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Analysis of two latest generation in-office therapies for the treatment of dry eye

by

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MASTER'S THESIS

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List of Abbreviations

TFOS DEWS	Tear Film and Ocular Surface Society Dry Eye Workshop
DED	Dry Eye Disease
IRPL	Intense Regulated Pulsed Light
QMR	Quantum Molecular Resonance
ADDE	Aqueous Decifiency Dry Eye
EDE	Evaporative Dry Eye
CL	Contact lens
VDT	Video Display Terminal
OSDI	Ocular Surface Disease Index
EFA	Essential fatty acids

1 Introduction

The Dry eye syndrome, also called dry eye disease (DED), is one of the most common eye conditions and a primary reason for visiting an eye health care professional.

DED is a multifactorial tear deficiency disorder of the ocular surface, characterized by different combinations of poor tear quality, decreased tear production and tear evaporation. People who suffer from DED usually complain about symptoms like fatigue, photophobia, fatigue, burning, itchiness, visual disturbance and irritation. Despite these symptoms do not lead to severe visual impairment and blindness, they are widely related to the reduction in vision-related quality of life and interfere with daily activities. Furthermore, the reduced production of tears may lead to a higher risk of ocular infection, ocular surface damage or to severe conditions like abrasion or corneal ulceration.

Hence my interest in this disease and my will to deepen the possible therapies.

I had the luck to collaborate with Dr. Luca Vigo, ophthalmologist specialized in the treatment of dry eye at the Clinic "Carones Vision", based in Milan.

Two in-office and device-assisted therapies used at Carones Clinic are the Intense Regulated Pulsed Light (IRPL®), used mainly in cases of evaporative dry eye and the Quantum Molecular Resonance (QMR®), utilized mainly in cases of aqueous deficiency dry eye.

The IRPL® treatment works by transferring high-powered light pulses on the periorbital zones, reactivating the function of the meibomian glands, while the QMR® one is a new therapy approved in 2018 which stimulates cellular and tissue regeneration applying low-power high-frequency electric fields.

The purpose of this study was to investigate the improvement of the disease in two different populations (aqueous decifiency dry eye group and evaporative dry eye group) in response to the mentioned therapies combined with an anti-inflammatory and hydrating therapy. Five indicators have been analyzed: the thickness of the tear lipid layer, the height of the tear meniscus, the NIBUT (Non-Invasive Tear Break Up Time), the OSDI (Ocular Surface Disease Index) and the osmolarity.

2 Literature review

2.1 Definition of dry eye and classification

2.1.1 Definition

In 2017 the Tear Film and Ocular Surface Society (TFOS) published the TFOS DEWS II, the report of the second TFOS International Dry Eye Workshop. The goal of TFOS DEWS II was to attain agreement on 1) an updated definition and classification of dry eye; 2) clarifyng the patterns, causes and effects of the disease; 3) providing recommendations for the diagnosis, management and treatment of dry eye, and 4) delineating clinical trial design for testing new therapies for dry eye.

The definition of dry eye disease given by the TFOS DEWS II is: *"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." [1]*

This definition recognizes the multifactorial nature of dry eye as a disease where loss of homeostasis of the tear film is the central pathophysiological issue.

2.1.2 Classification

The past classification scheme presented by the TFOS DEWS in 2007 sustained two essential categories disconnetted from each other: aqueous deficient, resulting from reduced tear secretion, and evaporative, resulting from excessive tear evaporation .

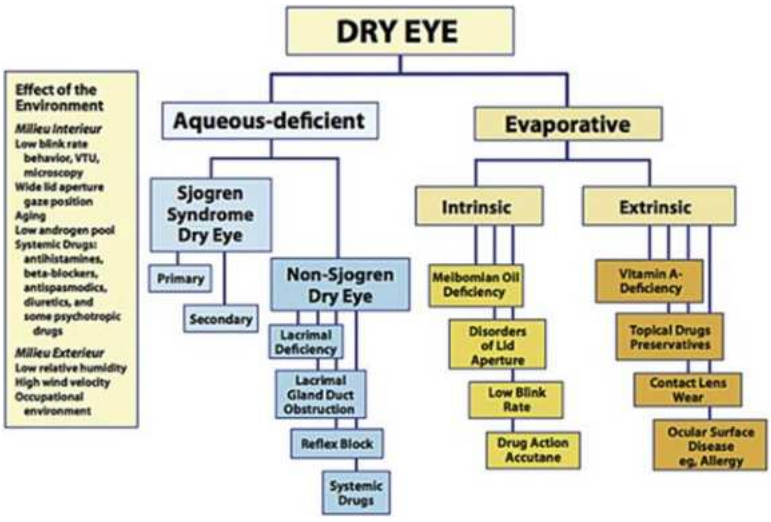


Figure 1 [Classification by TFOS DEWS]

The TFOS DEWS II report aims to eliminate that strict classification by showing that aqueous deficient and evaporative dry eye diagnoses exist on a continuum instead of as separated categories.

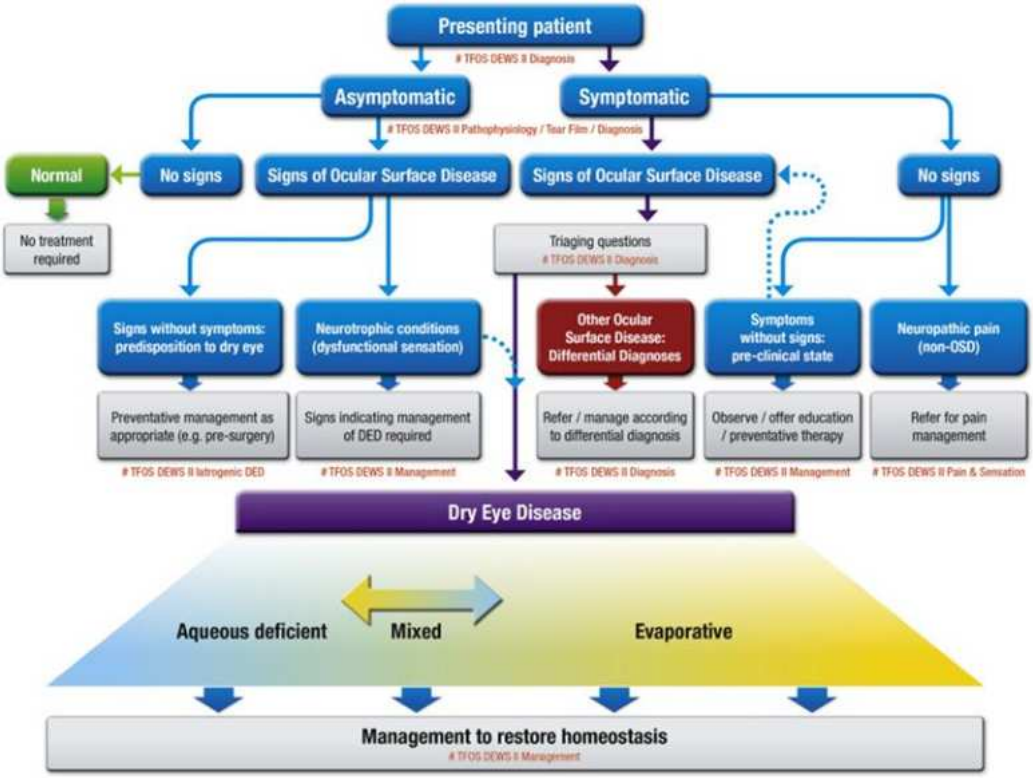


Figure 2 [Classification by TFOS DEWS II]

The management of dry eye disease can be challenging due to its multifactorial etiology. Deciding the major causative variable behind the dry eye is essential in order to choose the proper therapy. The goal of DED management is to reestablish the homeostasis of the surface of the eye and tear film. There is no single approach to dry eye administration that suits all the patients.

2.2 Epidemiology of the disease

Evaluation of large-scale DED predominance and rate has been blocked by divergences within the definition and diagnostic criteria among prior studies. When the diagnosis is based on symptoms (with or without signs), meta-analysis yields prevalence values range from 5% to 50%; when signs alone are utilized, the prevalence is up to 75% in certain studies. [2]

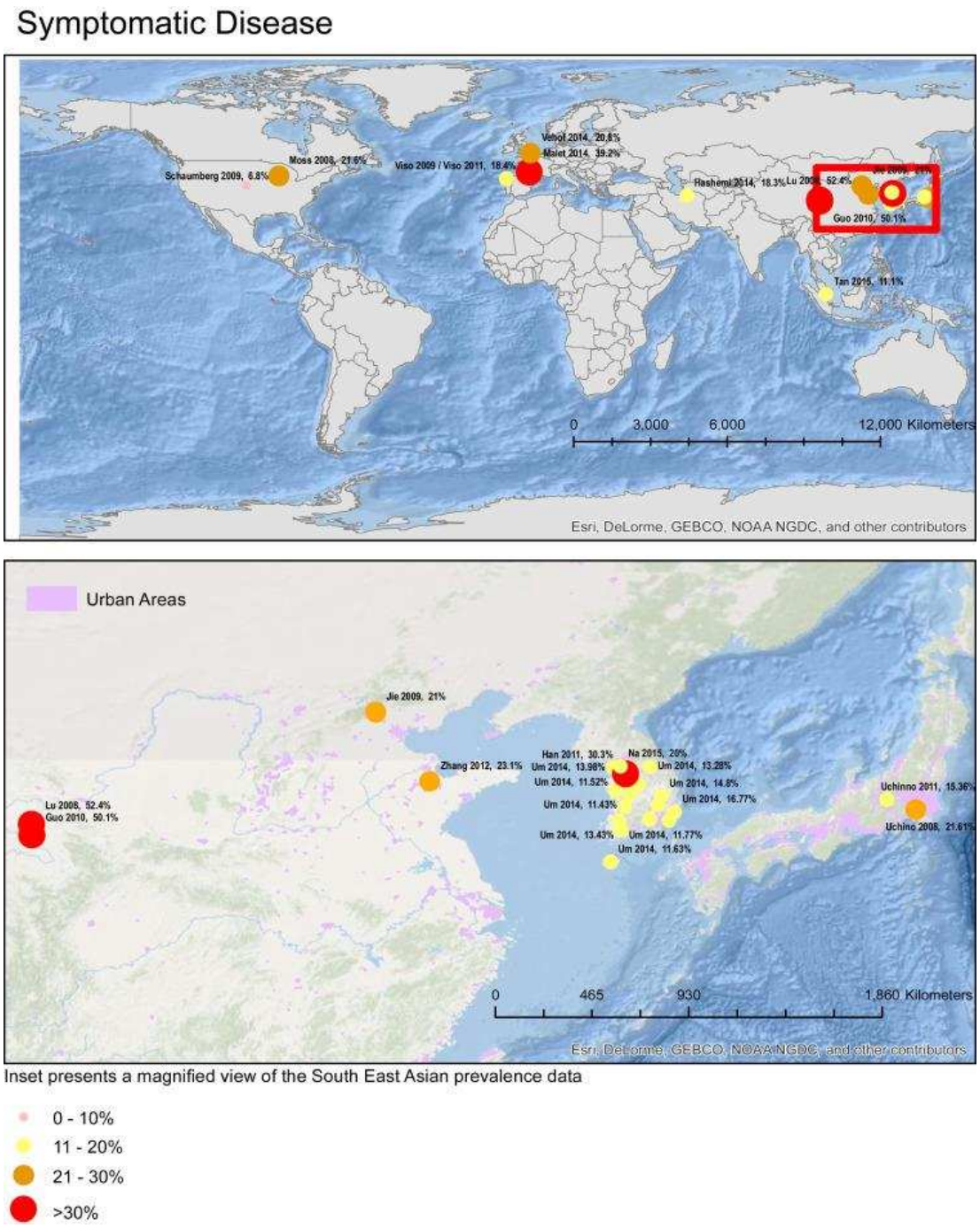


Figure 3: Prevalence map of symptomatic disease [3]

Predominance shows up to be higher in Asia than in Caucasian populations, with a pro of 1.5–2.2x that of Caucasians.

DED influences women twice as frequently as men [4].

This sex-related difference in DED prevalence is due to the effects of sex steroids (e.g. androgens, estrogens), insulin-like growth factor 1 and thyroid hormones, glucocorticoids, hypothalamic-pituitary hormones and insulin.

The meibomian gland function is mostly regulated by androgens. Lower production of androgens in women and the age-related reduction in androgens in both sexes [5] lead to an increased risk of dry eye in these populations.

Oestrogen appears to antagonize the actions of androgen, causing meibomian gland dysfunction and thus evaporative dry eye.

The conjunctiva cells display changes in mucin production according to the variation in hormone levels over the menstrual cycle. These changes in the conjunctival epithelium are absent post-menopause. The conjunctiva of post-menopausal women is more affected by inflammation and shows a diminished number of goblet cells. [6]

Women with autoimmune diseases such as Sjögren syndrome have an high probability to develop DED. [7]

Sjogren's syndrome is a disorder of the immune system, two most common symptoms are dry eyes and a dry mouth. 10% of people with significant aqueous deficient dry eye showed to have Sjogren syndrome. [8]

The lacrimal gland presents significant sex-related differences in its anatomy, physiology and pathophysiology. The lacrimal glands of elderly women present increased diffuse atrophy, orbital lobe and periductal fibrosis which may decrease the aqueous outflow. [9]

Also the corneal anatomy and physiology reveals some sex related differences. Alterations like variations in thickness, endothelial pigmentation, curvature and sensitivity, contact lens tolerance, visual acuity, hydration and body foreign sensation may occur during the menstrual cycle, pregnancy and menopause.

