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Myopic regression and recurrent Salzmann nodule degeneration after laser in situ keratomileusis in Ehlers Danlos Syndrome

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ABSTRACT

Purpose: We describe the first case of Ehlers Danlos Syndrome (EDS) reported in the English language ophthalmic literature to have undergone Laser In Situ Keratomileusis (LASIK) surgery.

Observations: We review our patient's specific postoperative complications of myopic regression, Salzmann nodular degeneration, and dry eye syndrome, as well as the risks and consequences of performing LASIK on patients with this collagen disorder.

Conclusions and importance: Refractive errors may prompt EDS patients to seek laser vision correction, placing them at increased risk for complications such as myopic regression, keratectasia, and dry eye syndrome. Aberrant wound healing and collagen dysfunction may have influenced our patient's myopic regression and Salzmann nodule degeneration post-LASIK. Currently, EDS is considered a relative contraindication in LASIK due to a presumed higher risk of postoperative keratectasia; however, we believe it is possible that not all forms of EDS need to be an absolute contraindication to LASIK. More research is warranted to determine preoperative risk stratification for laser vision surgery in each subtype of EDS.

1. Introduction

Ehlers Danlos Syndrome (EDS) is composed of a heterogenous group of inherited connective tissue disorders characterized by mutations altering collagen production or its fibrillar structure. The signs and symptoms associated with EDS vary depending on subtype, but all individuals show joint hypermobility, skin hyperextensibility, and tissue fragility. Other common findings include mitral valve prolapse, joint subluxation, arthralgias, hernia formation, and easy bruising.[1] The prevalence of EDS is estimated to be 1 in 5000 worldwide.[2] The subtypes of EDS were recently revised from a system of Roman numerals based on clinical presentation and mode of inheritance to one with descriptive names grouped to more accurately reflect their molecular and genetic origins.[1,3,4] In this update, the wide array of presentations described in the literature during the last several decades are reduced to 13 unique subtypes of EDS.[1]

Abnormal properties of collagen have been associated with aberrant structural changes in the shape and curvature of the cornea and sclera.[5] Therefore, EDS patients can present with ocular findings, including corneal thinning, keratoconus, cornea plana, ocular fragility, blue sclera, lens subluxation, and high myopia.[6–10] Significant refractive errors may prompt these patients to seek Laser In Situ Keratomileusis (LASIK), placing them at increased risk for complications such as myopic regression, keratectasia, dry eye syndrome, and neurotrophic cornea.[11–14] Some of the possible complications of LASIK overlap with disease processes that appear more frequently in EDS patients; thus, this syndrome is understood to be relative contraindication to LASIK.[7] To the best of our knowledge, we describe the first case of EDS reported in the English-language ophthalmic literature to have undergone LASIK, and we discuss the potential risks and ramifications of performing laser vision correction on patients with this collagen disorder.

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Table 1
Manifest refraction values and visual acuities over the post-operative period. UDVA = uncorrected distance visual acuity, CDVA = best corrected distance visual acuity, D = diopters.

Date	Right Eye (OD)					Left Eye (OS)				
	UDVA	Manifest Refraction			CDVA	UDVA	Manifest Refraction			CDVA
Preoperative	–	−2.00	–	–	20/20	–	−2.50	–	–	20/20
1 month postoperative	20/20	−0.50	–	–	–	20/20	−0.50	–	–	–
2 years postoperative	20/40	−0.75	+0.25	× 66	20/20	20/30	−1.00	+0.25	× 45	20/15
5 years postoperative	20/70	−1.75	+0.75	× 65	20/20	20/60	−1.50	–	–	20/15
11 years postoperative	–	−4.00	+1.00	× 165	20/15	–	−3.25	–	–	20/15
17 years postoperative	20/150	−4.00	+2.00	× 95	20/20	20/300	−5.50	+0.50	× 151	20/15

1.1. Case report

A 21-year-old, Caucasian woman with past medical history of hypermobile joints and intermittent arthralgias presented for refractive surgery evaluation for correction of myopia. She denied a history of connective tissue disease, diabetes, or abnormal scar formation. Medications included loratadine for seasonal allergies and citalopram for depression and generalized anxiety disorder. Past ocular and surgical histories were non-contributory. The patient was adopted, and family history was unknown. Preoperative manifest and cycloplegic refractions were −2.00 D in the right eye (OD) and −2.50 D in the left eye (OS) without astigmatism. Best corrected distance visual acuity (CDVA) was 20/20 OD and 20/20 OS (Table 1). Keratometry and pachymetry values over the pre- and postoperative years are reported in Table 2 and Fig. 1, respectively. The remaining external segment, anterior segment, and fundus exams were normal in both eyes (OU).

