Surgical Temporary Ocular Discomfort Syndrome

Subjects: Ophthalmology

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The term STODS (Surgical Temporary Ocular Discomfort Syndrome) has been coined to describe the ocular surface perturbations induced by surgery. As one of the most important refractive elements of the eye, Guided Ocular Surface and Lid Disease (GOLD) optimization is fundamental to success in achieving refractive outcomes and mitigating STODS. Effective GOLD optimization and the prevention/treatment of STODS requires an understanding of the molecular, cellular, and anatomic factors that influence ocular surface microenvironment and the associated perturbations induced by surgical intervention.

LASIK Keratopathy dry eye STODS LALEX SMILE

1. Introduction

Maintaining a healthy ocular microenvironment is requisite for tear-film stability and good vision [1]. In the wake of ocular surgery, all patients develop, in varying degrees, Surgical Temporary Ocular Discomfort Syndrome (STODS). To combat STODS, a molecular, cellular, and anatomic understanding of the ocular perturbations resulting from STODS is requisite. Armed exclusively with preservative-containing artificial tears, soap, and heat, numerous doctors and patients alike have found ocular surface microenvironment optimization to be an elusive goal.

STODS is a term popularized through the Refractive Surgery Alliance (https://www.refractivealliance.com/, (accessed on 6 December 2022)). Here, the researchers use STODS to describe the temporary disturbance to the ocular surface following ocular surgeries involving incisions (manual or laser-assisted) to the cornea. The importance of STODS is its distinction from “dry eye disease”. The proposed draft for LASIK Patient Labeling Recommendations from the United States Food and Drug Administration also lists moderate dry eye symptoms as a relative contraindication for treatment, so confidently navigating preoperative ocular surface abnormality, optimization, and postoperative STODS will only become of even greater importance for refractive surgeons in years to come [2]. STODS is likely due to corneal nerve plexus transection and attenuated by other factors including up-regulation of inflammatory mediators. Corneal nerve fiber bundles are known to decrease significantly after procedures like LASIK but substantially return by one year postoperatively; hence the temporary nature of the condition (**Figure 1**) [3].