The density of goblet cells and susceptibility to inflammation varies between men and women. Primary nasolacrimal duct obstruction is more frequent in females because of some anatomical differences like the shorter and narrower nasolacrimal ducts of females than those of men, which may predispose to chronic inflammation of the nasolacrimal drainage system. [10]

Contact lens (CL) wearers presents DED up to 4 times more than not CL wearers. [11]

Air pollutants, temperature and relative humidity can contribute to the onset of DED. A large population-based study conducted in Korea showed a significant correlation between high ozone levels and lower humidity. [12]

Symptoms like blink frequency rate, incomplete blinking and accelerated tear evaporation have been showed to be very common among visual display workers, causing tear film instability and mild epithelial damage. In a study conducted in Japan on 4393 workers it appeared that more than 4 hours of VDT use was related with an increased risk of DED. [13]

Vitamin A deficiency in the diet is a serious problem in certain parts of the world like Africa and it's associated to a form of DED which involve corneal issues like keratomalacia and preventable blindness.

DED could be a complication of LASIK surgery. A study conducted on both Asian and Caucasian people showed that Asians developed chronic dry eye after LASIK with a significant higher probability than Caucasians. [14]

Type 2 diabetes is considered a risk factor for DED, especially for people with diabetic retinopathy. [15]

2.3 Tear film and pathophysiology of dry eye

The tear film covers the cornea and the conjunctiva, with a precorneal thickness of 2.0 to 5.5 µm. It has been described in the past as a 3-layered structure composed of a mucin layer, an aqueous layer, and a lipid layer. Contrary to it, the TFOS DEWS II describes the tear film as a 2-layered interactive structure consisted of a mucoaqueous layer and a lipid layer. [16]

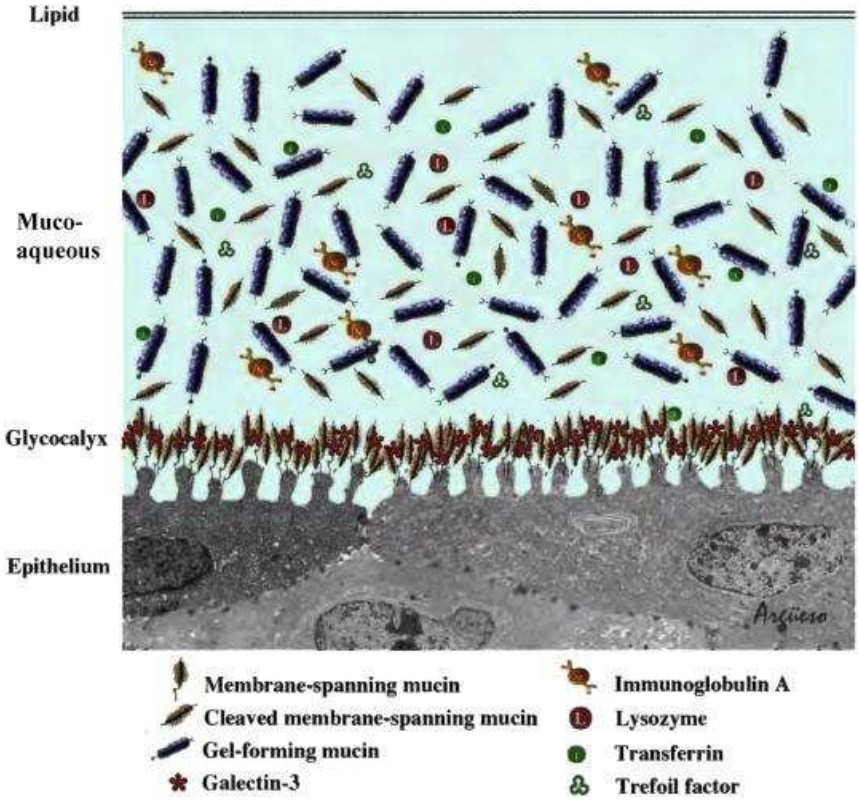


Figure 4: Tear film structure [17]

The tear film lipid layer is producted predominantly from the meibomian glands and covers the mucoaqueous layer with blinking.

Spreading is fast at first and then moderates and stabilizes after few seconds. The lipid layer has a dynamic nature which permits it to respond to the stress producted by the changing area of the air-tear interface during blinking. [18] It can be investigated with interferometry techniques. The color and brightness of the interference images are analyzed to show the lipid layer thickness. The lipid layer thickness has been demonstrated to be from 15 to 157 nm, with a mean of 42 nm. The classification by Guillon in divided in 5 groups of tear lipid layer according to the thickness oft the lipid layer: open meshwork (~15 nm), close meshwork (~30 nm), wave pattern (~30–80 nm), amorphous (~80 nm); color fringes (~80–300 nm); and abnormal color fringes (~600 nm).

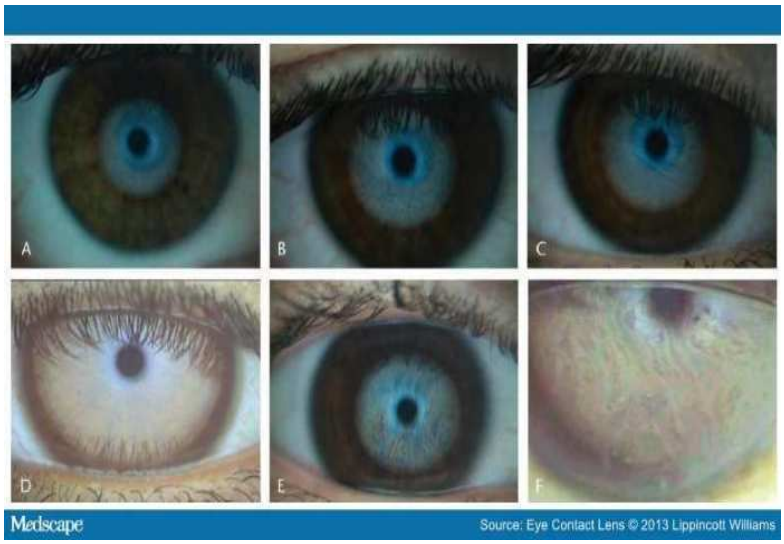


Figure 5: Guillon classification [17]

The mucoaqueous layer contains salts and various proteins producted by the lacrimal gland and conjunctiva. Mucins are essential to lubrication, barrier formation and hydration. The mucin genes (MUC) are at least 20 and are subdivided into secretory mucins and transmembrane mucins. The secretory mucins are classified in large gel-forming mucins and small soluble mucins. MUC2, MUC5AC, MUC5B, MUC6 and MUC19 are the gel forming mucins, MUC7, MUC8 and MUC9 are the small soluble mucins while 10 others have been characterized as transmembrane.[19] Ocular surface mucins are producted by corneal and conjunctival epithelia and lacrimal glands. Their role is to provide a barrier and prevent pathogens to bind to the ocular surface. They also contribute to mantain hydration in the tears. Low amount of MUC5AC have been correlated to dry eye and several studies have demonstrated that the production of mucins must be strictly regulated for ocular surface homeostasis. Transmembrane mucins bind to galectin-3 (a multivalent β-galactoside-binding lectin) to form an epithelial barrier on the apical glycocalyx [20]. Patients diagnosed with DED present high concentration of galectin-3 in tears associated with epithelial dysfunction because of an altered mucin glycosylation and a resultant loss of galectin-3 binding affinity and release of it in the tear film. Clusterin, a cytoprotective chaperone, inhibits MMP-9 and interacts with galectin-3 to improve ocular surface barrier disruption. High levels of MMP-9 have been associated to epithelial barrier disruption.

Human tear biomarkers are useful in the prediction and diagnosis of ocular surface disease. The first biomarkers identified by immunoassay are [21]:

- epidermal growth factor (EGF): decreased in Sjögren syndrome and aqueous deficient dry eye (ADDE), increased in evaporative dry eye due to MGD.
- interleukin 1α (IL-1α): augmented in Sjögren syndrome dry eye and MGD.
- interleukin 6 (IL-6): augmented in Sjögren syndrome dry eye.
- lactoferrin (LTF): decreased in Sjögren syndrome and non-Sjögren syndrome dry eye.
- lipocalin 1 (LCN1): a putative auto-antigen for Sjögren syndrome that is diminished in MGD.
- matrix metalloproteinase 9 (MMP-9): augmented in Sjögren syndrome dry eye, but normal in MGD.
- MUC5AC: low values in Sjögren syndrome dry eye.
- plasmin activity from plasminogen (PLG): high values in Sjögren syndrome dry eye.
- group IIA phospholipase A2 (PLA2G2A): augmented in dry eye.

Currently, the only commercial options to investigate the tear film biomarkers are Inflammadry® (MMP-9) and TearScan™ Lactoferrin Diagnostic Test Kit.

2.3.1 The Vicious Circle of Dry Eye Disease

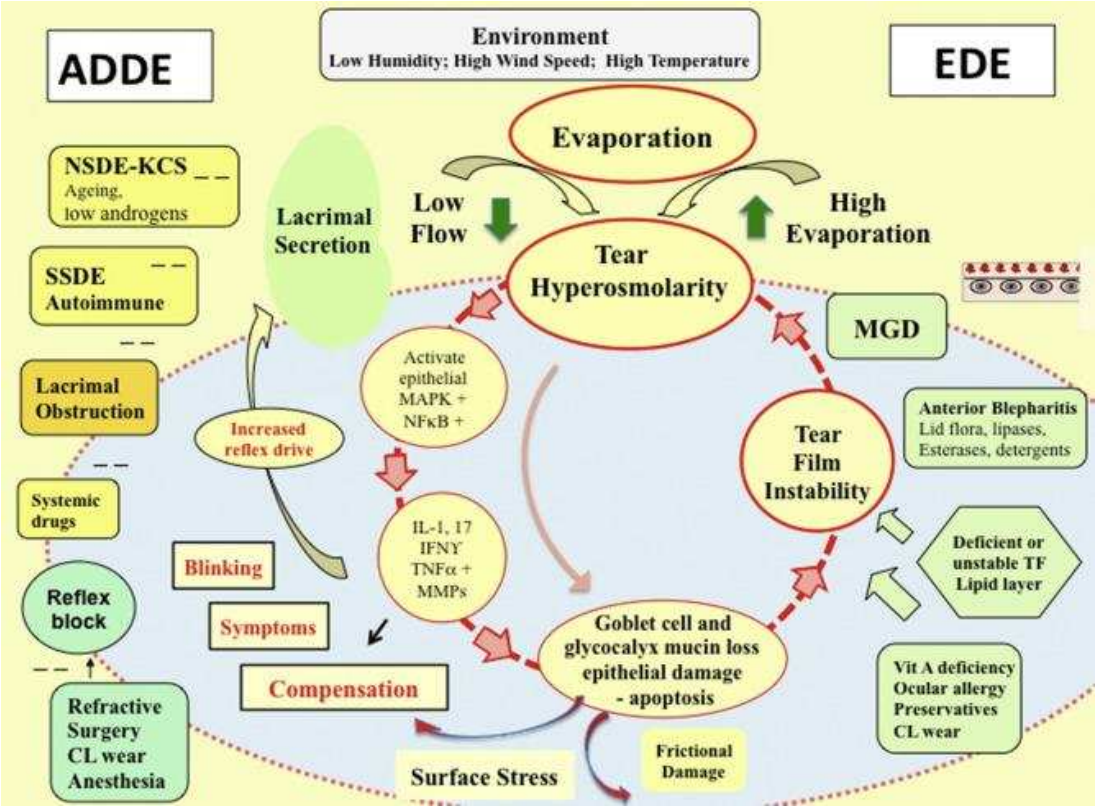


Figure 6: The vicious circle of dry eye disease

"The core mechanism of DED is tear hyperosmolarity, which is the hallmark of the disease. It damages the ocular surface both directly and by initiating inflammation. The cycle of events is shown at the centre of the figure. Two forms of DED are recognized, ADDE and EDE. In ADDE, tear hyperosmolarity results when lacrimal secretion is reduced, in conditions of normal evaporation from the eye. In EDE, tear hyperosmolarity osmolarity is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland. Since tear osmolarity can only rise as a result of tear evaporation in both ADDE and EDE, tear hyperosmolarity is due to evaporation from the ocular surface and in that sense, all forms of DED are evaporative. EDE is a hyper-evaporative state. In DED, tear hyperosmolarity is considered to set up a cascade of signaling events within surface epithelial cells, that leads to the release of inflammatory mediators and proteases. Such mediators, together with the tear hyperosmolarity itself, are conceived to cause goblet cell and epithelial cell loss and damage to the epithelial glycocalyx. Damage is reinforced by inflammatory mediators from activated T-cells, recruited to the ocular surface. The net result is the characteristic punctate epitheliopathy of DED and a tear film instability which leads at some point to early tear film break-up. This break-up exacerbates and amplifies tear hyperosmolarity and completes the Vicious Circle of events that lead to ocular surface damage. Ultimately this is thought to lead to self-perpetuation of the disease. Tear film instability can be initiated without the prior occurrence of tear hyperosmolarity, by conditions that affect the ocular surface, including xerophthalmia, ocular allergy, topical preservative use and contact lens wear. In this case, early tear film breakup (an Ocular Protection Index <1) is the primary basis for tear film hyperosmolarity at first experienced locally at the site of breakup and increasing in severity, at some

point being detectable in tear meniscus samples. This represents an ocular surface–related form of EDE. In MGD-related EDE tear hyperosmolarity results from a tear film lipid layer deficiency. In ADDE the onset of early break-up during the evolution of the disease, may add an evaporative element to the dry eye. There are various causes of ADDE. It may result from blocking the sensory drive to the lacrimal gland that is essential to maintain osmolar homeostasis. Bilateral topical anesthesia can cause both a reduction in tear secretion and blink rate. Dry eye due to such a reflex block can be caused by chronic abuse of topical anesthetics, trigeminal nerve damage and refractive surgery including LASIK surgery. The delivery of aqueous tears to the tear sac can also be reduced by obstruction of the lacrimal ducts, which can occur in any form of cicatricial conjunctival disease, such as trachoma, erythema multiforme, graft-versus-host-disease and chemical burns. A number of drugs in systemic use, such as antihistamines, beta-blockers, antispasmodics, diuretics and some psychotropic drugs, cause a reduction in lacrimal secretion and are risk factors for DED. Tear secretion rate falls in later life. The anti-glaucoma drugs pilocarpine and timolol also have direct effects on human meibomian gland epithelial cells that may influence their morphology, survival and/or proliferative capacity, and possibly promote MGD. In the western world the most common cause of ADDE is inflammatory infiltration of the lacrimal gland, encountered most severely in autoimmune disorders such as Sjogren *dry eye (SSDE) and, with lesser severity, in non-Sjogren dry eye (NSDE). Inflammation causes both acinar and ductal epithelial cell dysfunction and/or destruction and a potentially reversible neurosecretory block. A receptor block may also be caused by circulating antibodies to the muscarinic, M3 receptor. Inflammation is favoured by low tissue androgen levels. Epithelial injury and a defective glycocalyx, loss of tear volume and of goblet cell mucin, lead to increased frictional damage and friction-related symptoms. The tear hyperosmolarity and epithelial injury caused by DED, stimulates corneal nerve endings, leading to symptoms of discomfort, increased blink rate and, potentially, a compensatory reflex increase in lacrimal tear secretion." [22]*

2.4 Diagnostic methodology

Since the signs and symptoms of DED are poorly correlated, it is not possible to find a single gold-standard diagnostic marker for this complex condition.

