Chapter

Intense Pulse Laser Therapy and Dry Eye Disease

Sana Niazi and Farideh Doroodgar

Abstract

The high and increasing prevalence of Dry Eye Disease (DED) highlights the need for new treatment treatments and more effective management strategies for this chronic disease. After training, lid grooming, and various ocular lubricants, the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Management and Therapy Subcommittee recently proposed Intense Pulsed Light (IPL) as the second phase of therapy. Brief flashes of non-coherent light (400–1,200 nm) are delivered to the skin's surface using IPL technology. Toyos et al. found in 2005 that rosacea sufferers who were treated with IPL in the periocular region had a significant increase in their dry eye symptoms.

Keywords: intense pulse laser, dry eye disease, meibomian gland, MGD

1. Introduction

The lipid layer of the tear film is deficient when the activity of the meibomian glands is impaired, which protects the aqueous layer of the tear film and prevents it from evaporating. The cornea is exposed as the tear film is destabilized, which leads to the onset of DED symptoms [1]. Since facial rosacea is closely linked to Meibomian Gland Dysfunction (MGD) and blepharitis [1], the IPL intervention of rosacea may have removed pathological telangiectasia periocular area, eliminating a significant source of inflammation to the eyelids and, as a result, alleviating MGD and dry eye problems. Since Toyos' original publication, a slew of surveys and two Randomized Controlled Trials (RCT) [1, 2] have added to the body of evidence demonstrating the effectiveness (and safety) of IPL therapy for patients with DED caused by MGD [3]. Most of these studies showed that symptoms and a wide range of DED/MGD signals enhanced in these patients, such as Tear Breakup Time (TBUT), Non-Invasive Breakup Time (NIBUT), Schirmer examination, presence of phEx™. Tear inflammatory markers, lipid layer grade, lipid layer thickness, Corneal Fluorescein Staining (CFS), meibum consistency, meibum expressibility, and lid margin anomalies were investigated.

2. Definition and history of DED

Dry Eye Syndrome or Disease (DES or DED) is a chronic Ocular Surface Disease (OSD) that influences vision and, consequently, quality of life similar to angina pectoris.

The prevalence of DE varies by region and population, ranging from 5–50% and up to 75%. Female gender, Age, excessive cold or hot weather, low relative humidity,

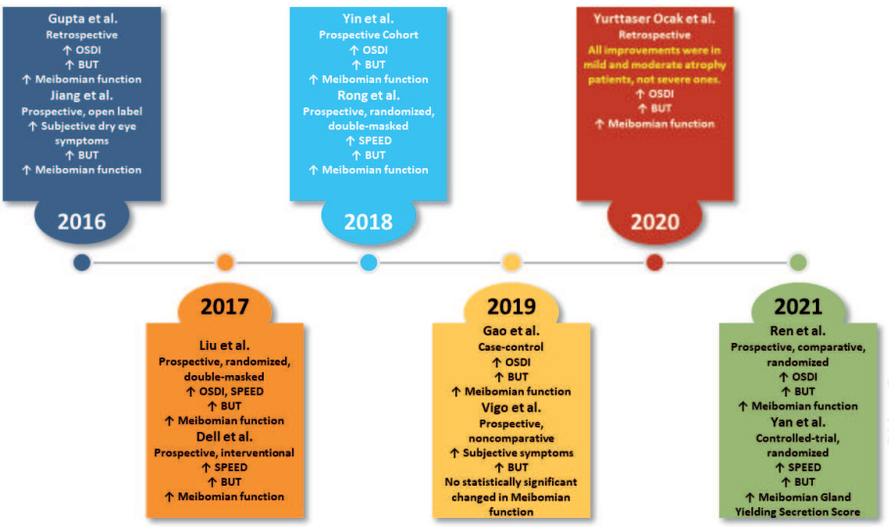

Figure 1.
Timeline diagram: IPL for DED treatment; ↑: Improvement, OSDI: Ocular surface disease index, BUT: Break up time, SPEED: Standard patient evaluation of eye dryness questionnaire.

proximity to video monitor terminals, contact lens wear, history of refractive surgery, smoking, and prescriptions are some risk factors [4–13].

Geographical area, research demographic differences, and a lack of consistent diagnosis criteria are thought to cause the significant disparity of prevalence worldwide (**Figure 1**) [13].

3. Diagnose of DED

There is not a gold standard for diagnosing dry eye disease. However, evaluations can arise from the following methods:

3.1 Standard patient evaluation of eye dryness (SPEED) questionnaire

This validated questionnaire [1, 14] asked the subject to grade the frequency and severity of four symptoms categories: (1) dryness, grittiness, or scratchiness; (2) soreness or irritation; (3) burning or watering; and (4) eye fatigue. For each of these symptom categories, the subject subs-cored the frequency using a 4-point scale (0 = never, 1 = sometimes, 2 = often, 3 = constant), and sub-scored the severity using a 5-point scale (0 = none, 1 = tolerable, 2 = uncomfortable, 3 = bothersome, 4 = intolerable). The SPEED score was calculated as the sum of these eight sub-scores. A SPEED score ≥ of 10 is widely accepted as indicating severe DED symptoms, 12. A cut-off value around six is often used to distinguish between asymptomatic/mild and moderate/severe symptoms.

3.2 Corneal fluorescein staining (CFS)

Assessment of corneal staining was evaluated as follow: [15]. Immediately following TBUT measurement and taking advantage of the residual staining in the ocular surface, the examiner observed four anatomical quadrants of the cornea (temporal superior, temporal inferior, nasal superior, nasal inferior) under the slit-lamp. Each quadrant was sub-scored using a 4-point scale; 0: no staining, 1: 1–30 instances of punctate staining, 2: 30 instances of punctate staining, without infused lesions or ulcers, or 3: the existence of infused lesions or ulcers. The sum of these

four sub-scores, ranging from 0 to 12, defined the CFS score. The CFS score was evaluated at baseline (BL) and follow-up (FU).