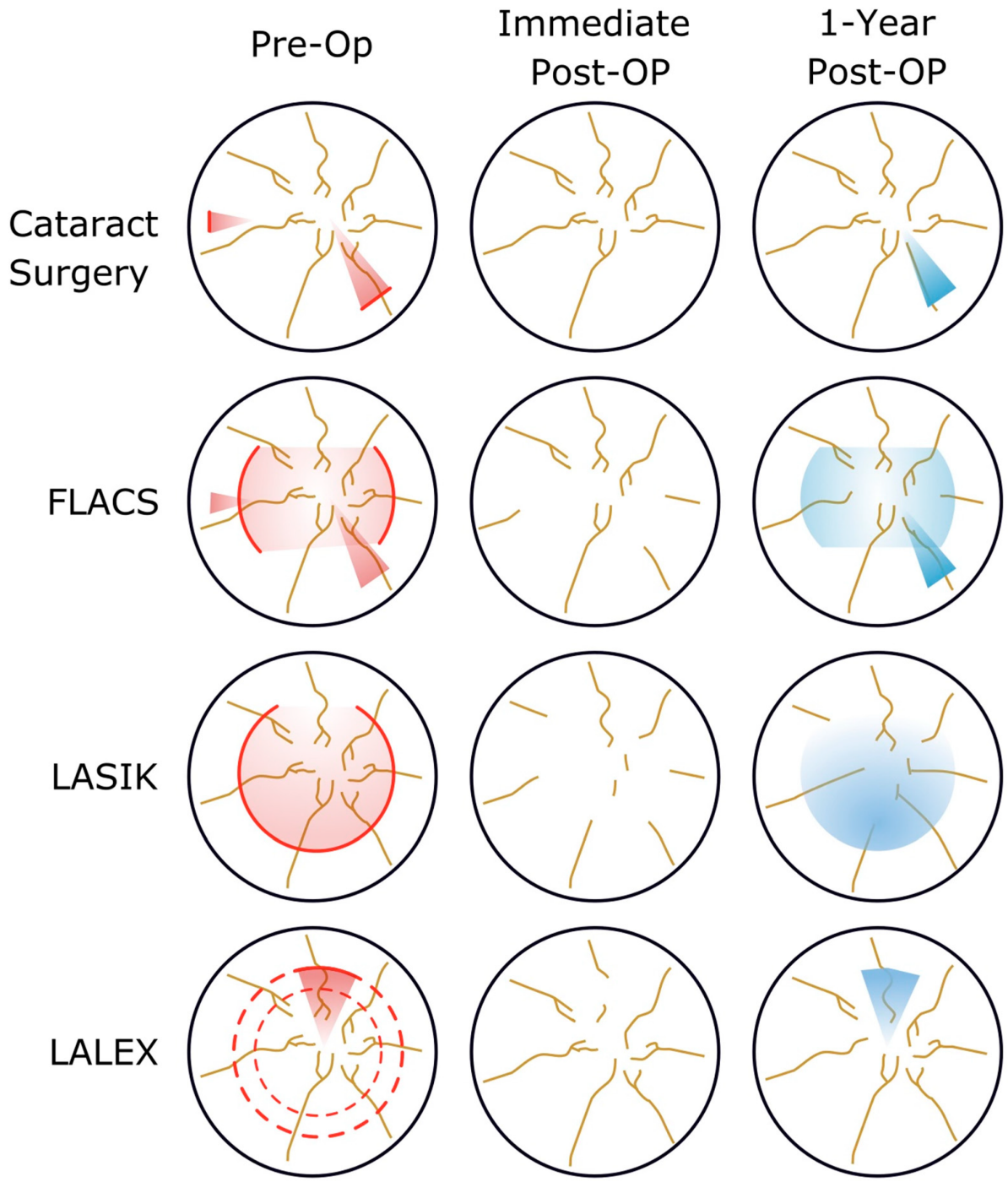


Figure 1. Neurotrophic Etiologies for Surgical Temporary Ocular Discomfort Syndrome (STODS) with a variety of corneal surgical interventions. Transection of nerve occurs in a varying amount with the variety of corneal surgeries as compared to cataract surgery without femtosecond arcs. When femtosecond arcs are employed, the potential for greater nerve transection and thus STODS develops. Similarly, LASIK transects more corneal nerves than LASIK; therefore one would expect greater STODS in the former surgery. Fortunately, by one year, all corneal surgeries are followed by robust nerve regrowth to nearly baseline levels.

A stable, healthy tear film not only maximizes the quality and accuracy of preoperative measurements for surgical planning but also provides the greatest postoperative vision [4]. To achieve and maintain refractive targets, a careful

coordination between optometrist, ophthalmologist, and patient is necessary. Effective co-management for the mitigation of STODS requires a proactive approach. This coordinated approach, or Guided Ocular Surface & Lid Disease (GOLD) optimization, is critical for achieving refractive targets and keeping patients 20/Happy. Surveillance for preoperative signs in the asymptomatic is of the utmost importance. Ensuring a stable tear film with non-invasive tear breakup time (NITBUT) and assessing glandular health with meibography is critical (**Figure 2**). As the researchers learned from the Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO), 80% of patients have clinically significant ocular surface disease prior to surgery but only 22% of these patients carry a diagnosis of dry eye disease (DED) [5]. While the importance of GOLD optimization and effective co-management for STODS mitigation is a growing topic of discussion, it remains a new topic with limited literature on what approaches are most efficacious or efficient.