Patient questionnaires

Quantifying the ocular surface symptoms is important to monitor the progression of the condition and the response to the treatments. It is therefore recommended to administer a symptom questionnaire at the beginning of the patient examination. The OSDI (ocular surface disease index) is the most widely used questionnaire for DED clinical trials. This survey contains 12 questions subdivided into three groups: symptoms of the eye, vision-related functions, and environmental factors. The OSDI scoring is based on a 0-100 scale, with the highest score representing greater disability. The OSDI survey is evaluated on a scale from 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time.

To find the total OSDI score it is used the following formula: OSDI = [(sum of scores for all questions answered) × 100] / [(Total number of questions answered) × 4]. An OSDI score of 0-12 indicates non dry eye; An OSDI score of 13-22 is classified as mild dry eye and An OSDI score of 23-32 indicates a moderate dry eye. An OSDI score > 32 indicates a severe dry eye.

Ocular Surface Disease Index® (OSDI®)²

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

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
5. Poor vision?	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)

Please turn over the questionnaire to calculate the patient's final OSDI® score.

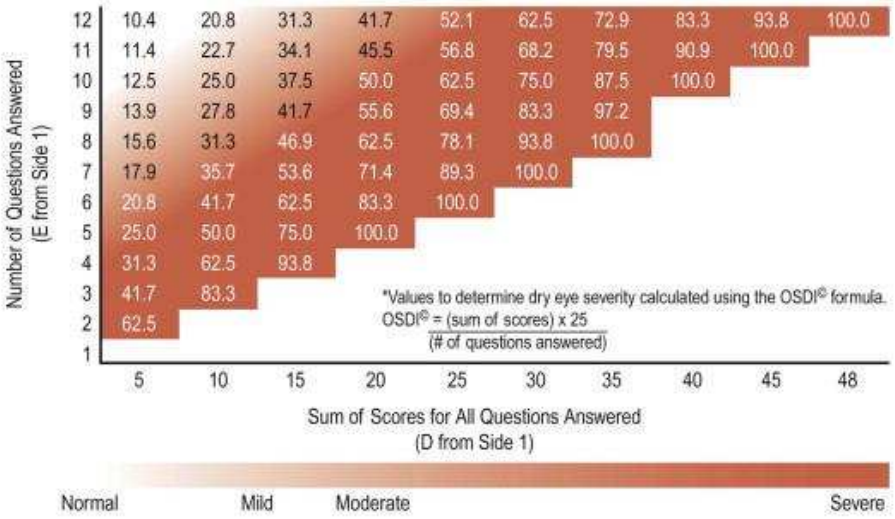
Figure 7: Osdi questionnaire pag1 [23]

Evaluating the OSDI© Score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



Patient's Name: _____ Date: _____

How long has the patient experienced dry eye disease? _____

Eye Care Professional's Comments: _____

1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Figure 8: Osdi questionnaire pag2 [23]

Tear film stability

Evaluating the stability of the tear film is one of the most important diagnostic criteria for diagnosing abnormality.

In clinical practice, the most frequently performed test is the tear film breakup time (TBUT); this is the interval of time between a complete blink and the appearance of the first break in the tear film. [24] Since tear film stability can be influenced by fluorescein, temperature, humidity and air circulation, non-invasive breakup time (NIBUT) measurements have become more in vogue in both clinical practice and research. Noninvasive tear break-up time test is executed by instruments like Tearscope [25], keratometers, or computerized systems, topographic analysis systems including videokeratoscopy, ocular surface thermography, or lateral shearing interferometry.

The cutoff value to categorize patients with symptoms of dry eye is 12 seconds for NIBUT and 8 seconds for TBUT. [26, 27]

Tear value

The tear film volume is critical for ocular surface health and its deficiency may be at the same time a key pathogenic mechanism and a diagnostic sign in DED patients. The tear meniscus height is used to evaluate the tear volume. Meniscometry is performed to evaluate the tear meniscus and can be executed using the slit lamp or with new digital meniscometry systems.

A tear meniscus height less than 0.20-0.22 mm is indicative of dry eye.

The Schirmer test is performed by setting a paper test strip in the temporal one third of lower eyelid and then measuring the length of the soaked part of the strip after 5 minutes. A value less than 5 mm is suggestive of dry eyes and less than 10 mm marginally dry eyes. The Phenol red thread test is performed in the same way but it takes 15 s for the reading. The thread is yellow and when it comes in contact with tears it changes to a light red color. A reading of less than 10 mm indicates dry eyes, less than 20 mm marginally dry eyes, and more than 20 mm normal tear volume. [28]

Tear film composition

The tear film osmolarity test is broadly defined as an objective numerical measure for diagnosing, grading severity, and managing treatment of DED. [29] Osmolarity generally augments with disease severity. It is classified as normal (302.2 ± 8.3 mOsm/L), mild-to-moderate (315.0 ± 11.4 mOsm/L) and severe (336.4 ± 22.3 mOsm/L). 316 mOsm/L is considered the cut-off to differentiate moderate to severe DED while 308 mOsm/L cut-off has become the considered threshold to help diagnose mild to moderate subjects. Abnormal osmolarity is defined also when the inter-eye difference is >8 mOsm/L. [16]

Damage to ocular surface

Punctate staining of the ocular surface is a common sign in case of DED and it is diagnosed instilling dyes like sodium fluorescein, rose bengal, and lissamine green. The clinical appearance of fluorescein staining occurs when a disruption in superficial cell tight junctions or defective glycocalyx are present. [30] Rose bengal stains dead, degenerated cells or ocular surface epithelial cells that are unprotected by mucin or glycocalyx. [31] Lissamine green colors epithelial cells only if the cell membrane is damaged, irrespective of the presence of mucin.

Inflammation of the ocular surface

The matrix metalloproteinases (MMPs) are proteases released into the tears in DED. The level of MMPs indicates the loss of ocular surface barrier function, since MMPs can crush tight junctions in the ocular surface epithelium.

InflammaDry is a fast (<10 min) immunoassay test to measure MMP-9 tear concentration in tears.

It is a nonquantitative test so patients with high MMP-9 levels will have the same test result as those with moderately high levels. Tear samples are collected from the inferior meniscus and the test is positive (meaning MMP-9 concentration is ≥40 ng/mL) when two lines (one blue and one pink) are visualized in the test window.

Interferometry and meibography

The superficial oily layer of the tear film is essential to retard evaporation of the tears, and, with the rest of the tear film to maintain an optically smooth surface over the cornea.

The thickness of the lipid layer of the tear film is estimated by a test called interferometry.

Meibography is performed to evaluate the meibomian gland morphological structure.

Performing only meibography is not considered sufficient to diagnose MGD, the results should be interpreted in the context of other clinical parameters. It has been demonstrated that the thickness of the lipid layer of the tear film measured by interferometry is correlated to the meibomian gland area determined by meibography. [32]

2.5 Current management and therapy of dry eye

Finding an appropriate management of DED is difficult because DED is a complex condition that varies from patient to patient. Identifying the degree to which EDE (likely related to MGD), ADDE and/or other ocular surface conditions contribute to the patient's presentation is critical to find out the proper therapy. The TFOS DEWS II proposed a flexible organizational tool to use when initiating treatment of DED. It is divided in four step, beginning with low-risk and commonly available therapies such as over-the-counter artificial tears for early stage disease, and progress to more advanced therapies for more severe forms of DED. [33] The final aim of DED management is to re-establish homeostasis of the ocular surface, by shattering the vicious cycle of the disease, and offering long-term options to prevent a return to the vicious cycle and a resurgence of symptoms.

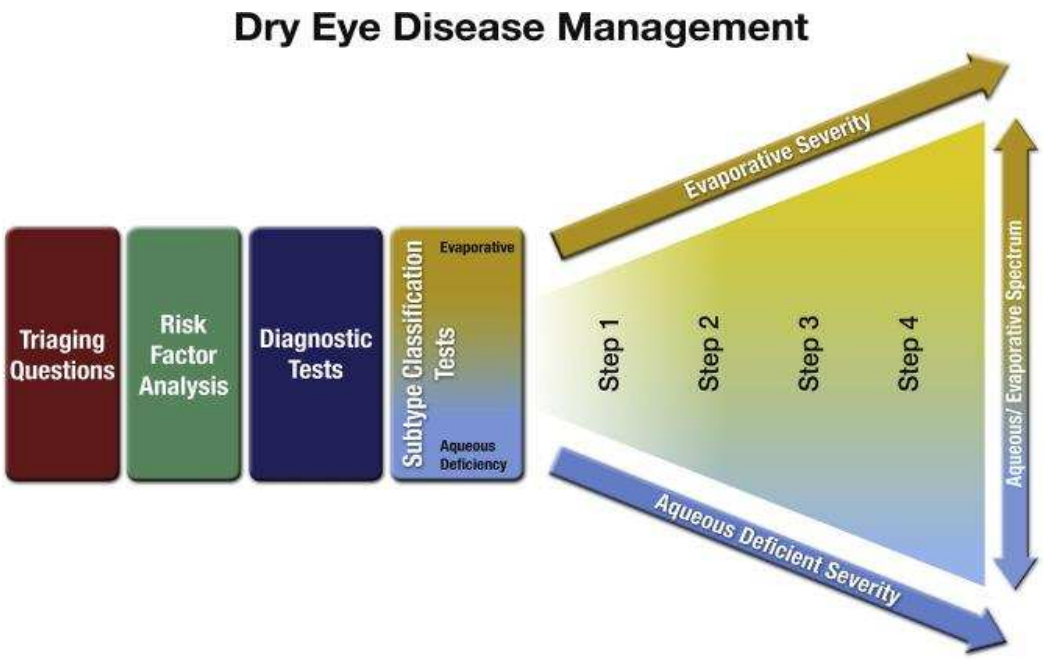


Figure 9: Dry Eye Management by TFOS DEWS II [34]

The steps proposed by TFOS DEWS II Management and Therapy report [34] are:

Step 1:

- Education regarding the condition, its management, treatment and prognosis.
- Modification of local environment.
- Education regarding potential dietary modifications: tear osmolarity increases with dehydration [35], the assumption of ω-3 and/or ω-6 EFA is still a controversial topic.
- Identification and potential modification/elimination of offending systemic and topical medications.
  Many drugs used for treating chronic illnesses can contribute to DED. A higher incidence of dry eye has been reported in individuals using antihistamines, beta-blockers,
  antidepressants, diuretics, anxiolytics, antipsychotics, anti-Parkinsonian drugs, isotretinoin, estrogen therapy and systemic chemotherapy.
  Preservatives may be associated with allergic, toxic or inflammatory reactions. Several studies have suggested that glaucoma medications may contribute to OSD and the development of dry eye.
- Ocular lubricants of various types.
  The artificial tears attempt to replace and/or supplement the natural tear film. However, these products do not target the underlying pathophysiology of DED.
  If MGD is present, then consider lipid-containing supplements.
- Lid hygiene and warm compresses of various types.

Step 2:
If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity.
- Tea tree oil treatment for Demodex (if present).
- Tear conservation: punctal occlusion, moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)

- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy.
- Prescription drugs to manage DED: topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present), topical corticosteroid (limited-duration), topical secretagogues, topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine), topical LFA-1 antagonist drugs (such as lifitegrast), oral macrolide or tetracycline antibiotics.

Step 3:

If above options are inadequate consider:

- Oral secretagogues.
  Oral secretagogues are pharmaceutical agents designed to stimulate secretion by target tissues via systemic administration. Cholinergic agents, such as pilocarpine and cevimeline, are available for oral administration for the treatment of dry mouth. Pilocarpine and cevimeline activate muscarinic acetylcholine receptors in the salivary and lacrimal glands to stimulate secretion. Clinical evaluation indicates that the main benefit of oral secretagogue therapy in patients with Sjogren syndrome is relieving the symptoms of dry mouth, although improvements in ocular symptoms have been observed. [36]
- Autologous/allogeneic serum eye drops.
  The advantage of autologous serum is that many of its biochemical characteristics, including pH, nutrient content, vitamins, fibronectin, growth factors such as epithelial growth factor (EGF) or nerve growth factor (NGF), are similar to that of human tears. Several *in vitro* and *in vivo* studies have shown that serum and other blood derivatives enhance corneal epithelial wound healing, probably due to these factors. [37]
  Serum was also found to inhibit the release of inflammatory cytokines and to increase the number of goblet cells and mucin expression in the conjunctiva in a clinical case series. [38]
- Therapeutic contact lens options: soft bandage lenses, rigid scleral lenses.