3.3 Composite eyelid score (CES) and change of compound eyelid score (CCES)

A Composite Eyelid Score (CES) was compounded based on the presence or absence of five abnormal anatomical features of the eyelids: (1) hyperemia of anterior lid margin; (2) thicken lid margin; (3) rounded lid margin; (4) hyper-keratinization of the lid margin; and (5) telangiectasia around meibomian gland orifices.

These five features were evaluated at BL and FU. Each one was sub-scored 1 if the abnormality was present, or 0 otherwise. In the analysis, CES was calculated as the sum of these five sub-scores, thus ranging from 0 (all five features absent) to 5 (all five features present). At FU, the examiner used photos of the eyelids captured at BL to determine whether there was an improvement (+1), no change (0), or a deterioration (21) for each of these features. The sum of these five sub-scores, ranging from 25 (if all five features deteriorated) to +5 (if all five features improved), was defined as the Change in CES (CCES).

3.4 Tear breakup time (TBUT)

The diagnosis subcommittee on the International Workshop on MGD proposed that TBUT ranges of 1 to 3 sec, 3 to 5 sec, and 5 to 7 sec indicate moderate, mild, and minimal severity levels, respectively.

3.5 Ocular surface disease index (OSDI)

OSDI (Allergan, Inc., Irvine, CA) is a frequently used instrument to assess DE and provides a quantifiable assessment of DE symptom frequency and the impact of these symptoms on vision-related functioning. It contains 12 items, and the score can range from 0 (no symptoms) to 100 (severe symptoms) points; 0 to 12 represents normal, 13 to 22 represents mild DED, 23 to 32 represents moderate DED, and greater than 33 represents severe DED.

3.6 Tear film lipid layer (TFLL) quality by TFLL interferometry

Noninvasive TFLL quality assessment was performed with DR-1 (Kowa, Nagoya, Japan). Yokoi DE severity grading system was performed. Grade 1: somewhat gray color, uniform distribution; grade 2: rather gray color, nonuniform distribution; grade 3: a few colors, nonuniform distribution; grade 4: many colors, nonuniform distribution; and grade 5: corneal surface partially. 24 of refractive, refractive.

3.7 Meibum gland (MG)

The quality of the meibum was assessed by expressing the meibomian glands with the Meibomian Gland Evaluator (MGE; Tear Science, Inc., Morrisville, NC), a standardized instrument developed by Korb et al., and then evaluating the quality of meibomian secretions [16]. MGE was applied for 15 glands (5 nasal+5 central+5 temporals) along the lower eyelid. For each gland, the examiner sub-scored the quality of the expressed meibum using a four-point scale: 0 (no secretion), 1 (inspissated or toothpaste-like secretion), 2 (cloudy liquid secretion), or 3 (clear liquid secretion). The sum of this 15 subs-cores, ranging from 0 to 45, defined the Meibomian Gland Yielding Secretion Score (MGYSS). MGYSS was evaluated at BL and FU [1].

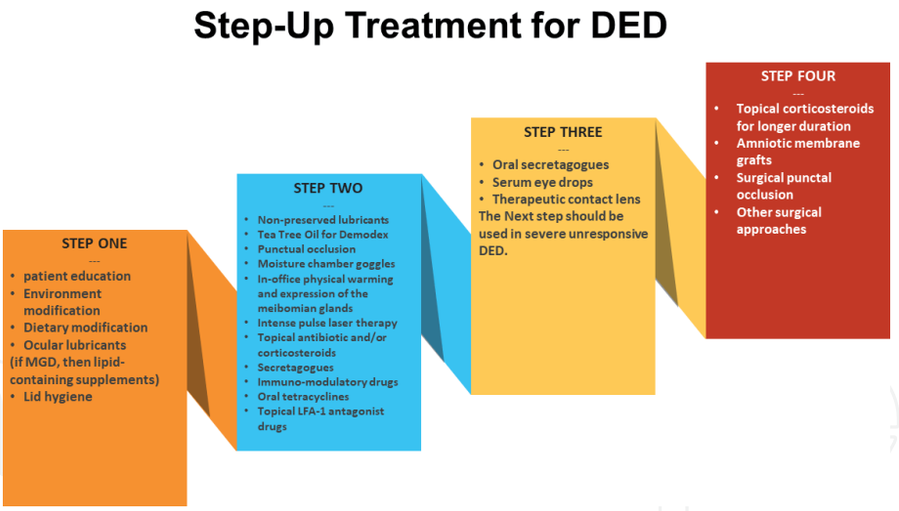

Figure 2.
Step-up treatment for DED.

4. Enhanced management and treatment for dry eye (DE)

The 2017 TFOS DEWS II provides guidelines for a stepped treatment protocol for DE, which targets each abnormality in the Tear Film-Oriented Diagnosis (TFOD) approach (**Figure 2**) [17–19].

4.1 Drug therapy

The inflammation, along with dry eye usually treats with topical corticosteroids. In cases with little satisfaction, a second-line drug is Topical cyclosporine A [20].

Lifitegrast 5% is a second topical anti-inflammatory ocular drop that got FDA approved In July 2016 for DED.

Other drugs include lipid-containing eye drop, artificial tear formulations with nanostructured lipid carriers as a synthetic TF in vivo, and castor oil emulsions are promising as Preservative-free drops, omega-3 fatty acid, supplementation, serum tears, topical azithromycin, oral and topical HA oral doxycycline, topical 3% Diquafosol and cholinergic.