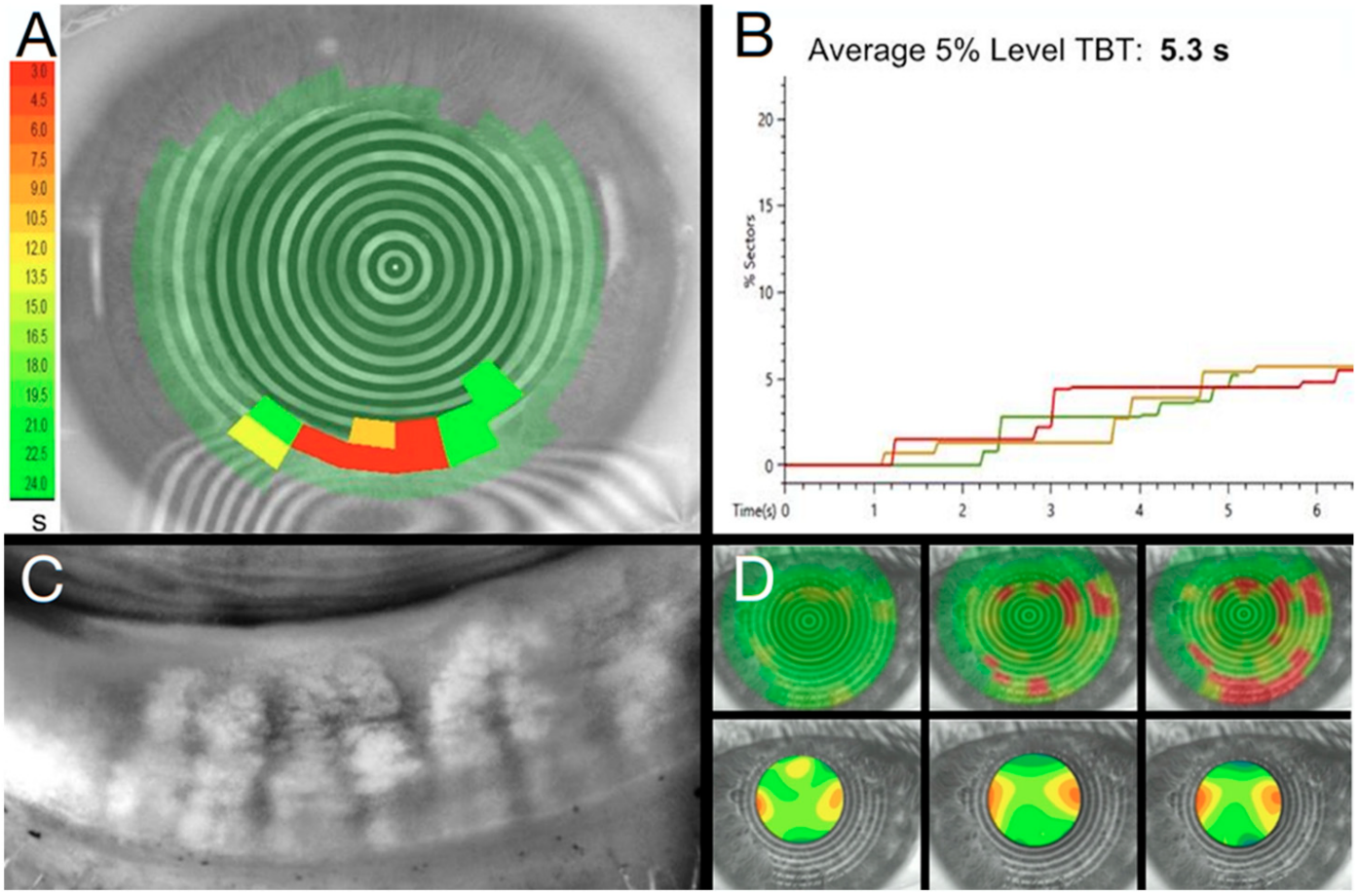


Figure 2. Non-invasive preoperative assessment with CA-800 (Topcon) Tear Film Analyzer. (**A**) Placido disk non-invasive tear breakup time (NITBUT) provides an objective measure of tear film stability (**B**). Through use of meibography (**C**) to demonstrate to patients contributing factors to tear film instability NITBUT with Zernike analysis of the resulting astigmatism, spherical aberration, coma, and higher order aberrations (**D**) to convey to patients the visual impact of tear film instability, clinicians can help patients better understand the impact of ocular surface disease even prior to surgery. Moreover, this analysis helps gauge IOL suitability and the likelihood of quality preoperative topography. A NITBUT of 1 s, for example, will undeniably result in poor topography as a Pentacam is captured over 2 s.