Step 4:

If above options are inadequate consider:

- Topical corticosteroid for longer duration.
- Amniotic membrane grafts.
  The amniotic membrane, the inner layer of the fetal membrane, has anti-inflammatory, anti-fibrotic, anti-angiogenic and anti-microbial properties. In effect, it creates a fetal environment that promotes corneal healing and helps return the ocular surface to a normal state.
  Amniotic membranes are not indicated for patients with mild dry eye who don't experience corneal changes.
- Surgical punctal occlusion.
- Other surgical approaches (eg tarsorrhaphy,the surgical fusion of the upper and lower eyelid margins and salivary gland transplantation).

2.6 The Quantum Molecular Resonance (QMR®) therapy

The QMR® technology was born to remedy to the high temperature emitted by electrosurgery devices which can cause extensive necrosis and tissue damage.

Quantum Molecular Resonance (QMR®) was born from an idea by Gianantonio Pozzato and developed by Telea Electronic Engineering Srl. QMR® is generated by means of alternate current of defined high-frequency (16 MHz) which break molecular bonds with minimal temperature elevation, so non-traumatic cut of the tissue and a soft coagulation, at temperatures lower than 50°C, are obtained. QMR® electro-surgical units are distributed worldwide for neurosurgery, spinal surgery, urology, otorhinolaryngology, oral surgery and dermatology. [39]

The QMR® technology, at much lower power and with higher frequency range than surgery, appeared to be very effective in stimulating cellular and tissue regeneration.

In 2018 the effects of QMR® treatment on human mesenchymal stromal cells has been observed, showing an involvment of the treatment on the angiogenesis and and in tissue regenearation. [40]

Quantum molecular resonance technology has been used also in hard-to-heal extremity wounds showing that the therapy can significantly ameliorate and accelerate the healing process. Indeed, histological analyses, post-treatment biopsies revealed a decreased amount of inflammatory cells and lower expression levels of metalloproteinases (e.g. MMP9). They observed increased capillary thrombosis as well as up-regulation of vascular endothelial growth factor (VEGF) expression. [41]

It was approved that QMR® regenerative stimulation may have a beneficial effect also on ocular diseases, e.g., dry eye.

The company Resono Eye Resonance launched the first QMR® device, called Rexon-eye®. It works by applying low-power high-frequency electric fields, capable of stimulating the metabolism and natural regeneration of cells. This treatment is delivered by contact electrodes built in a mask, which is worn by the patient over closed eyes. The treatment itself is comfortable, pleasant and relaxing and it consists of 4 treatment sessions of 20 minutes each, at one week intervals.

Figure 10: Rexon Eye [39]

The treatment addresses all types of the dry eye syndromes, both evaporative as well as aqueous deficient and it allows long-term benefits fort the patient, as evidenced by published studies in several subjective and objective measurements.

In 2017 a study conducted on 27 patients showed that the QMR® treatment could improved OSDI from 43.0±19.2 to 25.3±22.1. A significant improvement was showed also about TBUT and Schirmer scores and these effects were substantially maintained at 6-month and 12-month follow-up evaluations. No complications occurred and patients found the treatment satisfying. [42]

In 2019 it was shown that Quantum Molecular Resonance may have a relevant role in the treatment of evaporative dry eye disease. Twenty-five patients affected by MGD were enrolled. Corneal fluorescein staining improved by 62.5% ($P < 0.0001$), tear breakup time increased by 30.9% ($P < 0.0001$), and the Ocular Surface Disease Index score improved by 37% ($P < 0.001$). The meibum quality and the number of expressible meibomian glands also increased (35.7% and 12%, $P < 0.001$ and $P < 0.0001$, respectively). Schirmer test scores increased after treatment by 16.5% ($P = 0.01$). No adverse events were observed. [43]

Rexon Eye® is classified Class IIa According to Annex 9 of Directive 93/42 /EEC and s.m.i. (2007/47/EC): "Medical device for the treatments of the ocular surface disorders"

It has the European Patent Office patent EP 3 349 848 B1 "ELECTRO-STIMULATION DEVICE FOR THE TREATMENT OF DRY EYE" issued in Jul 2018 and the US Patent Office patent US 10,376,691 B2 "ELECTRODE SYSTEM, DEVICE AND METHOD FOR THE TREATMENT OF EYE DISEASES, IN PARTICULAR DRY EYE" issued in Aug 2019. Pending in Australia, Brazil, Canada, China, South Korea, Japan, India, Russia, South Africa.

2.7 The Intense Regulated Pulsed Light (IRPL®) therapy

The IRPL® therapy is the latest generation Intense Pulsed Light therapy for the treatment of evaporative dry eye. It works by conveying high-powered light pulses on the periorbital zones.

The thermal "shock" reactivates the function of the meibomian glands, so the production of the lipidic component essential for the correct preservation of the tear film.

E>EYE by E-Swin, the device used in this study, is the first medical device in the world using IRPL®.

Figure 11: E>Eye [42]

The session treatment takes few minutes: the patients are seated on a treatment chair and the patient wears an eyewear protection. Some optical gel is applied on the cheekbone and the temporal areas. A series of 5 flashes are applied under one eye, starting from the inner canthus to the temporal area. The same process is then repeated under the other eye.

The protocol of the treatment consists of 3 sessions as follows: - Day 0 - Day 15 - Day 45 - Day 75 (optional).

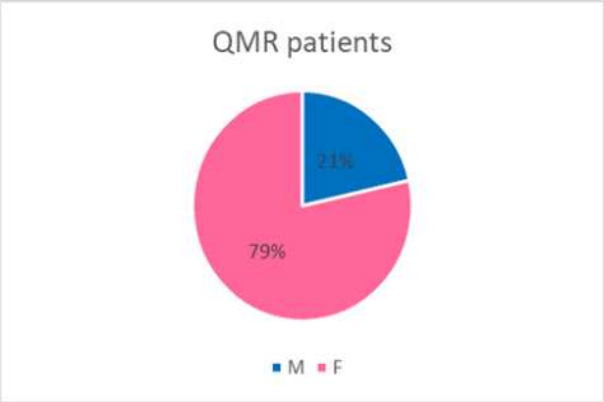
The Medical CE Certification (European Standard) TGA registration has been approved in 2013.

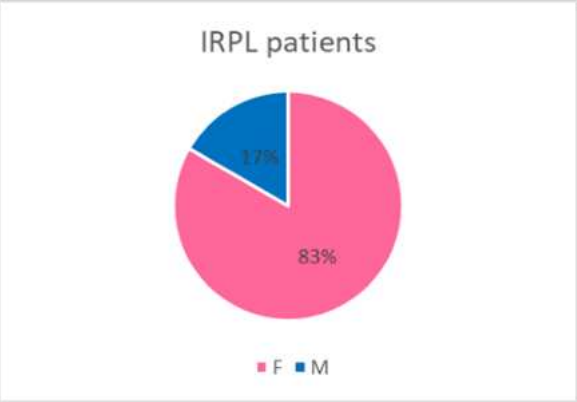
3 Participants

Thirty-two participants were divided in two groups based on the etiology of the disease.

Fourteen patients with a prevalence of ADDE signs were treated with the QMR® technology while eighteen patients with a majority of EDE were treated with the Intense Regulated Pulsed Light therapy (IRPL®).

The QMR® group was formed by 11 women and 3 men and the average age was 45yo. The IRPL® group consisted of 15 women and 3 men and the average age was 49yo.





3.1 Inclusion and exclusion criteria

INCLUSION CRITERIA FOR THE QMR® GROUP

- Able to read, understand and sign an informed consent form
- 30-70 years of age
- Diagnosis of ADDE as major causative factor behind the DED, so a mix of the following clinical signs: low tear volume, hyperosmolarity, inflammation, corneal and conjunctival staining, high OSDI score.

EXCLUSION CRITERIA FOR THE QMR® GROUP

- Eye infections over the past six months
- No non-removable electrical aid (e.g.,pacemakers)
- No skin diseases (e.g., acne, rosacea)
- No eye surgery in the last 3 months
- No anti-inflammatory use
- No antibiotic use
- No anti-glaucoma eye drops use.

INCLUSION CRITERIA FOR THE IRPL® GROUP

- Able to read, understand and sign an informed consent form
- 30-70 years of age
- Diagnosis of EDE as major causative factor behind the DED, so a mix of the following clinical sign: low NIBUT value, hyperosmolarity, high value of meibomian gland loss, high OSDI score.

EXCLUSION CRITERIA FOR THE IRPL® GROUP

- Contact lens wearer within the past 1 month and throughout the study
- Recent ocular surgery or eyelid surgery within the past 6 months
- Neuro-paralysis in the planned treatment area within the past 6 months
- Current use of punctual plugs
- Pre-cancerous lesions, skin cancer or pigmented lesions in the planned treatment area
- Uncontrolled infections or uncontrolled immunosuppressive diseases
- Subjects who have undergone refractive surgery within the past 6 months
- Diseases in the planned treatment area that could be stimulated by light at 560 nm to 1200 nm (e.g.,Herpes simplex 1 and 2, Systemic Lupus Erythematosus, porphyria)
- Use of photosensitive medications and/or herbs that may cause sensitivity to 560-1200 nm light exposure, such as isotretinoin, tetracycline, or St. John's Wort
- Any anti-glaucomatous eye drop uses within the past 3 months and throughout the study period.

The exclusion criteria are correlated to the instructions of the two devices.

3.2 Values before the treatment

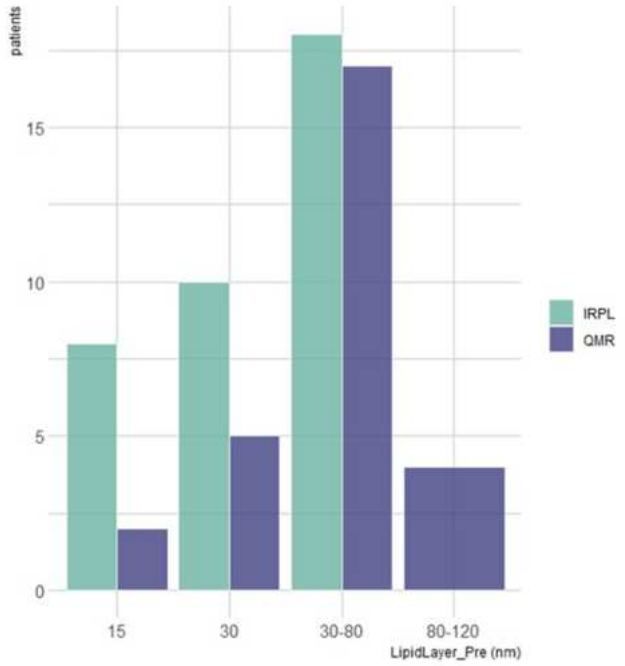
The mean values of the variables examined in the current study before the treatments are shown in the following table:

Variable	QMR® group	IRPL group
Lipid layer (nm)	30-80	30-80
Tear meniscus (mm)	0,18 +/- 0,12	0,21 +/- 0,07
Nibut (s)	8,3 +/- 3,8	6,7 +/- 4,4
OSDI	55 +/- 15	40 +/- 14
Osmolarity (mOsm/L)	301 +/- 12	304 +/- 19

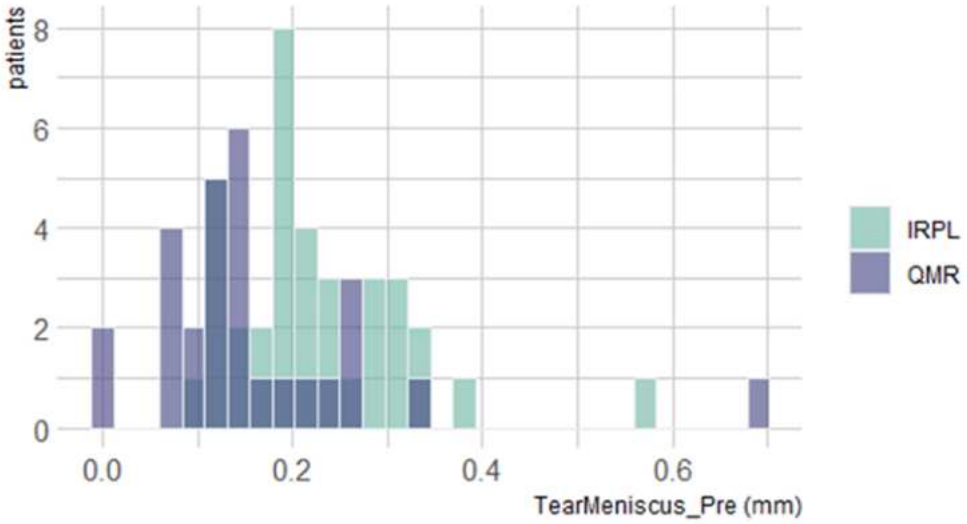
Table 1: values before the treatments

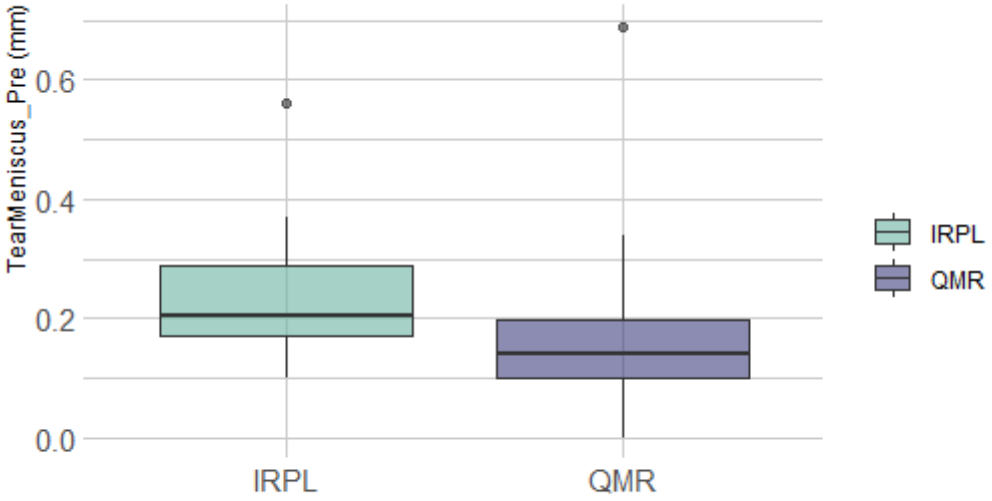
The same results are represented in the following graphs:

