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Phenotypic characterization of patients developing chronic dry eye and pain after refractive surgery: A cross-sectional study

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ABSTRACT

Purpose: To describe the clinical characteristics of patients suffering from chronic dry eye (DE) and pain after refractive surgery (RS).

Methods: Cross-sectional, observational, single-visit study. DE-, pain- and psychological-related symptoms were evaluated with specific questionnaires. DE-related tests evaluated tear osmolarity, conjunctival hyperemia, Meibomian gland dysfunction, tear stability and production, and ocular surface staining. Corneal mechanical sensitivity (Cochet-Bonnet) was measured pre/post topical anesthesia, and symptomatic variation post-anesthesia (anesthetic challenge test) was recorded. When pain was present, it was further categorized as neuropathic or nociceptive based on published criteria.

Results: We recruited 104 patients (39.5 ± 9.5 years). Most, 85.6%, had corneal RS as opposed to intraocular RS. Migraines, anxiety, depression ($p < 0.0001$), and central sensitization syndromes ($p = 0.0214$) were more frequent post-RS than pre-RS. Persistent DE-symptoms, severe in 86.5% patients, developed in a range of 0–204 months post-RS. Dryness and pain were the two most frequent symptoms. The only DE-related tests showing abnormal values were tear osmolarity (315.2 ± 17.1 mOsm/L; normal ≤308) and tear break-up time (4.1 ± 2.5 s; normal >7). Corneal sensitivity was 55.4 ± 7.0 mm, and decreased ($p < 0.0001$) after topical anesthesia, 6.0 ± 10.4 mm. However, it remained pathologically elevated, ≥10 mm in 61 (58.7%) patients. The normal symptomatic post-anesthesia improvement was absent in 58 (55.7%) patients. Ocular pain was present in 82 (78.8%) patients, and it was categorized as neuropathic in 66 (80.5%) of them, 63.5% of the entire cohort.

Conclusions: Chronic ocular pain and its neuropathic subtype were diagnosed in 78.8% and 63.5% respectively of patients seeking consultation for persistent symptomatic DE post-RS.

1. Introduction

There are an increased number of refractive surgery (RS) techniques, especially those that reshape the corneal stroma, available as alternatives to glasses or contact lenses. To achieve satisfactory results, RS requires a perfect match between the surgical parameters, potential variables, and each patient's profile. If that is accomplished, the general agreement is that more than 90% of appropriately selected patients achieve good uncorrected distance vision [1–4].

In addition to the well-known absolute and relative

Abbreviations: **CELab**, Controlled Environment Laboratory; **CCLRU**, Contact Lens Research Unit; **CL**, contact lenses; **DE**, dry eye; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **GRC**, Global Rating of Change; **HADS**, Hospital Anxiety and Depression Scale; **IASP**, International Association for the Study of Pain; **IOBA**, Institute of Applied Ophthalmobiology; **IQR**, interquartile range; **LASIK**, laser-assisted in situ keratomileusis; **LogMAR**, log (minimum angle of resolution); **mSIDEQ**, Modified Single Item Dry Eye Questionnaire; **NRS**, Numerical Rating Scale; **OSDI**, Ocular Surface Disease Index; **RS**, refractive surgery; **SD**, standard deviation; **TBUT**, tear break-up time; **VA**, visual acuity; **WFPRS**, Wong-Baker Faces Pain Rating Scale.

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contraindications of RS [1], there are postoperative complications, dry eye (DE) being the most common, that usually resolve after 6–12 months [5]. However, DE can persist in up to 20% of patients [5], and it becomes an even more worrisome situation when it is combined with ocular pain. This pain can be nociceptive, meaning that it is the consequence of some damage at the ocular surface, usually keratitis. It generally subsides when the cause is treated and disappears. However, the associated pain can also be neuropathic, meaning that there is no damage to the ocular surface that can explain the pain. This type of pain does not subside with the medications used to treat inflammation or nociceptive pain, and it will not abate unless treated in the early stages with an appropriate management of neuropathic pain [6–10].

Because both DE-related symptoms and neuropathic pain have a clear onset in RS patients, this suggests that the etiology of both is indeed a dysfunctional recovery of trigeminal nerve surgery-induced damage [11]. However, it is not known why this disabling symptomatology develops in some patients but not in others, and this is the key element that needs to be understood to avoid it in the future. To eventually accomplish this goal, it is fundamentally important to first know the phenotypic characteristic of these patients.

Thus, the aim of this study was to resolve a full phenotype of these patients by describing the clinical characteristics of those who consecutively came to our Institution after having developed chronic, usually severe DE-related symptoms and ocular pain after a RS procedure.

2. Methods

This cross-sectional, observational, single-visit study was approved by the Ethics Committee of the Valladolid University Clinical Hospital. All enrolled patients were informed of the aims of the study, and their written consent was obtained.