Uncomplicated LASIK was performed in both eyes on December 20th, 2001. A 180 μm, 8.5 mm diameter flap with superior hinge was created OU with a Hansatome microkeratome (Bausch & Lomb, Rochester, NY) using a 9.5-mm suction ring. Excimer laser ablation was performed with a VISX Star S3 Excimer Laser System (VISX Technology, California; software version 4.21). A 6.5 mm-diameter ablation zone was performed OD at a depth of 32 μm for a target spherical correction of −2.00 D. A 6.5-mm diameter ablation zone was performed OS at a depth of 38 μm for a target spherical correction of −2.33 D.

In the early postoperative period, the patient complained of dry eyes but achieved uncorrected distance visual acuity (UDVA) of 20/20 in each eye with manifest refractions of −0.25 + 0.75 × 23 OD and Plano +0.50 × 167 OS. Slit lamp examination displayed mild superficial punctate keratitis OU, but no signs of flap folds, infiltrates, debris, or other irregularities. Intraocular pressures remained normal throughout the pre- and postoperative periods. Two years after LASIK, the patient presented with increased dry eye sensations and itchiness. UDVA was 20/40 OD with a manifest refraction of −0.75 + 0.25 × 66 OD and 20/30 OS with −1.00 + 0.25 × 45 OS. On slit lamp examination, two Salzmann nodules were noted in the nasal and temporal cornea OD involving the flap edge. Similarly, two Salzmann nodules were seen in the left eye, involving the inferonasal and inferotemporal cornea and the flap edge. She returned to contact lens use for refractive correction. The patient was started on cyclosporine ophthalmic emulsion 0.05% (Restasis®, Allergan, Irvine, CA, USA) and frequent dosing of preservative-free, artificial tears; however, the patient continued to suffer from ocular surface inflammatory disorder.

Five years post-LASIK, the patient was diagnosed by her primary care physician with Ehlers Danlos syndrome after experiencing multiple miscarriages while on various fertility regimens. In our clinic, further myopic regression was noted; UDVA was 20/70 OD with −1.75 + 0.75 × 65 OD and 20/60 OS with −1.50 D sphere only. On slit-lamp examination, the Salzmann nodular degeneration was relatively unchanged, but moderate Meibomian gland dysfunction was noted with decreased tear break up time (TBUT) OU. Olopatadine drops were given for 'itchy, red eyes' in conjunction with cyclosporine and artificial tear use.

Seven years after surgery, punctal cautery of the right lower lid was performed after multiple, failed, punctal plugs. Superficial keratectomy of the larger, nasal Salzmann nodule OD was performed carefully to avoid flap dislocation. A short course of prednisolone acetate and Gatifloxacin were added to her treatment regimen. One-week after superficial keratectomy, slit-lamp examination revealed a well-healing epithelial defect OD with no evidence of flap necrosis or epithelial ingrowth.

Over the next several years, the patient developed multiple abdominal hernias, experienced a uterine tear, and underwent multiple reparative surgeries. Additionally, she was diagnosed with two disorders related to EDS: postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome. In 2014, she successfully delivered a son after several years of in-vitro fertilization. Per her report, the son is currently showing signs of Ehlers Danlos syndrome, including hypermobile joints, everted ankles, and severe myopia. The patient continued to experience poor night-time vision and severe, itchy, dry eye symptoms OU refractory to maximal medical treatment and aforementioned surgical management. Therefore, cautery of the left lower punctum was also performed. At 11 years post-LASIK, neovascularization of the temporal cornea OD was noted, measuring as 3 mm × 4 mm in dimension and extending into the adjacent Salzmann nodule in the form of a pseudopterygium. At 17 years post-LASIK, the pseudopterygium had progressed to 5 mm × 4 mm without involvement of the center of vision (Fig. 2). Additionally, the previously-