Lipid layer

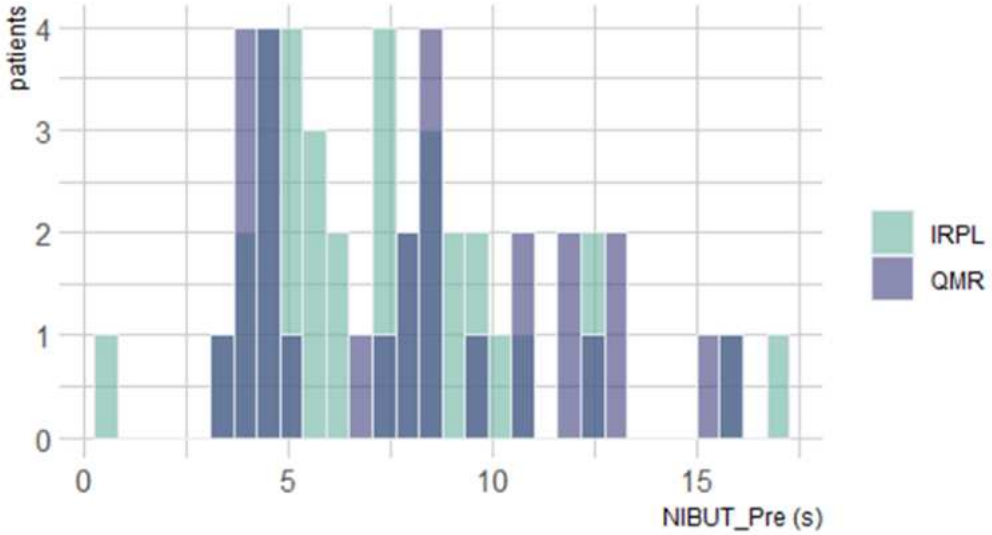


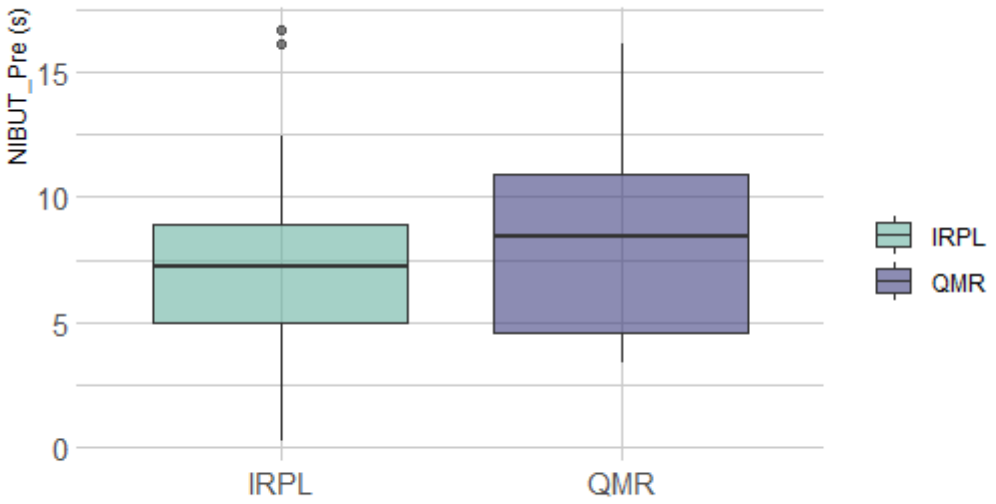
Tear meniscus



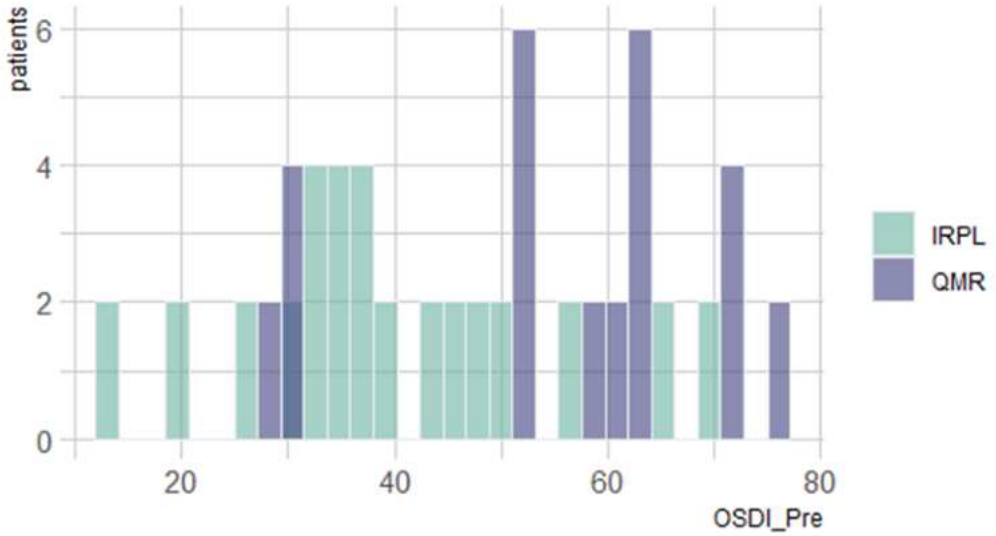

TearMeniscus_Pre (mm)
0.6
0.4
0.2
0.0
IRPL
QMR
IRPL
QMR

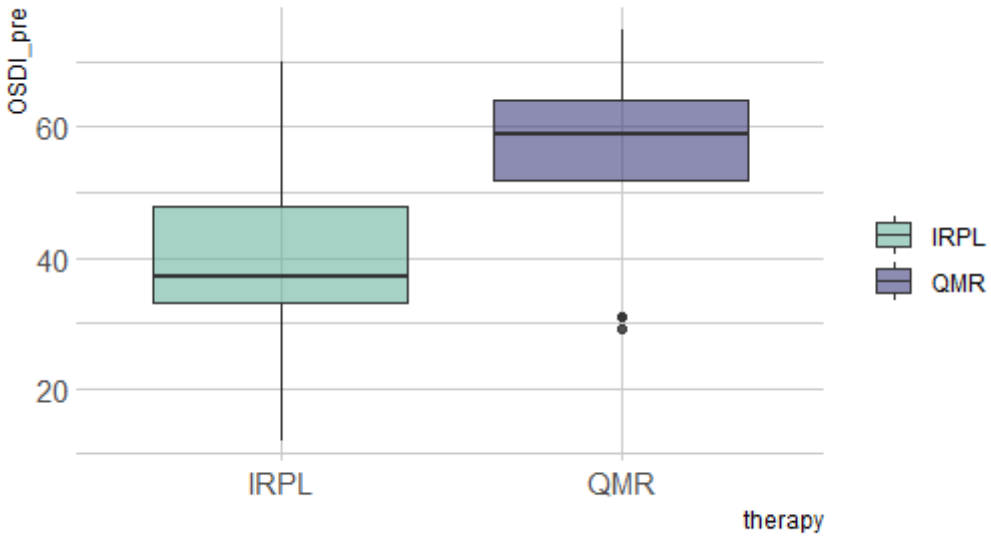
Nibut


patients
4
3
2
1
0
0
5
10
15
NIBUT_Pre (s)
IRPL
QMR

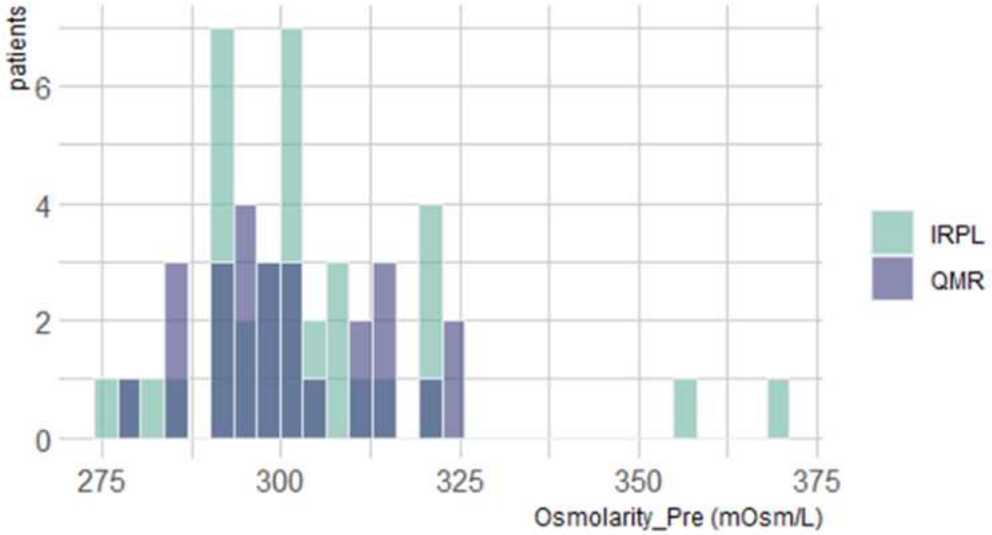

NIBUT_Pre (s)
15
10
5
0
IRPL
QMR
IRPL
QMR

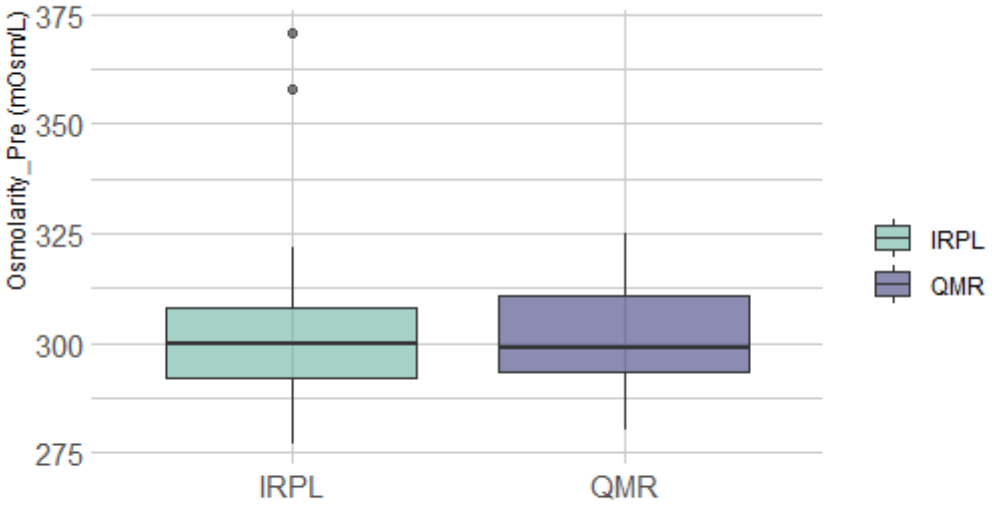
OSDI


patients
6
4
2
0
20
40
60
80
OSDI_Pre
IRPL
QMR


OSDI_pre
60
40
20
IRPL
QMR
therapy
IRPL
QMR

Osmolarity


patients
6
4
2
0
275
300
325
350
375
Osmolarity_Pre (mOsm/L)
IRPL
QMR


Osmolarity_Pre (mOsm/L)
375
350
325
300
275
IRPL
QMR
IRPL
QMR

4 Method

Five variables, measured before and after the treatment, were compared:

- The thickness of the tear lipid layer
- The height of the tear meniscus
- The NIBUT (Non-Invasive Tear Break Up Time)
- The OSDI (Ocular Surface Disease Index)
- The osmolarity

The QMR® therapy protocol consisted in 4 sessions, once a week. Every session lasted 20 minutes.

The IRPL® therapy protocol consisted in 3 sessions as follow: day 0, day 15, day 45. Every session lasted 10 min.

For both protocols, every patient was checked 1 month after the last treatment.

At the beginning of the IRPL and QMR treatments, all the patients were treated also with a therapy based on a corticosteroid and artificial tears. The medicines and the administration were the following:

- Cortivis® (Medivis): hydrocortisone sodium phosphate – 3.35 Mg/MI.
  Administered twice a day for two weeks.
- Cationorm® (Santen): cationic emulsion drops.
  Administered three times a day for all the IRPL®/QMR® therapy duration
- Thealoz Duo Gel® (Thea): trehalose 3%, sodium hyaluronate 0.15% and carbomer 0.25% in a preservative free gel formulation.
  Administered every night for all the IRPL®/QMR® therapy duration

The Lipid layer, the tear meniscus and the NIBUT were measured with the instrument IDRA by SBM Sistemi. IDRA is an ocular surface analyzer, a slitlamp mounted system for the analysis of the ocular surface. [23]

Figure 12: Idra [23]

The TearLab™ Osmolarity was used to measure the osmolarity values.

The percentage increments of every patient were calculated for each indicator. The mean of the percentage increments of each variable was used to compare the efficacy of the therapies.

Since the tear lipid layer is calculated in intervals, it was assigned a sequential number to each interval to calculate the percentage increase (15=1, 30=2, 30-80=3, 80=4, 80-120=5).