2. The Importance of Preoperative Optimization

First, patients should be counseled that an optimized ocular surface provides the greatest probably of the most accurate preoperative measurements possible, and thus, the most accurate outcome possible. This applies to keratometry, corneal tomography or topography, and biometry as well as current manifest refraction. Without a regular and stable ocular surface before surgery, patients should understand they might not be able to realize their full visual potential. Rapid tear breakup time (TBUT), punctate epithelial erosions, or low tear lakes with desiccation affect the reliability, reproducibility, and accuracy of the preoperative measurements (**Figure 3**) [6]. This therefore increases the possibility of a surgeon making an inappropriate IOL recommendation or selecting an incorrect IOL power leading to suboptimal visual outcomes for patients. A suboptimal ocular surface can have a profound impact on topography measurement [7].

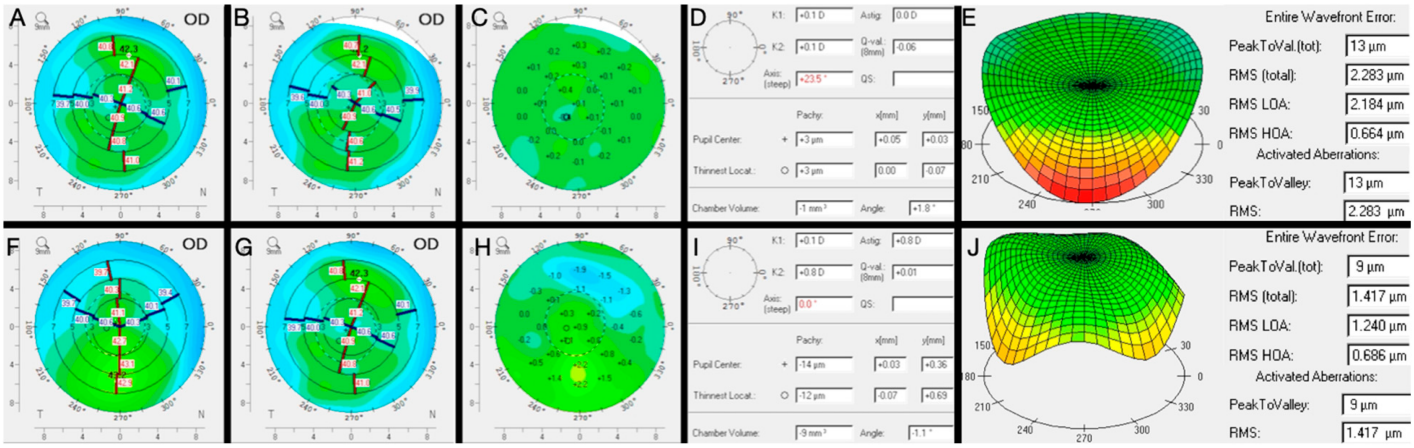
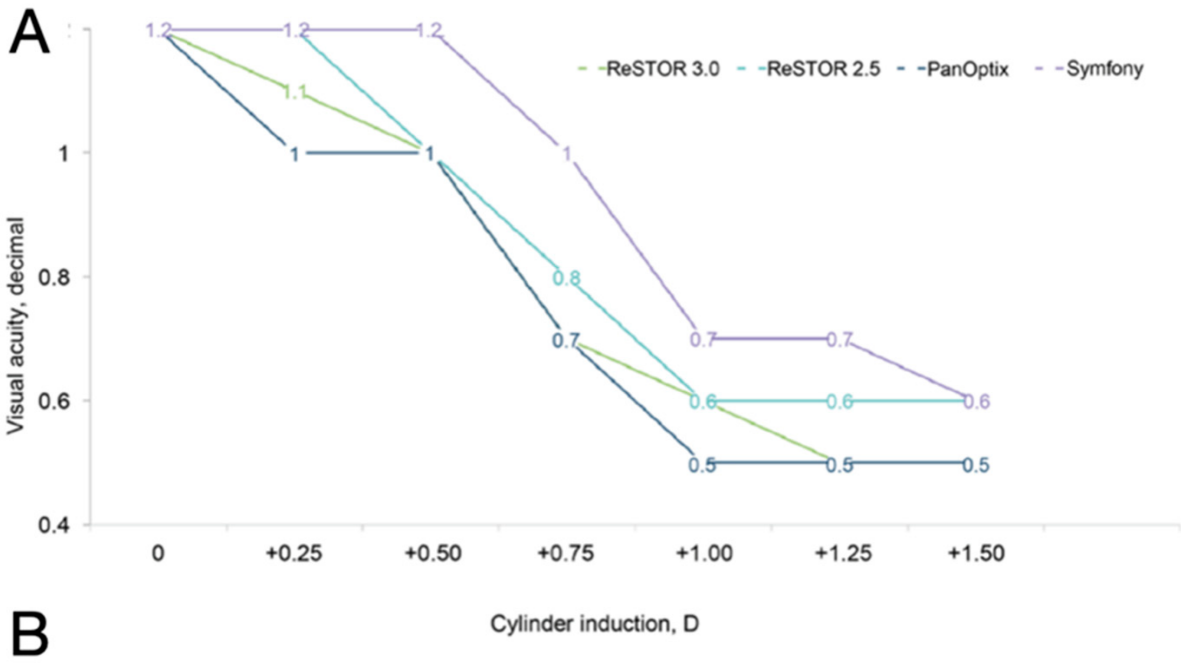