Table 2
Keratometry values over the postoperative period measured with Orbscan (Bausch & Lomb Incorporated, USA). D = diopters, Diff K = difference in K-values (astigmatism), BFS = best fitting sphere, A/P = anterior and posterior values. * = anterior curvature value only reported. ** = taken with Pentacam (Oculus Optikgeräte, Wetzlar, Germany).

Date	Right Eye (OD)				Left Eye (OS)			
	K Steep (D)	K Flat (D)	Diff K (D)	BFS A/P (mm)	K Steep (D)	K Flat (D)	Diff K (D)	BFS A/P (mm)
Preoperative	45.8	45.2	0.6	7.64/6.34	45.8	45.2	0.6	7.65/6.38
1 year postoperative	43.9	43.1	.8	7.73*	43.6	42.8	.8	7.75*
2 years postoperative	43.3	42.6	.8	7.80/6.34	43.4	42.3	1.1	7.84/6.37
7 years postoperative	43.4	41.1	2.2	7.89*	43.0	42.3	.7	7.84*
17 years postoperative**	44.2	41.0	3.2	7.92/6.35	43.0	42.5	.5	7.90/6.35

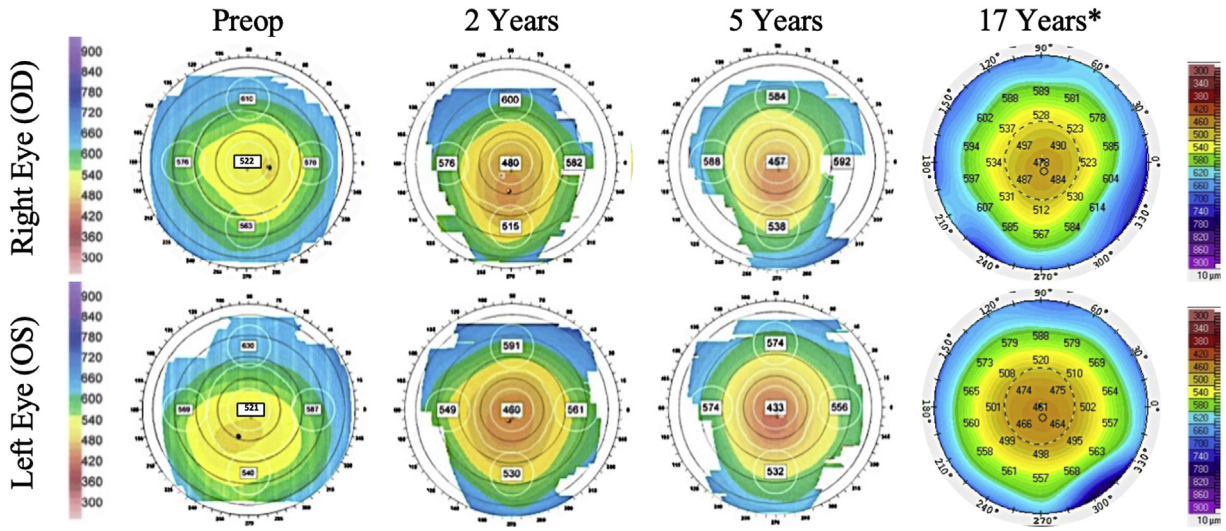

Fig. 1. Pachymetry values over the pre- and postoperative period measured with Orbscan (Bausch & Lomb Incorporated, USA). *taken with Pentacam (Oculus Optikgeräte, Wetzlar, Germany).

removed Salzmann nodule in the nasal cornea of the right eye re-occurred in the same location (Fig. 3). UDVA was 20/150 OD with a manifest refraction of −2.00 -2.00 × 005 OD representing further worsening of astigmatism in the right eye. UDVA was 20/300 OS with manifest refraction of −4.50 -0.50 × 61, indicating progressive myopic regression in the left eye. Conservative management of dry eye syndrome and Meibomian gland dysfunction was restarted, and no further surgical interventions were warranted at this time.