5 Results

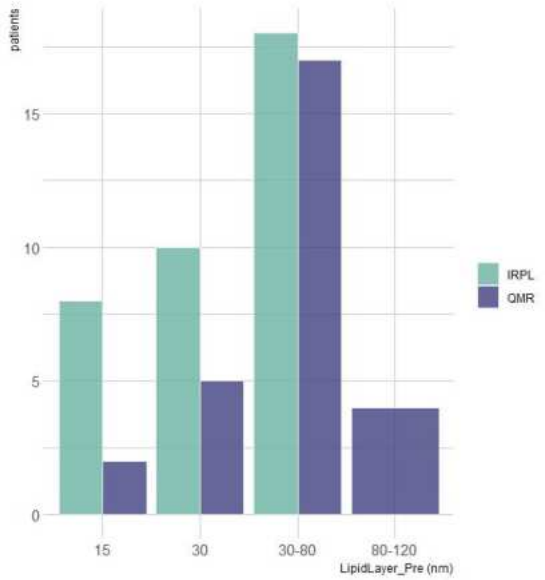
The mean of the percentage increases is listed in the following table, divided by therapy.

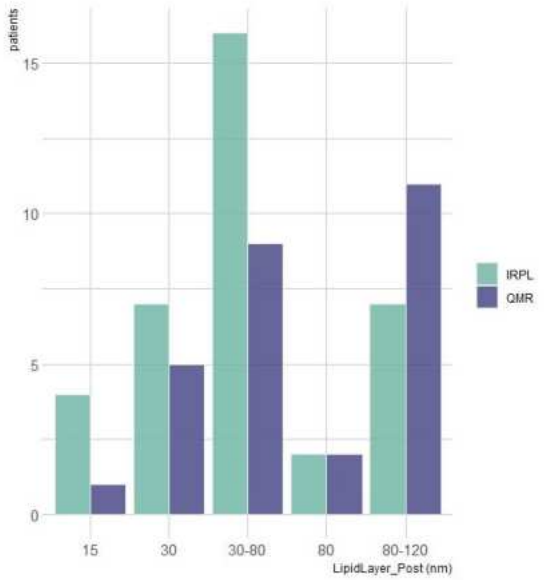
Variable	QMR® treatment	IRPL® treatment
Lipid layer	47 %	64 %
Tear meniscus	30 %	40 %
Nibut	27 %	52 %
OSDI	-22 %	-17%
Osmolarity	1%	-1%

Table 2: Percentage increases

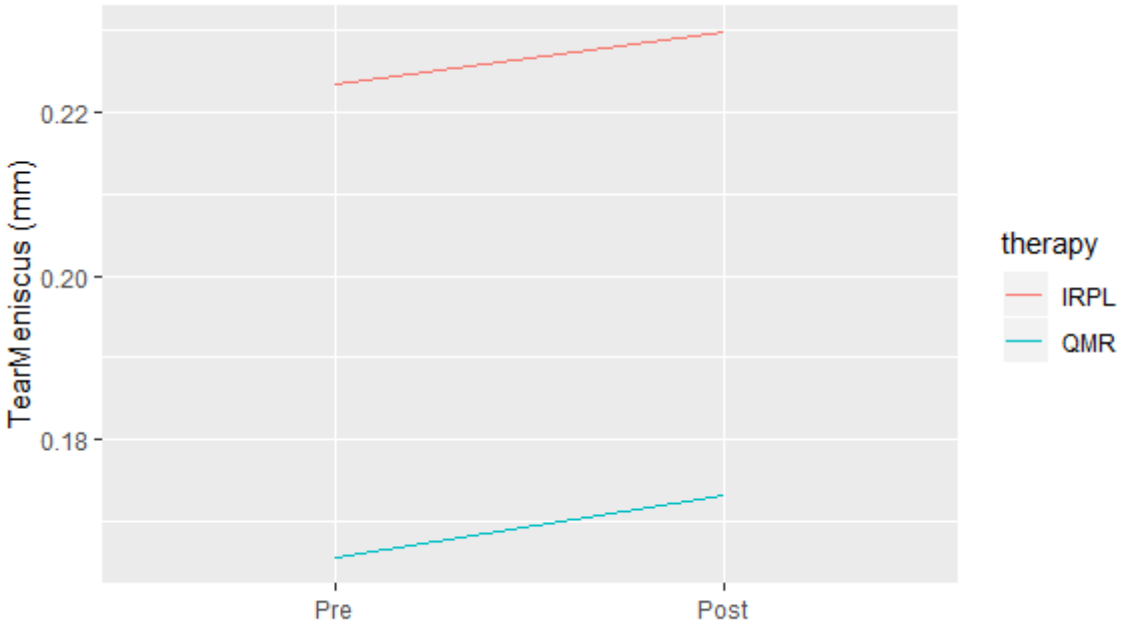
A graph for each variable was made to better show the results.