4.2 Procedures

Intense pulse light, lacrimal plug, lid massage and probing and expression of MG, warm compresses or vectored thermal pulsation, and amniotic membrane biologic corneal bandage lens have evolved to improve the signs and symptoms of DE.

5. Definition of IPL

An intense pulsed light (IPL) system is a non-laser large source of light that produces a non-coherent light output of broad wavelength, usually in the range of 500 to 1200 nm, using a high-performance flashbulb. Many modern tools create light pulses by transmitting bursts of electricity running through a xenon gas-filled chamber [21–23].

The usage of IPL in medicine is based on the fact that unique load transfer targets (chromophores) can absorb photons from a wide range of light wavelengths (absorptive band) without being specifically targeted by their highest absorption.

The IPL uses targeted photo thermolysis, in which thermally induced radiation harm is restricted to the selected epidermis and dermis textured targets at the cellular or tissue structural difference [24]. Toyos et al. reported improvements in MGD associated Dry Eye Disease (DED) cases in 2002 and was the first published report on using an IPL system in ophthalmology [25, 26]. IPL dilates the capillaries and causes them to involute using electromagnetic waves of specific wavelengths [27]. This causes the leaked inflammatory responses to be suppressed, interrupting the vicious cycle of inflammation and enhancing dry eye signs. In most cases, it also functions with the aid of thermal pulsation [28]. When chronic inflammation occurs, the structure of the meibum improves to contain many monounsaturated fats. Those fats have a melting point of close to 45°C, which is greater than body temp [29]. This meibum does not melt through the lipid coating of the tear film as it should, clogging the glands. Thermal pulsation treatment liquefies the meibum and clears the glands by combining continuous pressure and heat. Traditional manual expressing glands is ineffective, inconvenient for patients, and could result in scarring [29]. Thermal pulsation is an effective and safe treatment option. With these processes in mind, we have deduced that IPL will help alleviate the symptoms of DE [21, 30].

6. Causes of dry eye and applications of IPL

The surface epithelial and glandular tissues (cornea, bulbar and palpebral conjunctiva, lacrimal and accessory eyelid), the glycocalyx, and the tear film consist of the microenvironment of the ocular surface [31].

Systemic disorders such as rheumatoid arthritis, Sjogren's syndrome, thyroid eye disease, sleep apnea [32], cicatrizing disease of the conjunctiva, contact lens wear, and refractive laser surgery are the most underlying associated conditions with Refractory DE. DE signs after Laser-Assisted in Situ Keratomileuses (LASIK) are not standardized. There is a continuum of disorders such as neurotrophic disease, tear film dysfunction, aqueous tear deficiency, and neuropathic pain conditions. Cutting the corneal nerves during Laser ablation and creating the flap are probable reasons for post-refractive DE. Meibomian glands are adjusted sebaceous glands located inside the lower and upper eyelids, with ducts terminating along the eyelid borders and secreting meibum, contributing directly to the lipid portion [31, 33].

The Tear Film Lipid Layer (TFLL) leads to the tear film's consistency and stabilization. The presence of TFLL on the tear film's exterior layer decreases the tear film's evaporation.

Negative TFLL changes may trigger evaporative DE, as well as symptomatic and clinical ocular surface manifestations [34]. Inflammation and illness TFLL were shown to be slightly lower in post-LASIK eyes, along with worsening DE symptoms and reduced corneal sensitivity [35].

A previous study reported the improvement of refractory DE with polar and nonpolar lipid base, ofloxacin eye ointment [36]. Another study reported the correlation between the severity of DE with lipid layer thickness secondary to increased evaporation as the most common etiologies for increased osmolarity of the tear film [37].

Scanning electron microscopy showed that lipids expressed by the meibomian gland caused extensive damage to gram-positive and gram-negative bacteria and hence acts as a protective barrier against pathogens [38]. Thus, improvement of the TFLL maintains the homeostatic balance by protecting the ocular surface environment. Therefore, the progress of symptoms and reduction of artificial tears after refractive surgery is another positive report about IPL treatment. However, future study elucidates the duration and the optimal dose [39, 40].

7. Mechanisms of IPL for prevention of damage to the ocular surface

A better explanation of the mechanisms of IPL leads to a better treatment plan. Regarding several mechanisms, it would be nice to describe as follow:

Demodex folliculorum and Bacillus oleronius are common inhabitants of human hair follicles and sebaceous glands occasionally found in ocular rosacea. IPL increases mitochondrial activity and wound healing, decreasing lid marginal bacteria and Demodex by photocoagulation, improving elastosis, and connective tissue disorganization that occurs with MGD rosacea to relieve pain (**Figure 3**).

7.1 Effects on mucin and corneal nerve

Mucin plays many essential roles on the ocular surface, including maintaining lacrimal fluid, lubricating the ocular surface to facilitate flat blinking, forming a smooth spherical surface for clear vision, providing an ocular surface shield and trapping and eliminating contaminants and debris [41–43]. The tear film is divided into two layers, with the aqueous layer containing secreted mucin MUC5AC scattered across [42]. Xue et al. discovered no improvements in MU5AC expression after IPL procedures Utilizing conjunctival impression cytology,. IPL therapy has little effect on the density of nerve fibers and dendritic cells in the corneal sub-basal layer, according to research [44].

7.2 Pro- and anti-inflammatory molecule effects, as well as matrix metalloproteinase suppression

Factors that influence tear film stability and osmolarity can cause ocular injury and trigger an inflammatory cascade that leads to a strong immunological reaction, leading to further ocular surface injury, causing a self-perpetuating inflammatory loop [45]. By upregulating anti-inflammatory cytokines, downregulating proinflammatory cytokines, or both, IPL can disrupt the inflammatory cycle. Dry eye's inflammatory cascade is highly complex and little known. Nevertheless, at least part of IPL's positive effect on DED patients may come from messing with the pathology's inflammatory cycle's positive feedback loop [46]. Interference with the inflammatory process by modulating anti-inflammatory factors and Matrix Metalloproteinase (MMP), lowering the turnover of skin epithelial cells, reducing the rate of severe obstruction of the meibomian glands, and improving the levels of active oxidative species all aid in the prevention of dry eye symptoms.