Figure 3. The impact of tear film stability on corneal topography. Sequential same day (**A**,**B**) Scheimpflug image in the setting of unstable tear film demonstrating a difference (**C**) of 23.5 diopters on the axis of astigmatism (**D**). In addition to varying magnitude and axis of astigmatism, tear film instability also results in increased wavefront error (**E**). Repeat topography after GOLD optimization reveals a more regular astigmatism with less same day variability (**F**,**G**). The best fit topography prior to GOLD optimization (**A**) was compared to (**F**) which revealed a 0.8D increase in magnitude in astigmatism (**H**,**I**) as well as a decrease in wavefront error (**J**).

Multifocal and extended depth of focus (EDOF) presbyopia-correcting IOLs provide the greatest change for spectacle independence following cataract surgery but are exquisitely sensitive to ocular surface disease with more variability and dissatisfaction with vision than monofocal patients (**Figure 4**) [8][9][10]. These patients should be specifically counseled that GOLD optimization will remain paramount after surgery for the best possible outcome.



B

Plus values	+0.25 D	+0.50 D	+0.75 D	+1.00 D	+1.25 D	+1.50 D
ReSTOR 3.0	1.1 (1.1 - 1.2)	1.0 (0.9 - 1.2)	0.7 (0.7 - 0.9)	0.6 (0.6 - 0.7)	0.5 (0.5 - 0.6)	0.5 (0.4 - 0.5)
ReSTOR 2.5	1.2 (1.2)	1.0 (1.0 - 1.2)	0.8 (0.7 - 1.0)	0.6 (0.6 - 0.7)	0.6 (0.5 - 0.6)	0.6 (0.5 - 0.6)
PanOptix	1.1 (1.0 - 1.2)	1.0 (0.9 - 1.0)	0.7 (0.6 - 0.8)	0.5 (0.5 - 0.7)	0.5 (0.5 - 0.6)	0.5 (0.4 - 0.5)
Symfony	1.2 (1.2)	1.2 (1.2)	1.0 (0.8 - 1.0)	0.7 (0.7 - 0.9)	0.7 (0.6 - 0.8)	0.6 (0.6 - 0.7)

Figure 4. Mean visual acuity with four multifocal IOLs after the induction of different values of positive cylinder. Mean visual acuity (**A**) and patient satisfaction scores (**B**) with four multifocal IOLs after the induction of different values of positive cylinder (green 1/4 very satisfied; yellow 1/4 moderately satisfied; orange 1/4 not satisfied; red 1/4 not at all satisfied). Values are reported as median, with range in brackets [11].