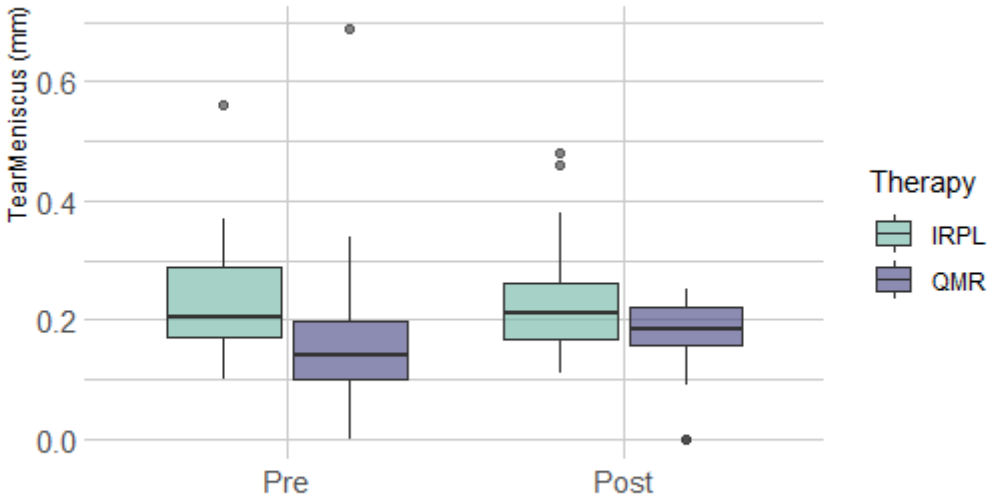
Tear lipid layer



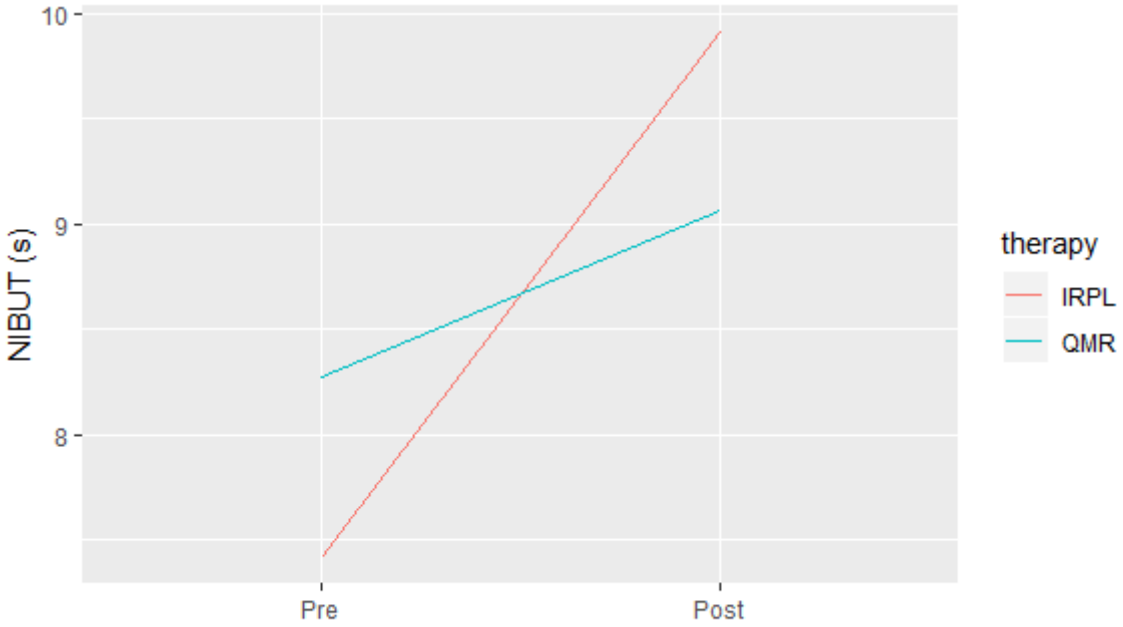


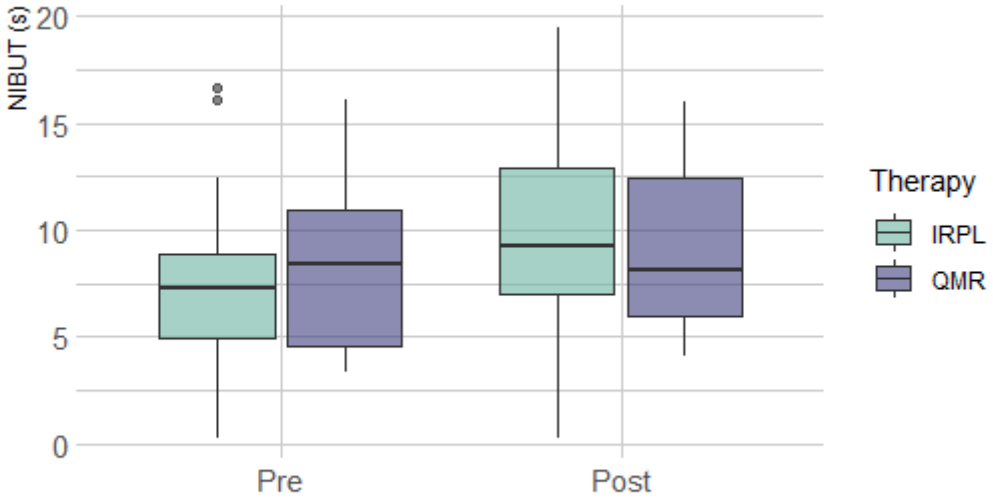
Tear meniscus



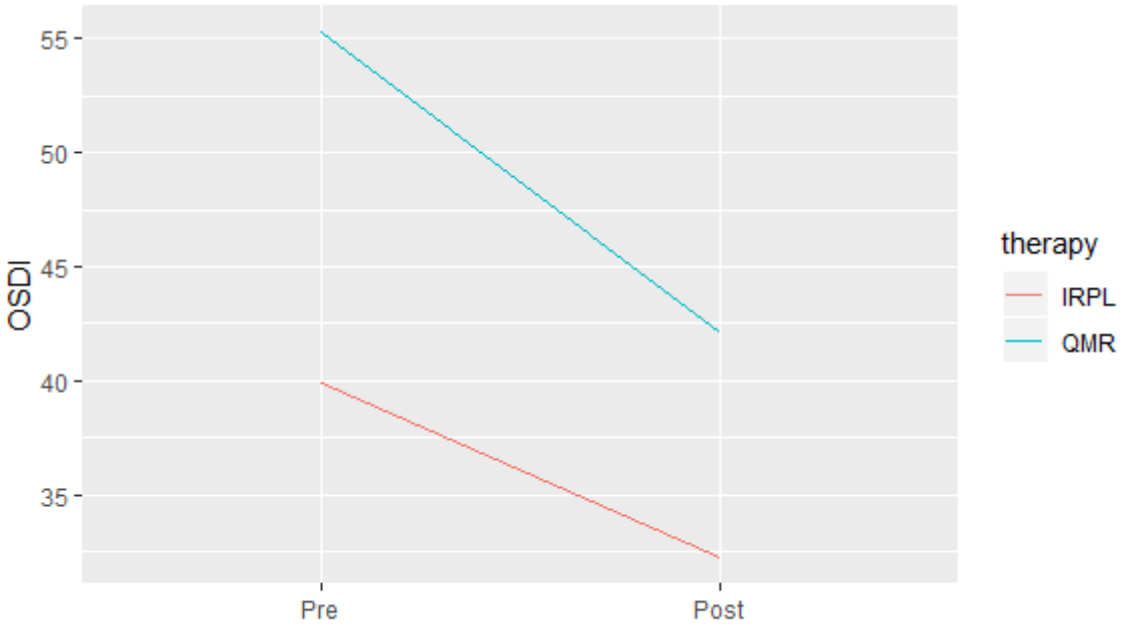


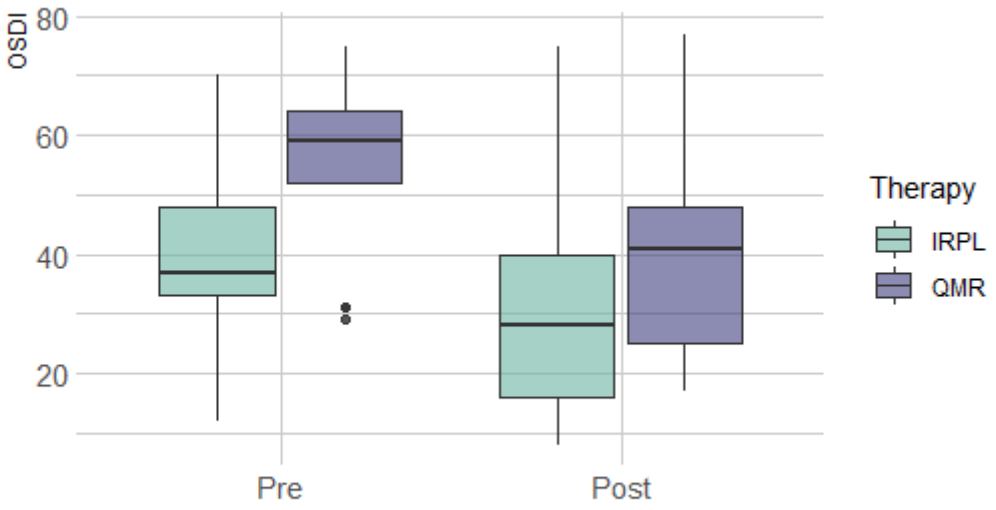
Nibut


10
9
8
NIBUT (s)
Pre
Post
therapy
IRPL
QMR

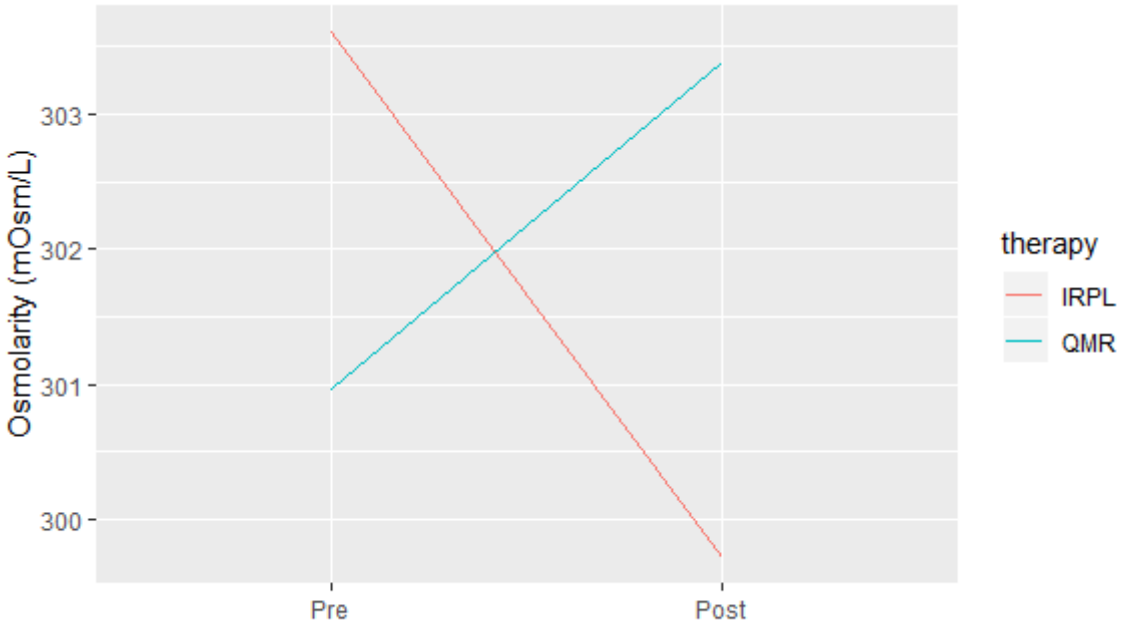

NIBUT (s)
20
15
10
5
0
Pre
Post
Therapy
IRPL
QMR

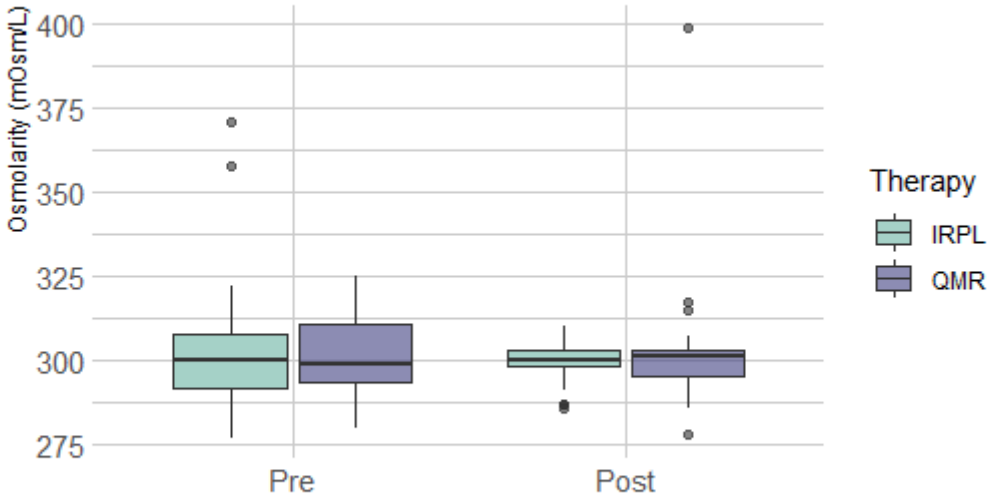
OSDI


55
50
45
40
35
OSDI
Pre
Post
therapy
IRPL
QMR


80
60
40
20
OSDI
Pre
Post
Therapy
IRPL
QMR

Osmolarity


Osmolarity (mOsm/L)
303
302
301
300
Pre
Post
therapy
IRPL
QMR


Osmolarity (mOsm/L)
400
375
350
325
300
275
Pre
Post
Therapy
IRPL
QMR

6 Discussion

The values found before the treatments were consisted with the literature concerning the etiology of the disease; the patients affected mainly by ADDE presented lower values of tear meniscus and OSDI, while the EDE group reported lower results of LLT, Nibut and osmolarity.

The thickness of the tear lipid layer, the NIBUT and the osmolarity of the tear film were most affected by the IRPL® therapy.

The tear meniscus had a similar improvement with both therapies, even if the starting values of the ADDE group were quite lower.

The OSDI score decreased both ways, although the QMR® therapy seemed to be slightly more effective.

The findings were in agreement with the outcomes of other articles.

A study conducted in 2019 by Vigo, Taroni et al. demonstrated that the IRPL® therapy had a great impact on NIBUT, LLT and osmolarity. [44]

Another study conducted in 2020 on the efficacy of the IRPL® therapy on patients with MGD showed considerable improvement in TBT, Schirmer test and OSDI score. [45]

7 Conclusions

Both therapies, combined with the anti-inflammatory and hydrating therapy, showed great results. The percentage increases of the indicators were correlated to the etiology of the disease.

The thickness of the tear lipid layer, the NIBUT and the osmolarity of the tear film were most affected by the IRPL® therapy.

The tear meniscus had a similar improvement with both therapies, though the starting values were quite lower in the QMR® group.

The OSDI score decreases both ways, even if the QMR® therapy seemed to be slightly more effective.

Appendix

Tables of the results

QMR® therapy

Pat nr.	Sex	Age	Eye	Lipid layer			Tear meniscus			NIBUT		
				pre	post		pre	post		pre	post	
1	F	48	OD	15	80	++	0,15	0,22	47%	16,1	15,9	-1%
			OS	30	30-80	+	0,23	0,21	-9%	15,5	16,0	3%
2	F	48	OD	30	30-80	+	0,26	0,22	-15%	7,7	13,5	75%
			OS	30-80	80-120	+	0,26	0,21	-19%	13,2	14,0	6%
3	F	47	OD	30-80	30-80	=	0,10	0,22	120%	12,0	12,6	5%
			OS	15	80-120	+++	0,13	0,17	31%	13,1	13,4	2%
4	M	51	OD	30-80	30-80	=	0,13	0,09	-31%	4,0	7,6	90%
			OS	30-80	30-80	=	0,08	0,11	38%	4,5	8,2	82%
5	F	44	OD	30	80-120	++	0,06	0,16	167%	5,1	8,1	59%
			OS	30	30-80	+	0,10	0,18	80%	7,6	12,4	63%
6	F	65	OD	30-80	30-80	=	0,08	0,16	100%	3,7	11,9	220%
			OS	30-80	30-80	=	0,12	0,17	42%	4,0	12,8	220%
7	F	36	OD	30-80	30-80	=	0,14	0,20	43%	6,7	7,1	6%
			OS	80-120	80	=	0,15	0,25	67%	8,6	9,3	8%
8	M	52	OD	30-80	30	=	0,13	0,15	15%	4,0	4,6	15%
			OS	30-80	30	=	0,08	0,11	38%	4,5	6,0	33%
9	F	40	OD	30-80	30	=	0,34	0,24	-29%	8,6	9,6	12%
			OS	30-80	15	-	0,27	0,20	-26%	10,5	9,6	-9%
10	M	40	OD	30-80	80-120	+	0,13	0,24	85%	11,8	4,1	-65%
			OS	30-80	80-120	+	0,22	0,25	14%	10,6	5,6	-47%
11	F	32	OD	30	80-120	++	0,16	0,22	38%	8,7	6,7	-23%
			OS	30-80	80-120	+	0,15	0,22	47%	8,2	8,2	0%
12	F	47	OD	30-80	80-120	+	0,14	0,19	36%	4,6	5,5	20%
			OS	30-80	80-120	+	0,15	0,17	13%	3,4	5,7	68%
13	F	39	OD	30-80	80-120	+	0,19	0,11	-42%	9,5	6,7	-29%
			OS	80-120	80-120	=	0,69	0,18	-74%	12,2	6,8	-44%
14	F	50	OD	80-	30	-	0,00	0,00	#####	8,7	5,8	-33%

			OS	120 80- 120	30	-	0,00	0,00	#####	4,6	6,0	30%
Mean		45,6					0,18	0,19	30%	8,3	9,1	27%
SD		7,4					0,12	0,05	54%	3,8	3,5	67%

Pat nr.	Sex	Age	Eye	OSDI			Osmolarity		
				pre	post		pre	post	
1	F	48	OD	52	44	-15%	292	290	-1%
			OS	52	44	-15%	284	295	4%
2	F	48	OD	52	48	-8%	286	286	0%
			OS	52	48	-8%	280	278	-1%
3	F	47	OD	31	30	-3%	285	304	7%
			OS	31	30	-3%	292	301	3%
4	M	51	OD	64	77	20%	311	302	-3%
			OS	64	77	20%	314	296	-6%
5	F	44	OD	58	25	-57%	294	290	-1%
			OS	58	25	-57%	299	298	0%
6	F	65	OD	62	22	-65%	293	301	3%
			OS	62	22	-65%	294	303	3%
7	F	36	OD	29	38	31%	305	302	-1%
			OS	29	38	31%	300	399	33%
8	M	52	OD	64	73	14%	311	301	-3%
			OS	64	73	14%	314	307	-2%
9	F	67	OD	72	46	-36%	320	302	-6%
			OS	72	46	-36%	315	301	-4%
10	M	40	OD	31	17	-45%	325	305	-6%
			OS	31	17	-45%	325	303	-7%
11	F	32	OD	60	21	-65%	299	295	-1%
			OS	60	21	-65%	300	295	-2%
12	F	47	OD	75	75	0%	295	317	7%
			OS	75	75	0%	300	315	5%
13	F	39	OD	52	27	-48%	295	300	2%
			OS	52	27	-48%	297	302	2%
14	F	40	OD	72	46	-36%			
			OS	72	46	-36%			
Mean		46,9		55	42	-22%	301	303	1%
SD		9,9		15	20	32%	12	21	8%

IRPL® therapy

Pat nr.	Sex	Age	Eye	Lipid layer			Tear meniscus			NIBUT		
				pre	post		pre	post		pre	post	
1	F	38	OD	30	15	-	0,29	0,30	3%	7,5	8,6	15%

			OS	30	15	-	0,23	0,14	-39%	0,3	0,3	3%
2	M	67	OD	30	80	+	0,18	0,48	167%	4,9	4,0	-18%
			OS	30	80-120	++	0,15	0,46	207%	4,3	3,8	-12%
3	F	48	OD	30-80	30-80	=	0,10	0,22	120%	9,7	18,0	86%
			OS	15	80-120	+++	0,13	0,17	31%	7,4	13,1	77%
4	F	44	OD	15	30-80	++	0,11	0,27	145%	4,5	3,4	-24%
			OS	15	30-80	++	0,13	0,21	62%	3,4	3,7	9%
5	F	69	OD	30-80	30-80	=	0,29	0,21	-28%	5,0	12,9	158%
			OS	30-80	30-80	=	0,31	0,15	-52%	4,8	15,6	225%
6	M	53	OD	15	30-80	++	0,27	0,26	-4%	16,1	19,5	21%
			OS	15	30-80	++	0,30	0,27	-10%	16,7	17,7	6%
7	F	32	OD	30-80	30	-	0,18	0,16	-11%	4,2	8,6	105%
			OS	30-80	30-80	=	0,24	0,20	-17%	4,2	7,1	69%
8	F	62	OD	30	30	=	0,23	0,32	39%	5,9	6,6	12%
			OS	30-80	15	-	0,19	0,25	32%	8,7	8,2	-6%
9	F	52	OD	30-80	30-80	=	0,17	0,13	-24%	5,9	6,6	12%
			OS	30-80	30-80	=	0,20	0,11	-45%	8,7	8,2	-6%
10	F	33	OD	15	80-120	+++	0,22	0,21	-5%	8,1	11,6	43%
			OS	15	80	++	0,21	0,26	24%	5,0	13,4	168%
11	F	29	OD	30	30-80	+	0,18	0,23	28%	7,9	6,7	-15%
			OS	30-80	30-80	=	0,18	0,24	33%	9,5	8,7	-8%
12	F	46	OD	30	30	=	0,18	0,20	11%	6,1	7,2	18%
			OS	30	30-80	+	0,11	0,17	55%	10,5	7,8	-26%
13	F	69	OD	30-80	30-80	=	0,29	0,21	-28%	5,0	12,9	158%
			OS	30-80	30-80	=	0,31	0,15	-52%	4,8	15,6	225%
14	F	34	OD	30	30-80	+	0,20	0,26	30%	6,1	13,4	120%
			OS	15	15	=	0,14	0,21	50%	5,7	15,9	179%
15	F	51	OD	30-80	30	-	0,34	0,28	-18%	8,8	10,6	20%
			OS	30-80	30	-	0,33	0,29	-12%	12,4	9,0	-27%
16	M	49	OD	30-80	80-120	+	0,17	0,21	24%	9,3	10,7	15%
			OS	30-80	80-120	+	0,21	0,16	-24%	7,6	12,0	58%
17	F	46	OD	30-80	30	-	0,13	0,13	0%	10,0	9,6	-4%
			OS	30-80	30	-	0,21	0,14	-33%	12,4	5,7	-54%
18	F	70	OD	30	80-120	++	0,37	0,23	-38%	8,5	9,7	14%
			OS	30-80	80-120	=	0,56	0,38	-32%	7,1	10,5	48%
Mean		49,8					0,21	0,25	40%	6,7	9,9	52%
SD		12,5					0,07	0,10	79%	4,4	4,5	77%