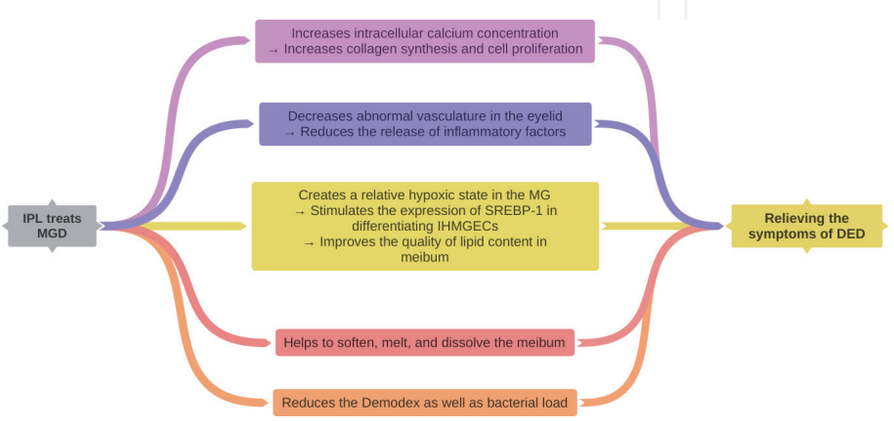

Figure 3.
IPL treats MGD; IHMGEC: Immortalized human MG epithelial cells; SREBP-1: Sterol regulatory element-binding protein 1.

8. Adverse events and advantages

There were no adverse effects with the IPL. Nevertheless, the relationship between Intense Pulsed Light (IPL) and Meibomian Gland Expression (MGX), or Warm Compresses (WC) and MGX, on the one hand, and MGX on the other hand, maybe non-linear and complex. Since IPL can be expensive in some clinics, it's essential to know if persistent eyelid warmth at home accompanied by WC/MGX can produce comparable results as IPL/MGX. However, Broadband Light (BBL) technology has the potential to cause damage. Just transient side changes were reported, such as hyperpigmentation, eyelash thinning, and slight conjunctival abrasion. The lid thinning has been seen by using higher settings than those prescribed in this report, and the suspected abrasion was most likely caused by slight damage caused by the corneal shields in the close eyelids' environment, rather than the BBL therapy itself. Other warnings that can help to reduce the low risk of transient lash thinning include scraping any gel that may couple with the light from the lashes and wrapping a metallic wrap around the edges of the cylinder to keep the treatment confined to the 7 mm circular adaptor's treatment area. To prevent any long-term risks, proper procedure and the use of correctly mounted, well-polished metallic eye shields are critical for corneal protection. It's important to remember that systems vary, and configurations can be tailored to the equipment in use and specific patient characteristics (skin texture, sun sensitivity, light-sensitizing drugs, and so on), with a thorough knowledge of the tissue effects at different settings/parameters [1].

8.1 IPL care has a risk vs. benefit ratio

Gupta et al. proved that IPL therapy for evaporative DED is a safe treatment in a study [47].

IPL appears to be a reliable and successful therapy for patients with evaporative DED, based on changes in quantitative clinical test results and subjective OSDI scoring evidence. The oil flow score and TBUT all increased significantly. There were no significant differences in intraocular pressure or acuity. There were no reports of ocular side effects. Some research found no adverse effects following IPL therapy and a substantial increase in MGD symptoms. In Chinese MGD cases with darker skin types (Fitzpatrick skin types III-IV), IPL treatment has also been effective and safe. Rong et al. found that strong pulsed light directly exposed to the eyelids, together with meibomian gland expression, effectively treats MGD [48].

IPL, in combination with MGX, was a safe and successful treatment for MGD. However, we must remember that the light beam emitted will be directed on a particular region, selectively damaging specific targets in the area being treated (e.g., capillaries, brown spots, or tattoo color in the skin), causing them to be eliminated or the region to be replaced with new cells—depending on the preferred procedure. IPL's effects can also be unwelcome, resulting in dangers like burns, blistering, and discomfort. Keloids and skin pigmentation are common severe symptoms. As a result, before proceeding with the procedure, the practitioner should advise the worried patients about the risks and benefits of IPL therapy. In meibomian gland dysfunction, intensive pulsed light therapy affects tear proteins, lipids, and inflammatory markers by controlling the amounts of total lipids, cholesterol, triglycerides, and phospholipids in the tear; IPL helps to alleviate the symptoms of DED. After IPL treatment, Ahmed et al. found substantial differences in tear protein concentrations and molecular weight [49]. The molecular weights of tear lysozyme, albumin, and lactoferrin were the most affected. The tears of MGD patients had

slightly smaller levels of anionic phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol on thin-layer chromatography, however typical levels of zwitterionic neutral phospholipid phosphatidylcholine. After IPL treatment, these anionic phospholipids demonstrated impressive improvement. IPL enhances tear protein and lipid content and structure. Several studies have found IPL therapy reduces interleukin-6, interleukin-17A, and prostaglandin E2 levels in DED patients' tear fluid. Furthermore, they stated that a reduction in these inflammatory factors was related to decreased signs and symptoms. These decreases in inflammatory factors were linked to increases in corneal staining ratings, indicating that ocular surface epithelial damage had improved. According to some reports, changes in IL-6, IL-17A, and IL-1 levels were lowest one week after IPL, which was earlier than the appearance of clinical result peaks at one month. This means that increases in tear cytokine levels could be more sensitive indicators of IPL symptoms than clinical signs. IPL has an impact on the MGD meibum.

