eye** or **Left eye** box above). If your symptoms are the same in both eyes, tick both the **Right eye** and **Left eye** boxes and complete just one questionnaire.

1. Report the type of SYMPTOMS you experience and when they occur:

SYMPTOMS	AT THIS VISIT		WITHIN PAST 72 HRS		WITHIN PAST 3 MONTHS	
	YES	NO	YES	NO	YES	NO
Dryness, Grittiness or Scratchiness	☐	☐	☐	☐	☐	☐
Soreness or Irritation	☐	☐	☐	☐	☐	☐
Burning or Watering	☐	☐	☐	☐	☐	☐
Eye Fatigue	☐	☐	☐	☐	☐	☐

2. Report the FREQUENCY of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3
Dryness, Grittiness or Scratchiness	☐	☐	☐	☐
Soreness or Irritation	☐	☐	☐	☐
Burning or Watering	☐	☐	☐	☐
Eye Fatigue	☐	☐	☐	☐

0 = Never 1 = Sometimes 2 = Often 3 = Constant

3. Report the SEVERITY of your symptoms using the rating list below:

SYMPTOMS	0	1	2	3	4
Dryness, Grittiness or Scratchiness	☐	☐	☐	☐	☐
Soreness or Irritation	☐	☐	☐	☐	☐
Burning or Watering	☐	☐	☐	☐	☐
Eye Fatigue	☐	☐	☐	☐	☐

0 = No problems
1 = Tolerable - not perfect but not uncomfortable
2 = Uncomfortable - irritating but does not interfere with my day
3 = Bothersome - irritating and interferes with my day
4 = Intolerable - unable to perform my daily tasks

4. Do you use eye drops for lubrication? ◯YES ◯NO If yes, which drops and how often?

For office use only:

SPEED score (sum of Q2, Q3)	
Full SPEED score (sum of Q1, Q2, Q3)	

APPENDEX B: OSDI Dry Eye Questionnaire

Dry Eye Questionnaire - OSDI

Name: _____ **Date:** _____ ☐ **Right eye** ☐ **Left eye**

Please answer the following questions by ticking the box beside the number that best represents each answer. Please complete one questionnaire for the **Right eye** and the other questionnaire for the **Left eye** (and tick the **Right eye** or **Left eye** box above). If your symptoms are the same in both eyes, tick both the **Right eye** and **Left eye** boxes and complete just one questionnaire.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2. Eyes that feel gritty?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3. Painful or sore eyes?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4. Blurred vision?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5. Poor vision?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Subtotal score for answers 1 to 5 _____ **A**

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A
7. Driving at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A
8. Working with a computer or bank machine (ATM)?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A
9. Watching TV?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A

Subtotal score for answers 6 to 9 _____ **B**

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A
11. Places or areas with low humidity (very dry)?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A
12. Areas that are air conditioned?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ N/A

Subtotal score for answers 10 to 12 _____ **C**

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) _____ **D**

Total number of questions answered
(do not include questions answered N/A) _____ **E**

For office use only:

FINAL score = (D x 25) / E	

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