2. Discussion

Our patient was diagnosed via genetic panel with vascular EDS (vEDS, previously EDS type IV), usually characterized by a defect in type III and more rarely in type I collagen.[1] The human cornea relies on collagen to maintain its structural integrity, with type I collagen composing 75% of the vertebrate eye.[15] Interestingly, type III collagen is expressed in smaller amounts but is increased during wound healing and inflammation.[16] Mutations in collagen present a unique challenge when considering refractive surgery in patients with EDS, as their roles in Salzmann nodular degeneration, myopic regression, keratoconus, and dry eye syndrome remain unclear.

Dysfunctional tear syndrome (DTS) is a common LASIK complication[17] and disorder in EDS patients naïve to refractive surgery. For example a few studies have reported significantly reduced TBUT in EDS patients.[18–20] Cazzato et al. postulated that dry-eye symptoms could be a part of an underlying small nerve fiber disease in these patients.[19] Perhaps nerve fiber abnormalities in EDS patients in conjunction with the neural destruction caused by LASIK[13,21,22] would place these patients at higher risk for postoperative, dry eye syndrome. Some of our patient's ocular symptoms, such as itchy, uncomfortable eyes, can be explained by the widespread degranulation of inflammatory mediators seen in Mast Cell Activation Syndrome (MCAS).[23] Interestingly, this EDS patient has concurrent POTS disease and MCAS, which has been identified as a possible, novel disease cluster.[24]

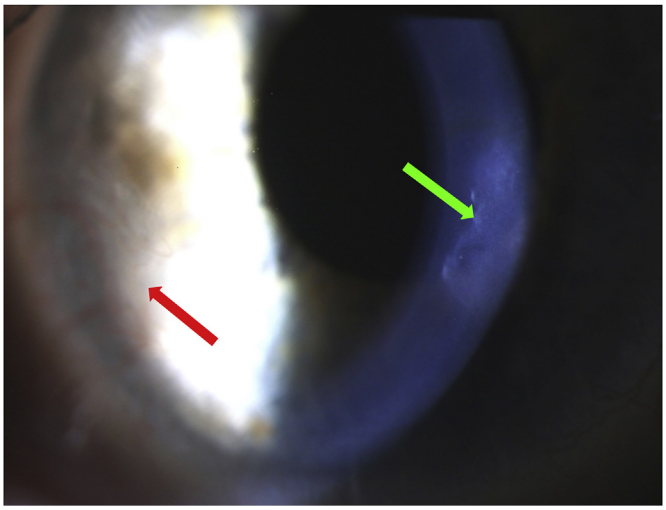

Fig. 3. Slit lamp examination of the right eye 17 years after LASIK surgery showing the recurrence of the nasal Salzmann nodule located at the 4 o'clock position (green arrow). A pseudopterygium (red arrow) can also be seen extending into the adjacent inferotemporal Salzmann nodule. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Our patient's chronic dry eye syndrome, along with the abnormal

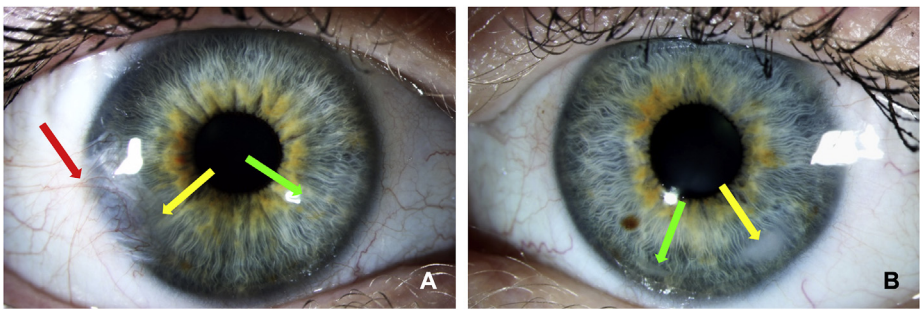

Fig. 2. Slit lamp examination at 17 years post LASIK. A = Right eye; two Salzmann nodules are located at the 4 o'clock (nasal; green arrow) and 8 o'clock (temporal; yellow arrow) positions, involving the LASIK flap edge. A 3 mm × 4 mm pseudopterygium (red arrow) is extending into the adjacent Salzmann nodule. B = Left eye; two Salzmann nodules are located at the 5 o'clock (inferotemporal; yellow arrow) and 7 o'clock (inferonasal; green arrow) positions; both involve the LASIK flap edge. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