IPL has been shown in several trials to help release clogged meibum by thermal pulsation treatment. MGD is a critical contributor to dry eye illness with Sjogren disease, according to Godin et al. study's and should not be underestimated when evaluating care choices [50].

The meibum was able to clear its clogged ducts with the aid of thermal pulsation. Thermal pulsation is a treatment choice for patients with Sjogren's disease who have dry eye and MGD symptoms, and it will increase meibum consistency directly. Another research by yin et al. found that after therapy, TBUT, OSDI, MG expressibility, meibum quality, and MG dropout increased. IPL therapy significantly increased MG microstructure indices such as meibum, MG Acinar Unit Density (AUD), MG Acinar Longest Diameter (ALD), and the positive rate of Inflammatory Cells (ICs) across glandular structures. These results indicate that IPL therapy helps DED patients with MGD symptoms. It also increases eyelid hygiene and related ocular-surface indices, MG function, and MG macrostructure. Moreover, in MGD cases, IPL therapy primarily enhanced MG microstructure and reduces MG inflammation. MGD causes a difference in meibum content and quantity, which contributes to evaporative dry eye and ocular surface damage, increasing dry eye symptoms in certain people, according to Chhadva et al. on the meibum of MGD patients [51]. These modifications can be systemically managed with IPL, reducing the patient's difficulty [23, 31].

8.2 The advantages of IPL

Sufferers with refractory meibomian gland dysfunction are treated with intense pulsed light. Even more, research suggests that using strong pulsed light to treat MGD cases tends to alleviate dry eye symptoms. The aim of Arita et al. research.'s was to see whether strong pulsed light (IPL) combined with meibomian gland expression (MGX) could help with refractory meibomian gland dysfunction (MGD). Her findings indicated that combining IPL and MGX improved tear film homeostasis and alleviated ocular symptoms in cases with refractory MGD, making it a potential treatment option for this disorder. The meibomian gland activity was increased, the tear film was balanced, and ocular surface inflammation was reduced after IPL therapy. Meibum consistency, meibum expressibility, lid margin abnormality, ocular surface staining, tear film breakup period (TBUT), and the Ocular Surface Disease Index (OSDI) all improved significantly after IPL. Low meibum expressibility and a short TBUT were linked to a more significant improvement in the OSDI. Sufferers with refractory obstructive meibomian gland dysfunction responded well to IPL therapy combined with meibomian gland probing. Huang et al. discovered that, in comparison to IPL or Meibomian Gland Probing (MGP) alone, the mixture

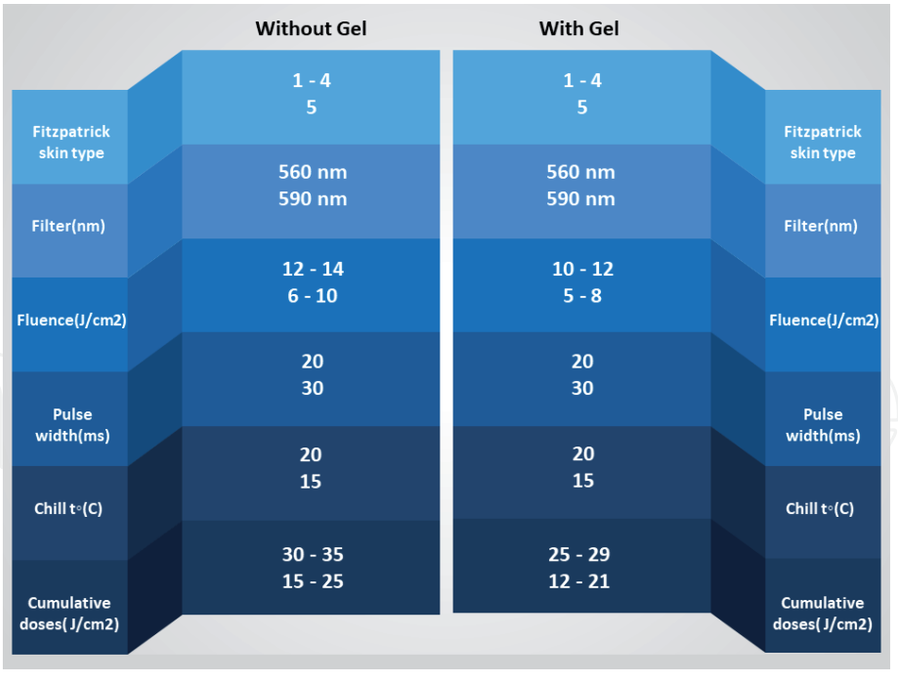

Figure 4.
Comparison of methods of IPL with and without gel.

MGP-IPL showed the most remarkable results in relieving all symptoms and signs and assisting patients in achieving long-term symptom relief [21, 52].

8.3 Evolution methods of IPL

The novel IPL/BBL from the high-intensity red (560–580 nm) to infrared (580–1200 nm) wavelengths of light may also improve blepharitis and DE by reducing Demodex and harmful bacteria [53]. This safe and effective protocol treats both the upper eyelid (more meibomian glands) and lower eyelids. It is now an off-label adaptation for ocular rosacea treatment (a form of MGD DED). Significant improvement of periocular symptomatology, MGD blepharitis symptoms, OSDI scores, and recurrence were observed with IPL/BBL after one year (**Figure 4**).