3. Key Elements to Preoperative Evaluation

Whether patient is an outside referral or established in the practice, the surgeon must evaluation their corneal health preoperatively. There are components to the ocular surface exam with some clues evident when entering the room. Excessive or frequent blinking, skin manifestations of rosacea, blepharitis, incomplete blink, lagophthalmos, or eye rubbing are often evident from across the room. Elucidating details regarding contact lens wear, ocular comfort, or symptoms of dry eye or blepharitis also help in guiding both the exam and final IOL recommendation.

Classic clues for ocular surface abnormality include anterior blepharitis, meibomian gland dysfunction, punctate corneal staining, anterior basement membrane corneal dystrophy, or Salzman's nodules, many of which are common in the cataractous population [12][13]. For a more objective analysis of the ocular surface, corneal tomography/topography shows fluctuating and significant irregularity [7]. A traditional way to assess the corneal tear film is tear breakup time (TBUT). This is an "invasive" assessment that involves placing fluorescein in the tear film and timing its evaporation, which is considered normal if >10 s [14].

New methods such as NITBUT have been gaining popularity and typically involve video topography (**Figure 2**) [15]. Examples include the CA-800 (Topcon, Tokyo, Japan), TearCheck (ESW Vision, Houdan, France), and Keratograph 5M (Oculus, Wetzlar, Germany). Results are comparable to traditional TBUT but may be more repeatable and reliable since they are a noninvasive test [16]. Importantly, it can be incorporated with a dropless preoperative evaluation that will not interfere with topography. As many groups use an anesthetic/fluorescein solution for applanation tonometry and TBUT, assessment of corneal sensation with an esthesiometer is precluded. As corneal sensation may play a central role in STODS, it is important to assess corneal sensation both pre- and postoperatively. For this reason, devices such as iCare (Vantaa, Finland), that do not require anesthetic for use, may be ideal in the refractive surgery setting.

4. Molecular Changes in Ocular Surface Abnormality and during Refractive Surgery

Striving for GOLD optimization and the prevention/treatment of STODS requires an understanding of the molecular factors that influence ocular surface changes during surgery. Several mechanisms have been proposed and studied. Cataract surgery alone leads to ocular surface changes and dry eye syndrome through several mechanisms that disrupt tear film stability [17]. Corneal nerve destruction (**Figure 1**) during wound creation, triggering the inflammatory cycle, goblet cell loss, and meibomian gland dysfunction have all been reported after cataract surgery [18][19]. Ocular surface inflammation appears to play a dominate role over tear secretion [17]. Longer operative times, light or heat from the microscope, use of a lid speculum, and the severity of intraocular inflammation can all impact the postoperative ocular surface [20]. Misuse of postoperative drops is also among the major contributors to STODS [21].

One of the best studied theories involves a cycle of ocular surface inflammation comprised of both soluble and cellular mediators [22]. For example, patients with and without Sjögren's syndrome appear to have identical T-cell activation and infiltration with upregulation of CD3, CD4, CD8, CD11a, and HLA-DR, the latter two markers specific to lymphocyte activation [23]. Additionally, increased inflammatory cytokines such as interleukin 1 (IL-1) and upregulation of matrix metalloproteinases (MMPs) have been demonstrated in the tear film of patients with dry eye symptoms and ocular surface diseases [24]. Other responses to ocular surface stress include hyperosmolarity and increase in MMPs mediated by intracellular pathways including mitogen-activated protein (MAP) kinase and inflammatory cytokines. This results in a cycle where hyperosmolarity then induces inflammation of limbal epithelial cells by further upregulating inflammatory cytokines [25].