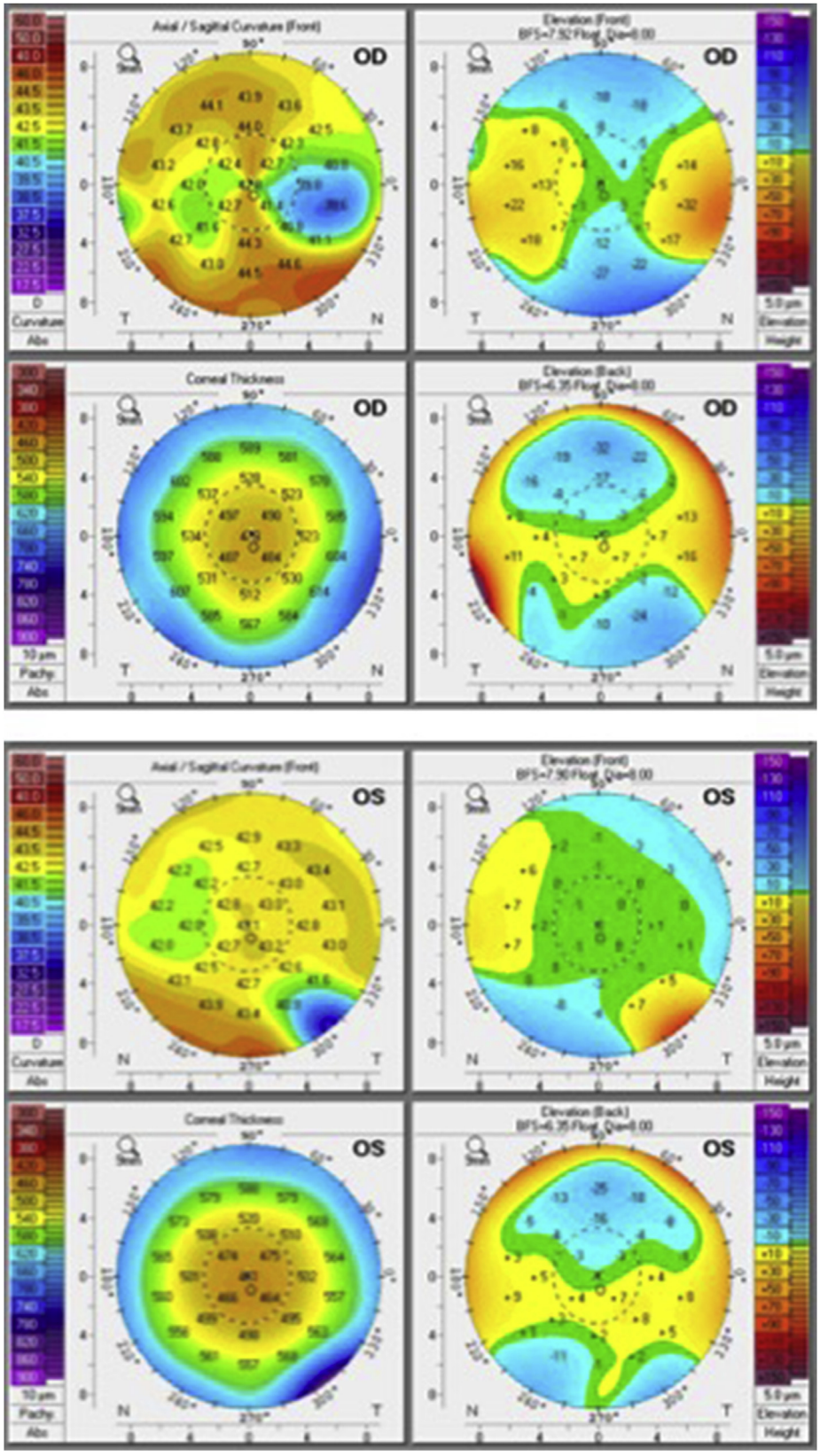

Fig. 4. Pentacam (Oculus Optikgeräte, Wetzlar, Germany) topographies of the right and left eye during the 17th postoperative year.