9. Discussion

Two types of IPL devices (E. Eye; E-SWIN, Paris, France, and Lumenis M22; Tel Aviv, Israel) were used in the studies. The E. Eye device produces a wavelength from 580 to 1200 nm, whereas the Lumenis M22 produces a 400 to 1200 nm wavelength. The broader wavelength of Lumenis M22 can theoretically achieve a better bactericidal effect. The light between 400 and 700 nm (415 most effectively absorbed) for *Propionibacterium acnes*, 500 nm, probably induces photo-thermolysis of vessels and prevents the leakage of inflammatory cytokines into the ocular surface. The yellow wavelength of IPL can target the oxyhemoglobin in superficial skin vessels, which have light absorption peaks of 578 nm. The sustained reduction in telangiectasia (decrease leakage of interleukins such as IL-17A and IL-6) was observed in patients with rosacea-related MGD after repeated IPL administration. On the contrary, the red-light spectrum (580–1200 nm) delivered by the E. Eye device has a more inadequate bactericidal effect. Still, it can potentially penetrate deeper into the skin and target the underlying sebaceous glands. And the use of the protective eye goggles is unclear or different between studies.

The different wavelength is another confounding factor, although 500 to 600 nm was used in most studies.

There are two intense pulsed light patterns: Optimal Pulse Technology (OPT) with three (3 weeks duration) consecutive treatments (10–14 J/cm^2) is more effective in improving MG function in lower eyelids and partial tear film signs than Intense Regulated Pulsed Light (IRPL) with four treatments (9–13 J/cm^2) on days (D)1, D15, D45, and D75 treatment. The method of light patterns used in each study causes a little disagreement.

Moreover, discrepancies between the ocular symptoms and signs of dry eye and the significant association of sleep disorders and ocular surface problems are common [54].

Besides, dry eye symptoms are more highly correlated with non-ocular conditions (sometimes somatization) than dry eye signs. The questionnaire does not any focus on a specific drug history for insomnia or antidepressants with anticholinergic effects.

It is also not irrational to conclude that identical findings would have been observed in a particular demographic with various skin type dispensation [23]. Another restriction was the lack of a gold standard for diagnosing and using TBUT as the essential result measure. Many reports of DED use tear breakup time; as a result, measure, but this outcome measure is troublesome for many reasons [23]. This procedure has a mild specificity/sensitivity. The findings are depending on the amount of coloring (fluorescein) ingrained in the eye, and the method is highly subjective to the observer's estimation. As a result, TBUT varies from one investigator to the next, even within the same investigator. While this averaging approach minimized TBUT measurement uncertainty, a more accurate and quantitative primary result indicator (e.g., NIBUT) may be a better option for investigation.

And finally, in the present pandemic, the eye route of infection must be considered so each sufferer should be treated as a potential coronavirus carrier. As a potentially beneficial method for treating and relieving the effects of DES and avoiding COVID-19, various compounds may be added into the food and then used as ready-made supplements. Polyunsaturated fatty acids had the most reported medicinal benefit, as they help alleviate the disease's infectious aspect. Vitamins, omega acids, and other nutritional nutrients can be discussed with each person individually.

10. Conclusion

To summarize, IPL is an attractive alternative solution for sufferers with DED caused by MGD, and that the effect of IPL is real rather than a placebo effect.

11. Take-home messages

It is essential to address the following points:

1. As we know, the MGD is not yet an approved indication for IPL therapy by the United States Food and Drug Administration. Regarding the safety of IPL and reported adverse events (14% of patients: cheek swelling, conjunctival cyst, floaters, blistering, hair loss at brow and forehead, light sensitivity, and facial redness). The IPL treatment should adhere to lower eyelids for now and in the presence of ocular protection due to the report about uveitis and iris damage. Although adverse effects usually resolved without treatment within one week

and iris damage has been reported during cosmetic IPL therapy on the upper eyelids by no ophthalmologic health care workers.

2. When we discuss about Intense Pulse Laser as a new treatment, confounding factors should be borne in mind: Age, baseline Ocular Surface Disease Index, MGD severity are potential factors that may influence the effects of IPL [55]. Some factors are difficult to control, such as patients' lifestyle, hormone levels, mood, and environment, which may affect the therapeutic effect of IPL treatment as follows:

   - Increased exercise and higher estrogen levels were also associated with improved tear quantity during the ovulation phase [56].
   - The majority of the available studies on nutritional supplementation [57] for DED did not evaluate the micronutrient dietary intake nor their plasma level, representing the major limitation of the existing literature. However, Epitropoulos et al., Malhotra et al., and Oleñik et al. showed significant improvement in OSDI, TBUT, lid margin inflammation, and meibum expressibility placebo, using Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) [57].
   - On the other hand, sleep deprivation reduces androgen levels parasympathetic activity. It makes high levels of stress hormones (norepinephrine and cortisol) and reduce tear secretion lacrimal system function that reversed after 14 days of rest [58] (**Table 1**).

Abbreviations	Definitions
BBL	Broadband Light
BL	Baseline
BUT	Breakup Time
CCES	Change of Compound Eyelid Score
CES	Composite Eyelid Score
CFS	Corneal Fluorescein Staining
DE	Dry Eye
DED	Dry Eye Disease
DES	Dry Eye Syndrome
FU	Follow-up
ICs	Inflammatory Cells
IHMGEC	Immortalized Human MG Epithelial Cells
IPL	Intense Pulsed Light
IRPL	Intense Regulated Pulsed Light
LASIK	Laser-Assisted in Situ Keratomileuses
MG	Meibomian Gland
MG ALD	Meibomian Gland Acinar Longest Diameter
MG AUD	Meibomian Gland Acinar Unit Density
MGD	Meibomian Gland Dysfunction
MGE	Meibomian Gland Evaluator

Abbreviations	Definitions
MGP	Meibomian Gland Probing
MGX	Meibomian Gland Expression
MGYSS	Meibomian Gland Yielding Secretion Score
MMP	Matrix Metalloproteinase
NIBUT	Non-Invasive Breakup Time
OPT	Optimal Pulse Technology
OSD	Ocular Surface Disease
OSDI	Ocular Surface Disease Index
RCTs	Randomized Controlled Trials
SPEED	Standard Patient Evaluation of Eye Dryness Questionnaire
SREBP-1	Sterol Regulatory Element-Binding Protein 1
TBUT	Tear Breakup Time
TFLL	Tear Film Lipid Layer
TFOD	Tear Film-Oriented Diagnosis
TFOS DEWS II	Tear Film & Ocular Surface Society Dry Eye Workshop II
WC	Warm Compresses

Table 1.
Abbreviations and definitions.