The degree to which patients have these various perturbations at baseline and their susceptibility to such perturbations has underlying genetic causes [3]. Rosacea and elevated levels of MMPs are an area ripe for exploring genetic underpinnings that can contribute to STODS. It has been reported that 80% of persons with rosacea have concurrent MGD. Though poorly understood, early research suggests gene-gene and gene-environment interactions are central to rosacea's developments. Whether through inherited genes or through epigenetic modifications that occur through environmental influence, understanding how genes impact STODS is critical [25].

It does appear that certain ocular insults result in chronic ocular surface disease. So instead of STODS, a patient develops Surgical Chronic Ocular Discomfort Syndrome or SCODS. The genetic risk factors as well as epigenetic modifications that occur in the setting of ocular surgery are areas requiring further research. For example, currently there is no evidence to support the idea that epigenetic modifications occurring in longstanding STODS may contribute to the development of SCODS. Alternatively, the insult may cause purely neurogenic and inflammatory changes that are better blunted by certain genetic predispositions in lieu of epigenetic modifications.

Additionally, dysregulation of the balance between proteases and protease-inhibitors has been observed in ocular surface disease. These include MMPs but also cathepsins and plasminogen activators (and their relevant inhibitors) [26]. MMPs, serine proteases, and cysteine proteases are all shown to be upregulated in ocular surface disease and all play a role in protease-activated receptor (PAR) inflammatory signaling [26].

The concept of the eye biome has increased in popularity recently with evidence for a distinct microbiome in those with dry eye disease compared to healthy individuals [27]. As expected, those with a blepharitis component have increased prevalence of *Streptophyta*, *Corynebacterium*, and *Enhydrobacter* [28]. Meibomian gland dysfunction has been associated with increased bacteria on the ocular surface and an increase in bacterial load has been associated with decreased goblet cell density [29][30]. In this way, alterations in the ocular microbiome have major effects on tear film stability.

Since the most optimal therapy would involve tailoring the treatment to the pathophysiology, certain surgical techniques induce unique changes. Following Photorefractive Keratectomy (PRK), new neurites emerge from the severed nerve endings into the epithelial-stroma interface as early as the first week after surgery [31]. There is around 85–95% sensitivity recovery after PRK by 3 months that is directly related to the intensity of the laser application [32][33][34][35]. Laser In-Situ Keratomileusis (LASIK) on the other hand severs both stromal and sub-basal nerves during flap creation with direct ablation of the stromal nerve plexus [36][37]. There is typically under 10% of the sub-basal nerves remaining after LASIK with evidence for both continued regression after surgery since the nerves are unable to connect with the flap leading to significantly reduced nerve density up to 5 years postoperatively (**Figure 1**) [3][38][39][40][41][42][43]. Laser-Assisted Lenticule Extraction (LALEX) shows superior postoperative corneal sensitivity compared to LASIK, likely because the nerves outside the lenticule area remain untouched [37][44]. Femtosecond lasers used for cataract surgery (e.g., capsulotomies) have also been associated with a dose-dependent induction of cell-induced inflammation [45]. The use of the femtosecond laser in LASIK surgery does not appear to alter corneal sensitivity or dry eye outcomes compared to LASIK alone. In fact,

femtosecond flaps may have superior postoperative tear film stability compared to mechanically created flaps [46][47][48]. Cell-mediated inflammation still plays a major role in ocular surface disease following PRK, LASIK, and LALEX [21].

Understanding that there's no definitive cure for dry eye and the patient will never be able to abandon caring for their ocular surface is perhaps the best way to ensure happy patients and happy surgeons. In particular we must understand that although STODS may be temporary, if left untreated it can create a chronic inflammation or Surgical Chronic Ocular Disease Syndrome (SCODS). The effective refractive surgeon will identify the various intrinsic factors such as genetic propensity, ocular surface disease prior to surgical intervention, and various anatomical factors that may increase the risk of STODS to SCODS conversion. They will not be flat-footed and reactionary, but instead, proactive in mitigating STODS at the gate and ensuring it never becomes SCODS.

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