wound healing in EDS, may have predisposed her to Salzmann nodular degeneration, characterized by subepithelial, nodular thickening of the extracellular matrix.[25,26] Several case reports have also described Salzmann nodule formation after LASIK surgery.[21,27] Defects in Bowman's membrane, specifically due to the action of metalloproteinase-2 (MMP-2) or mechanical disruption during LASIK flap formation, allow for keratinocyte migration, fibroblastic differentiation, and subsequent subepithelial deposition of extracellular matrix in the form of Salzmann

nodules.[25,28,29] These usually resolve with conservative management, and the majority of refractory nodules will not recur after nodulectomy.[28] Our patient's Salzmann nodules abnormally persisted despite conservative medical and surgical treatment. No studies have evaluated the possible direct association of EDS and Salzmann nodular degeneration; however, defects in wound healing could predispose EDS individuals to longer epithelial regeneration times and provide sufficient conditions for Salzmann nodule formation. In addition, limbal stem cell deficiency secondary to chronic ocular surface disease may explain our patient's pseudopterygium formation.

In cases of high myopia (i.e. ≤ -6.00 D), recurrence of myopia after LASIK is a common complication.[30,31] Our patient experienced myopic regression after LASIK to values greater than her original prescription, possibly due to secondary changes in the cornea, lenticule, or axial length. No lenticular changes, including cataract formation, were found on exam throughout the postoperative period. However, lenticular myopia cannot be ruled out at this time. Potential corneal mechanisms for this myopic shift include corneal ectasia, corneal edema, stromal synthesis, epithelial ingrowth, and compensatory epithelial hyperplasia.[12,32] In the last mechanism, the epithelium thickens after flattening of the corneal surface in LASIK for myopic correction, and this is correlated to the degree of regression of myopia.[32] In our patient, pachymetry of the different corneal layers was unfortunately not measured; thus, it is difficult to assess if stromal synthesis or compensatory epithelial hyperplasia are causative factors in her myopic regression.

Another leading theory in the development of myopic regression after LASIK involves decreased corneal integrity due to mechanical weakening and subsequent anterior movement of the cornea. Subsequently, changes in anterior and posterior curvature cause increased positive refractive power leading to myopic regression.[31] Our patient experienced the opposite trend as her corneal refractive power decreased over the postoperative period, outlined by the K flat and K steep values of the right and left eyes in Table 2. Furthermore, posterior curvature did not significantly change over the postoperative period in either eye. Studies have not evaluated the changes in corneal integrity post-LASIK in EDS patients. However, the classic type of EDS (previously type II or mitis type), associated mainly with defects in collagen type V synthesis, has been shown to be associated with decreased central corneal thickness (CCT) in surgically naïve patients.[33] This finding, along with increased corneal laxity due to structural abnormalities in collagen[34] could possibly place EDS patients at higher risk for anterior movement of the cornea post-LASIK. However, our patient with vEDS did not have significant changes in CCT. These findings suggest a cause of myopic regression in our patient other than corneal changes.

Thus, axial elongation due to scleral weakness may be a causative factor. It is widely accepted in the literature that anterior-posterior length increases in myopic eyes.[35] Several studies inducing myopia in animal models have suggested that changes in collagen synthesis and fibrillar structure play an integral role in the axial elongation seen in myopia.[36–39] Additionally, mutations leading to structural and quantitative deficiencies in collagen have been linked to autosomal dominant transmission of myopia and axial elongation in a Caucasian population.[40] More research is warranted to determine if mutations in collagen are implicated in the frequent development of myopia in EDS patients. If this is true, perhaps our patient's myopic regression post-LASIK was due to poor scleral integrity and axial elongation, and not as a direct consequence of the surgery itself. However, axial length was not measured in our patient. It is also important to note that whether collagen weakening is a cause or consequence of myopia remains controversial.[41]