Pat nr.	Sex	Age	Eye	OSDI			Osmolarity		
				pre	post		pre	post	
1	F	38	OD	70	52	-26%	311	301	-3%
			OS	70	52	-26%	308	298	-3%
2	M	67	OD	56	27	-52%	307	303	-1%
			OS	56	27	-52%	298	305	2%
3	F	48	OD	31	30	-3%	285	304	7%
			OS	31	30	-3%	292	301	3%

4	F	44	OD	48	14	-71%	292	304	4%
			OS	48	14	-71%	296	304	3%
5	F	69	OD	35	22	-37%	320	300	-6%
			OS	35	22	-37%	322	310	-4%
6	M	53	OD	37	37	0%	299	299	0%
			OS	37	37	0%	303	298	-2%
7	F	32	OD	27	29	7%	371	299	-19%
			OS	27	29	7%	358	299	-16%
8	F	62	OD	33	40	21%	301	302	0%
			OS	33	40	21%	300	299	0%
9	F	67	OD	50	35	-30%	304	307	1%
			OS	50	35	-30%	314	297	-5%
10	F	33	OD	33	15	-55%	302	287	-5%
			OS	33	15	-55%	292	287	-2%
11	F	29	OD	19	8	-58%	301	299	-1%
			OS	19	8	-58%	308	298	-3%
12	F	46	OD	44	65	48%	292	300	3%
			OS	44	65	48%	291	291	0%
13	F	69	OD	35	22	-37%	320	300	-6%
			OS	35	22	-37%	322	310	-4%
14	F	34	OD	12	16	33%	300	301	0%
			OS	12	16	33%	293	299	2%
15	F	51	OD	65	54	-17%	305	298	-2%
			OS	65	54	-17%	300	309	3%
16	M	49	OD	46	75	63%	282	302	7%
			OS	46	75	63%	297	304	2%
17	F	46	OD	37	15	-59%	292	303	4%
			OS	37	15	-59%	295	299	1%
18	F	70	OD	40	25	-38%	280	287	3%
			OS	40	25	-38%	277	286	3%
Mean		53,2		40	32	-17%	304	300	-1%
SD		12,5		14	18	39%	19	6	5%

Declaration

I declare that this thesis was composed by myself and that this work has not been submitted for any other degree or processional qualification except as specified.

References

[1] Craig JP, Nichols KK, Akpek EK*, et al.* TFOS DEWS II Definition and Classification Report. The Ocular Surface 2017; 15(3): 276–83
[https://doi.org/10.1016/j.jtos.2017.05.008]

[2] Stapleton F, Alves M, Bunya VY*, et al.* TFOS DEWS II Epidemiology Report. The Ocular Surface 2017; 15(3): 334–65
[https://doi.org/10.1016/j.jtos.2017.05.003]

[3] Ahn JM, Lee SH, Rim THT*, et al.* Prevalence of and Risk Factors Associated With Dry Eye: The Korea National Health and Nutrition Examination Survey 2010–2011. American Journal of Ophthalmology 2014; 158(6): 1205-1214.e7
[https://doi.org/10.1016/j.ajo.2014.08.021]

[4] Schaumberg DA, Uchino M, Christen WG, Semba RD, Buring JE, Li JZ. Patient reported differences in dry eye disease between men and women: impact, management, and patient satisfaction. PLoS ONE 2013; 8(9): e76121
[https://doi.org/10.1371/journal.pone.0076121][PMID: 24098772]

[5] Tong L, Saw S-M, Lamoureux EL*, et al.* A Questionnaire-Based Assessment of Symptoms Associated with Tear Film Dysfunction and Lid Margin Disease in an Asian Population (vol 16, pg 31, 2009). OPHTHALMIC EPIDEMIOLOGY 2009; 16(2): 142.

[6] Snellingen T, Rao GN, Shrestha JK, Huq F, Cheng H. Quantitative and morphological characteristics of the human corneal endothelium in relation to age, gender, and ethnicity in cataract populations of South Asia. Cornea 2001; 20(1): 55–8.

[7] Brandt JE, Priori R, Valesini G, Fairweather D. Sex differences in Sjögren's syndrome: a comprehensive review of immune mechanisms. Biol Sex Differ 2015; 6: 19
[https://doi.org/10.1186/s13293-015-0037-7][PMID: 26535108]

[8] Liew MSH, Zhang M, Kim E, Akpek EK. Prevalence and predictors of Sjogren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. Br J Ophthalmol 2012; 96(12): 1498–503
[https://doi.org/10.1136/bjophthalmol-2012-301767][PMID: 23001257]

[9] Obata H, Yamamoto S, Horiuchi H, Machinami R. Histopathologic Study of Human Lacrimal Gland. Ophthalmology 1995; 102(4): 678–86
[https://doi.org/10.1016/S0161-6420(95)30971-2]

[10] Shigeta K-I, Takegoshi H, Kikuchi S. Sex and age differences in the bony nasolacrimal canal: an anatomical study. Arch Ophthalmol 2007; 125(12): 1677–81
[https://doi.org/10.1001/archopht.125.12.1677][PMID: 18071122]

[11] Dumbleton K, Caffery B, Dogru M*, et al.* The TFOS International Workshop on Contact Lens Discomfort: report of the subcommittee on epidemiology. Invest Ophthalmol Vis Sci 2013; 54(11): TFOS20-36
[https://doi.org/10.1167/iovs.13-13125][PMID: 24058130]

[12] Hwang SH, Choi Y-H, Paik HJ, Wee WR, Kim MK, Kim DH. Potential Importance of Ozone in the Association Between Outdoor Air Pollution and Dry Eye Disease in South Korea. JAMA Ophthalmol 2016; 134(5): 503–10
[https://doi.org/10.1001/jamaophthalmol.2016.0139][PMID: 26967354]

[13] Uchino M, Schaumberg DA, Dogru M*, et al.* Prevalence of dry eye disease among Japanese visual display terminal users. Ophthalmology 2008; 115(11): 1982–8 [https://doi.org/10.1016/j.ophtha.2008.06.022][PMID: 18708259]

[14] Albietz JM, Lenton LM, McLennan SG. Dry eye after LASIK: comparison of outcomes for Asian and Caucasian eyes. Clin Exp Optom 2005; 88(2): 89–96 [https://doi.org/10.1111/j.1444-0938.2005.tb06673.x][PMID: 15807640]

[15] Najafi L, Malek M, Valojerdi AE*, et al.* Dry eye and its correlation to diabetes microvascular complications in people with type 2 diabetes mellitus. J Diabetes Complicat 2013; 27(5): 459–62 [https://doi.org/10.1016/j.jdiacomp.2013.04.006][PMID: 23726741]

[16] Willcox MDP, Argüeso P, Georgiev GA*, et al.* TFOS DEWS II Tear Film Report. The Ocular Surface 2017; 15(3): 366–403 [https://doi.org/10.1016/j.jtos.2017.03.006]

[17] IDRA - Ocular Surface Analyser | Clarion Medical Technologies; 2020 [cited 2020 March 17] Available from: URL: https://www.clarionmedical.com/en-CA/Vision/Diagnostics/SBM-Sistemi-Ocular-Surface-Analyzer-O-S-A-1#Interferometry.

[18] Kulovesi P, Telenius J, Koivuniemi A*, et al.* Molecular organization of the tear fluid lipid layer. Biophys J 2010; 99(8): 2559–67 [https://doi.org/10.1016/j.bpj.2010.08.001][PMID: 20959097]

[19] Corfield AP. Mucins: a biologically relevant glycan barrier in mucosal protection. Biochim Biophys Acta 2015; 1850(1): 236–52 [https://doi.org/10.1016/j.bbagen.2014.05.003][PMID: 24821013]

[20] Argüeso P, Guzman-Aranguez A, Mantelli F, Cao Z, Ricciuto J, Panjwani N. Association of cell surface mucins with galectin-3 contributes to the ocular surface epithelial barrier. Journal of Biological Chemistry 2009; 284(34): 23037–45.

[21] TFOS DEWS II REPORT - Tear Film - TFOS - Tear Film & Ocular Surface Society; 2020.000Z [cited 2020 May 21] Available from: URL: https://www.tfosdewsreport.org/report-tear_film/82_36/en/.

[22] Bron AJ, Paiva CS de, Chauhan SK*, et al.* TFOS DEWS II pathophysiology report. The Ocular Surface 2017; 15(3): 438–510 [https://doi.org/10.1016/j.jtos.2017.05.011][PMID: 28736340]

[23] Idra Description – SBM Sistemi; 2020 [cited 2020 March 24] Available from: URL: https://www.sbmsistemi.com/v19/idra-description/.

[24] Wolffsohn JS, Arita R, Chalmers R*, et al.* TFOS DEWS II Diagnostic Methodology report. The Ocular Surface 2017; 15(3): 539–74 [https://doi.org/10.1016/j.jtos.2017.05.001][PMID: 28736342]

[25] Guillon J-P. Non-invasive tearscope plus routine for contact lens fitting. Contact Lens and Anterior Eye 1998; 21: S31-S40 [https://doi.org/10.1016/S1367-0484(98)80035-0]

[26] Vidas Pauk S, Petriček I, Jukić T*, et al.* NONINVASIVE TEAR FILM BREAK-UP TIME ASSESSMENT USING HANDHELD LIPID LAYER EXAMINATION INSTRUMENT. Acta Clin Croat 2019; 58(1): 63–71 [https://doi.org/10.20471/acc.2019.58.01.09][PMID: 31363327]

[27] Kaur S, Ho C, Abdul Mutalib H, Ghazali R. The Relationship Between Tear Ferning Patterns and Non-invasive Tear Break-up Time in Normal Asian Population. Journal of Optometry 2015; 9 [https://doi.org/10.1016/j.optom.2015.10.004]

[28] Saleh TA, McDermott B, Bates AK, Ewings P. Phenol red thread test vs Schirmer's test: a comparative study. Eye (Lond) 2006; 20(8): 913–5 [https://doi.org/10.1038/sj.eye.6702052][PMID: 16082393]

[29] Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. Clinical ophthalmology (Auckland, NZ) 2015; 9: 2039.

[30] Bron AJ, Argüeso P, Irkec M, Bright FV. Clinical staining of the ocular surface: mechanisms and interpretations. Progress in retinal and eye research 2015; 44: 36–61.

[31] Khan-Lim D, Berry M. Still confused about rose bengal? Current eye research 2004; 29(4-5): 311–7.

[32] Eom Y, Lee J-S, Kang S-Y, Kim HM, Song J-S. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. American Journal of Ophthalmology 2013; 155(6): 1104–10.

[33] Baudouin C, Aragona P, van Setten G*, et al.* Diagnosing the severity of dry eye: a clear and practical algorithm. British journal of ophthalmology 2014; 98(9): 1168–76.

[34] Jones L, Downie LE, Korb D*, et al.* TFOS DEWS II Management and Therapy Report. The Ocular Surface 2017; 15(3): 575–628 [https://doi.org/10.1016/j.jtos.2017.05.006][PMID: 28736343]

[35] Fortes MB, Diment BC, Di Felice U*, et al.* Tear fluid osmolarity as a potential marker of hydration status. Med Sci Sports Exerc 2011; 43(8): 1590–7 [https://doi.org/10.1249/MSS.0b013e31820e7cb6][PMID: 21233774]

[36] Vivino FB, Al-Hashimi I, Khan Z*, et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. Archives of internal medicine 1999; 159(2): 174–81.

[37] Akyol-Salman I. Effects of autologous serum eye drops on corneal wound healing after superficial keratectomy in rabbits. Cornea 2006; 25(10): 1178–81 [https://doi.org/10.1097/01.ico.0000208817.40237.8c][PMID: 17172894]

[38] López-García JS, García-Lozano I, Rivas L, Giménez C, Acera A, Suárez-Cortés T. Effects of autologous serum eye drops on conjunctival expression of MUC5AC in patients with ocular surface disorders. Cornea 2016; 35(3): 336–41.

[39] Technology - Telea Medical; 2020 [cited 2020 March 26] Available from: URL: https://teleamedical.com/en/technology/.

[40] Sella S, Adami V, Amati E*, et al.* In-vitro analysis of Quantum Molecular Resonance effects on human mesenchymal stromal cells. PLoS ONE 2018; 13(1): e0190082 [https://doi.org/10.1371/journal.pone.0190082][PMID: 29293552]

[41] Fraccalvieri M, Salomone M, Di Santo C, Ruka E, Morozzo U, Bruschi S. Quantum molecular resonance technology in hard-to-heal extremity wounds: histological and clinical results. Int Wound J 2017; 14(6): 1313–22 [https://doi.org/10.1111/iwj.12805][PMID: 28857452]

[42] Pedrotti E, Bosello F, Fasolo A*, et al.* Transcutaneous periorbital electrical stimulation in the treatment of dry eye. British journal of ophthalmology 2017; 101(6): 814 [https://doi.org/10.1136/bjophthalmol-2016-308678]

[43] Ferrari G, Colucci A, Barbariga M, Ruggeri A, Rama P. High Frequency Electrotherapy for the Treatment of Meibomian Gland Dysfunction. Cornea 2019; 38(11): 1424–9 [https://doi.org/10.1097/ICO.0000000000002063][PMID: 31356415]

[44] Vigo L, Taroni L, Bernabei F*, et al.* Ocular Surface Workup in Patients with Meibomian Gland Dysfunction Treated with Intense Regulated Pulsed Light. Diagnostics (Basel) 2019; 9(4) [https://doi.org/10.3390/diagnostics9040147][PMID: 31614910]

[45] Karaca EE, Evren Kemer Ö, Özek D. Intense regulated pulse light for the meibomian gland dysfunction. Eur J Ophthalmol 2020; 30(2): 289–92 [https://doi.org/10.1177/1120672118817687][PMID: 30514116]