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References

[1] Yan, X., et al., The efficacy of intense pulsed light combined with Meibomian gland expression for the treatment of dry eye disease due to Meibomian gland dysfunction: A Multicenter, randomized controlled trial. Eye and contact lens, 2021. 47(1): p. 45-53.

[2] Arita, R., et al., Multicenter study of intense pulsed light therapy for patients with refractory meibomian gland dysfunction. Cornea, 2018. 37(12): p. 1566.

[3] Toyos, R., C. Buffa, and S. Youngerman, Case Report: Dry-Eye Symptoms Improve with Intense Pulsed Light Treatment. Eye World News Magazine, 2005.

[4] Bakkar, M.M., et al., Epidemiology of symptoms of dry eye disease (DED) in Jordan: A cross-sectional non-clinical population-based study. Contact Lens and Anterior Eye, 2016. 39(3): p. 197-202.

[5] Hashemi, H., et al., Prevalence of dry eye syndrome in an adult population. Clinical and experimental ophthalmology, 2014. 42(3): p. 242-248.

[6] Lee, A., et al., Prevalence and risk factors associated with dry eye symptoms: A population based study in Indonesia. British Journal of Ophthalmology, 2002. 86(12): p. 1347-1351.

[7] Moss, S.E., R. Klein, and B.E. Klein, Prevalence of and risk factors for dry eye syndrome. Archives of ophthalmology, 2000. 118(9): p. 1264-1268.

[8] Onwubiko, S.N., et al., Dry eye disease: Prevalence, distribution and determinants in a hospital-based population. Contact Lens and Anterior Eye, 2014. 37(3): p. 157-161.

[9] Sendecka, M., A. Baryluk, and M. Polz-Dacewicz, Prevalence and risk factors of dry eye syndrome. Przeglad epidemiologiczny, 2004. 58(1): p. 227-233.

[10] Uchino, M., et al., Prevalence and risk factors of dry eye disease in Japan: Koumi study. Ophthalmology, 2011. 118(12): p. 2361-2367.

[11] Vehof, J., et al., Prevalence and risk factors of dry eye disease in a British female cohort. British Journal of Ophthalmology, 2014. 98(12): p. 1712-1717.

[12] Asbell, P., et al., Defining the needs and preferences of patients with dry eye disease. BMJ open ophthalmology, 2019. 4(1): p. e000315.

[13] Shanti, Y., et al., Prevalence and associated risk factors of dry eye disease in 16 northern west bank towns in Palestine: A cross-sectional study. BMC ophthalmology, 2020. 20(1): p. 1-8.

[14] Ngo, W., et al., Psychometric properties and validation of the standard patient evaluation of eye dryness questionnaire. Cornea, 2013. 32(9): p. 1204-1210.

[15] CDGoOS, C., Experts' consensus about clinical diagnosis and treatment of dry eye (2013). Chin Jophthalmol, 2013. 49: p. 73-75.

[16] Korb, D.R. and C.A. Blackie, Meibomian gland diagnostic expressibility: Correlation with dry eye symptoms and gland location. Cornea, 2008. 27(10): p. 1142-1147.

[17] Jones, L., et al., TFOS DEWS II management and therapy report. The Ocular Surface, 2017. 15(3): p. 575-628.

[18] Wolffsohn, J.S., et al., TFOS DEWS II diagnostic methodology report. The ocular surface, 2017. 15(3): p. 539-574.

[19] Hantera, M.M., trends in dry eye disease management worldwide. Clinical ophthalmology (Auckland, N.Z.), 2021. 15: p. 165-173.

[20] Buckley, R.J., Assessment and management of dry eye disease. Eye, 2018. 32(2): p. 200-203.

[21] Suwal, A., et al., Use of intense pulsed light to mitigate Meibomian gland dysfunction for dry eye disease. International journal of medical sciences, 2020. 17(10): p. 1385-1392.

[22] Raulin, C., B. Greve, and H. Grema, IPL technology: A review. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery, 2003. 32(2): p. 78-87.

[23] Zhang-Nunes, S., et al., Safety and efficacy of an augmented intense pulse light protocol for dry eye syndrome and Blepharitis. Photobiomodulation, Photomedicine, and Laser Surgery, 2020. 39(3): p. 178-184.

[24] Anderson, R.R. and J.A. Parrish, Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. Science, 1983. 220(4596): p. 524-527.

[25] Toyos, R., W. McGill, and D. Briscoe, Intense pulsed light treatment for dry eye disease due to meibomian gland dysfunction; a 3-year retrospective study. Photomedicine and laser surgery, 2015. 33(1): p. 41-46.

[26] Song, W. and X. Yan, Research progress of intense pulsed light treatment on meibomian gland dysfunction and relevant dry eye diseases. [Zhonghua yan ke za zhi] Chinese journal of ophthalmology, 2018. 54(2): p. 140-143.

[27] Onesti, M. and P. Fioramonti, Intense Pulsed Light Systems, in International Textbook of Aesthetic Surgery. 2016, Springer. p. 1123-1131.