Our patient's decline in visual acuity in the right eye is likely also affected by mechanical distortion from Salzmann nodule and pseudopterygium formation (Fig. 2A). For example, Table 1 shows much higher progression of myopia OS and more astigmatism induced OD over the post-operative period. The right eye appears to have less myopic regression than the left eye as their spherical measurements were -2.00 D OD and -4.50 D OS. However, we believe this to be the effect of the pseudopterygium inducing astigmatic change in the right eye and masking its true myopic progression. Pterygia have been shown to demonstrate flattening of the cornea in their respective meridians and centrally at their apex. This is thought to be due to tractional forces from fibrovascular proliferation, although other mechanisms have been proposed.[42,43] These changes in anterior curvature of the right eye are demonstrated by a larger difference in K-values OD (Table 2) and by asymmetric bow tie pattern on topography in the right eye (Fig. 4) showing flattening in the axis of the pseudopterygium. The effect of the temporal Salzmann nodule OS can be seen as a large positive deviation from the best fit sphere in the inferotemporal cornea in Fig. 4, although it does not involve the visual axis. Removal of the pseudopterygium could potentially reduce refractive astigmatism and topographic irregularity of the right eye at the expense of increasing the myopic spherical power.[44]

Another rare but well-described complication of LASIK is corneal ectasia, described as keratometric steepening with or without associated corneal thinning.[11,45] Risk factors for the development of keratectasia post-LASIK include abnormal preoperative corneal topography, younger age, higher myopia, decreased residual stromal bed thickness, and preoperative corneal thinning.[11,45,46] Currently, EDS patients have a presumed higher risk for developing keratectasia, classifying EDS as a contraindication to LASIK surgery.[7]

There has been mixed anecdotal evidence suggesting an association between EDS and keratoconus.[8–10] Robertson et al. reported 50% of patients with keratoconus had concomitant joint hypermotility, mainly due to classic EDS.[10] Galperin et al. described a patient with benign joint hypermobility syndrome who developed keratectasia after LASIK surgery; however, this disorder is classified as a distinct syndrome, separate from EDS.[1,47] This area remains controversial as several studies, mainly in patients with classic EDS, have not demonstrated this association.[18,34,48,49] For example, a study by Cameron identified 11 patients with kyphoscoliotic EDS (previously type VI) with limbus-to-limbus corneal thinning but no instances of keratoconus.[8] It is possible that collagen defects may predispose EDS patients to keratectasia post-LASIK, even if keratoconus has not been proven to be associated with surgically-naïve EDS patients. More research needs to be done to elucidate the associations of the different types of EDS with corneal thinning, keratectasia, and keratoconus to better understand the risks involved in performing laser vision correction on these individuals. Of the risk factors for myopic regression post-LASIK, our patient only met criteria for younger age and did not develop keratectasia or keratoconus.

3. Conclusions

In summary, we describe the first patient with Ehlers Danlos Syndrome to have undergone LASIK surgery and be published in the academic literature. Our patient experienced postoperative complications, such as myopic regression, Salzmann nodular degeneration, and dry eye syndrome, possibly influenced by her underlying disorder of collagen synthesis. Due to lack of clinical evidence suggesting a corneal cause of her progressive myopia, it is possible that axial lengthening, influenced by collagen dysfunction, may be an origin of myopia in this patient. Furthermore, the persistence and recurrence of Salzmann nodules documented in this case may be due to aberrant wound healing in EDS in the setting of mechanical disruption of Bowman's membrane from LASIK. Currently, EDS is considered a relative contraindication in LASIK due to a presumed higher risk of developing postoperative keratectasia; however, since the various forms of EDS have differing molecular origins and disruptions in the function of specific types of collagen, we believe it is possible that not all forms of EDS need to be an absolute contraindication to LASIK. More research is warranted to study

ocular manifestations in each subtype of EDS to determine preoperative risk stratification for laser vision surgery.

4. Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

All authors report no financial interests to disclose.

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