[28] Vegunta, S., D. Patel, and J.F. Shen, Combination therapy of intense pulsed light therapy and meibomian gland expression (IPL/MGX) can improve dry eye symptoms and meibomian gland function in patients with refractory dry eye: A retrospective analysis. Cornea, 2016. 35(3): p. 318-322.

[29] Macsai, M.S., The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). Transactions of the American Ophthalmological Society, 2008. 106: p. 336.

[30] Sambhi, R.-D.S., et al., Intense pulsed light therapy with meibomian gland expression for dry eye disease. Canadian Journal of Ophthalmology, 2020.

[31] Pazo, E.E., et al., Intense pulse light for treating post-LASIK refractory dry eye. Photobiomodul Photomed Laser Surg, 2021. 39(3): p. 155-163.

[32] Bommert, C.M., et al., Sleep apnea and dry eye: How sleep apnea affects the eye surface. Ophtha Therapy, 2020. 7(2): p. 103-107.

[33] Greiner, J.V., Long-term (12-month) improvement in meibomian gland function and reduced dry eye symptoms with a single thermal pulsation treatment. Clinical and Experimental Ophthalmology, 2013. 41(6): p. 524-530.

[34] Blackie, C.A., et al., The relationship between dry eye symptoms and lipid layer thickness. Cornea, 2009. 28(7).

[35] Toda, I., Dry eye after LASIK. Investigative Ophthalmology and Visual Science, 2018. 59(14): p. DES109-DES115.

[36] Goto, E., et al., Successful Tear Lipid Layer Treatment for Refractory Dry Eye in Office Workers by Low-Dose Lipid Application on the Full-Length

Eyelid Margin. American Journal of Ophthalmology, 2006. 142(2): p. 264-270.e1.

[37] Foulks, G.N., The correlation between the tear film lipid layer and dry eye disease. Survey of Ophthalmology, 2007. 52(4): p. 369-374.

[38] Mudgil, P., Antimicrobial role of human Meibomian lipids at the ocular surface. Investigative Ophthalmology and Visual Science, 2014. 55(11): p. 7272-7277.

[39] O'Neil, E.C., et al., Advances in dry eye disease treatment. Current opinion in ophthalmology, 2019. 30(3): p. 166-178.

[40] Lam, P.Y., et al., A review on evidence-based treatments for Meibomian gland dysfunction. Eye and Contact Lens, 2020. 46(1): p. 3-16.

[41] Moniaux, N., et al., Structural organization and classification of the human mucin genes. Front Biosci, 2001. 6(1): p. D1192-DD206.

[42] Gipson, I.K. and P. Argueso, Role of mucins in the function of the corneal and conjunctival epithelia. Int Rev Cytol, 2003. 231(1): p. 1-49.

[43] Gipson, I.K., Y. Hori, and P. Argüeso, Character of ocular surface mucins and their alteration in dry eye disease. The ocular surface, 2004. 2(2): p. 131-148.

[44] Xue, A.L., et al., Randomised double-masked placebo-controlled trial of the cumulative treatment efficacy profile of intense pulsed light therapy for meibomian gland dysfunction. Ocul Surf, 2020. 18(2): p. 286-297.

[45] Yagci, A. and C. Gurdal, The role and treatment of inflammation in dry eye disease. International Ophthalmology, 2014. 34(6): p. 1291-1301.

[46] Dell, S.J., Intense pulsed light for evaporative dry eye disease. Clinical ophthalmology (Auckland, NZ), 2017. 11: p. 1167.

[47] Gupta, P.K., et al., Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease. Canadian Journal of Ophthalmology, 2016. 51(4): p. 249-253.

[48] Rong, B., et al., Intense pulsed light applied directly on eyelids combined with meibomian gland expression to treat meibomian gland dysfunction. Photomedicine and laser surgery, 2018. 36(6): p. 326-332.

[49] Ahmed, S.A., et al., Effect of intense pulsed light therapy on tear proteins and lipids in meibomian gland dysfunction. Journal of ophthalmic and vision research, 2019. 14(1): p. 3.

[50] Godin, M.R., S.S. Stinnett, and P.K. Gupta, Outcomes of thermal pulsation treatment for dry eye syndrome in patients with sjogren disease. Cornea, 2018. 37(9): p. 1155-1158.

[51] Chhadva, P., R. Goldhardt, and A. Galor, Meibomian gland disease: The role of gland dysfunction in dry eye disease. Ophthalmology, 2017. 124(11): p. S20-S26.

[52] Huang, X., et al., Clinic results of Intraductal Meibomian gland probing combined intense pulsed light in treating patients with refractory obstructive Meibomian gland dysfunction: A randomized controlled Trial. 2019.

[53] Cheng, S.-n., et al., Intense pulsed light therapy for patients with meibomian gland dysfunction and ocular demodex infestation. Current medical science, 2019. 39(5): p. 800-809.

[54] Lee, W., et al., The association between sleep duration and dry eye syndrome among Korean adults. Sleep Medicine, 2015. 16(11): p. 1327-1331.

[55] Chen, C., et al., Factors Influencing the Effectiveness of Intense Pulsed Light for Meibomian Gland Dysfunction. 2020, Research Square.

[56] Colorado, L.H., et al., Associations between the menstrual cycle, lifestyle factors and clinical assessment of the ocular surface: A prospective observational study. BMC women's health, 2020. 20(1): p. 23.

[57] Pellegrini, M., et al., The role of nutrition and nutritional supplements in ocular surface diseases. Nutrients, 2020. 12(4): p. 952.

[58] Monaco, G. and G. Casalino, Superficial keratectomy followed by intense pulsed light for Salzmann's nodular degeneration and coexisting meibomian gland dysfunction. European Journal of Ophthalmology, 2020: p. 1120672120964691.