2.1. Patients and study design

This study included patients who developed DE-related persistent symptoms and chronic ocular pain after undergoing RS. They were recruited on-line from a patient association in which all had refractive surgery. The inclusion criteria were (a) DE-related persistent symptoms or established DE disease [12] and/or chronic ocular pain (defined below) in at least one eye following RS and continuing for at least 3 months before recruitment, and (b) assurance that both eyes were asymptomatic before RS and did not require the use of lubricants unless needed for contact lens (CL)-related discomfort [13]. Exclusion criteria were (a) failure to discontinue CL use at least 15 days before the study; (b) failure to discontinue any topical medication, including topical blood derivatives, at least 7 days before the study, and topical cyclosporine, tacrolimus or steroids at least 4 weeks before the study; (c) failure to discontinue artificial tears and lubricants at least 12 h before the study; (d) presence of any ocular surface disease, except DE disease; (e) any concomitant inflammatory ophthalmic disease; and (f) any ocular surgery, except the RS pertinent to this study.

From November 2015 to November 2018, the patients were evaluated between 9.00 and 13.00 h by the same investigators. Examinations were conducted under the so-called “simulated normal environment conditions”, set at 23°C and 50% relative humidity, in our Controlled Environment Laboratory (CELab) (www.visionrd.com/celab/) [14,15]. The purpose of this was to normalize the conditions in which clinical evaluations would be performed, thus minimizing the variation of a changing external environment [14].

2.2. Clinical questionnaires

The *Ocular Surface Disease Index (OSDI) questionnaire* defines the severity of DE-related symptoms according to the following scoring: mild (score 13–22), moderate (score 23–32), and severe (score 33–100). Patients with a score <13 were considered asymptomatic and excluded [16]. Within each OSDI questionnaire, the responses were analyzed in three groups: Group 1 questions assessed ocular surface symptoms (1–5 questions, score 0–20); Group 2 questions assessed vision-related tasks (6–9 questions, score 0–16); and Group 3 questions assessed the influence of environmental factors (10–12 questions, score 0–12) [17].

The *Modified Single-Item Dry Eye Questionnaire (mSIDEQ)* evaluates the frequency of dryness, foreign body sensation, burning, pain, itching, photophobia, and blurred vision on a scale from 0 to 4 (0 = absence of symptom; 1 = rarely felt; 2 = sometimes felt; 3 = always felt but without affecting daily activities; 4 = always felt with affected daily activities) (range, 0–28) [18].

The *Numerical Rating Scale (NRS)* rates the pain intensity of each symptom on a 0–10 scale: 0–1 = none, 2–4 = mild, 5–7 = moderate, 8–10 = severe [19]. The *Wong-Baker Faces Pain Rating Scale (WFPRS)* [20,21] uses 6 different faces, with a numerical equivalence, horizontally lined up to express an increasing level of pain intensity from left to right (0 = no pain; 2 = discomfort; 4 = light pain; 6 = moderate pain; 8 = , intense pain; 10 = unbearable pain) [22]. Both scales were used to rate each patient’s main or chief ocular symptom. Patients who did not choose pain as their main symptom were asked to rate their ocular pain again on both scales.

The *Hospital Anxiety and Depression Scale (HADS)* assesses the level of anxiety and depression. It consists of a 14-item self-reported scale (range, 0–42), in which the overall score is obtained from the sum of two 7-item subscales (range, 0–21 for each). The subscale cut-off points were 0–7 = normal; 8–10 = borderline; and >10 = existence of a clinical problem [23]. The total HADS score was obtained by summing each subscale [24,25].

2.3. Visual assessment

High (100%) and low (10%) contrast visual acuity (VA) was assessed with and without the use of eyeglasses. The evaluation was performed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart using the 22″ liquid crystal display screen (Topcon CO LDT, Tokyo, Japan) at a 4-m distance. It was recorded in log (minimum angle of resolution) (LogMAR) units [26].

2.4. Clinical tests

The following tests were performed in the given order:

Tear osmolarity was assessed in each eye using a nanosmometer (TearLab Corporation, San Diego, CA, USA). Values > 308 mOsm/L were considered abnormal [27].

Slit-lamp examination (SL-D7, Topcon Corporation, Tokyo, Japan) evaluated bulbar conjunctival hyperemia and Meibomian gland dysfunction for each eye following the Efron scale (range, 0–4) [28].

Tear stability was evaluated as the tear break-up time (TBUT). The mean of three consecutive measurements was calculated. Values ≤ 7 s were considered abnormal [29,30].

Ocular surface integrity was evaluated with fluorescein corneal staining using the Oxford scale (range, 0–5) [31] and the Cornea and Contact Lens Research Unit (CCLRU) grading scale (range, 0–5) [32]. Immediately after, temporal and nasal conjunctival staining was assessed using Lissamine green strips (I-DEW green, Entod Research Cell UK Ltd, London, UK) with Oxford scale. For both scales, staining ≥1 was considered abnormal.

Corneal tactile sensitivity was evaluated by Cochet-Bonnet esthesiometry (Luneau Ophthalmology, Chartres, France) of both central corneas before and after topical anesthesia following standard protocols (range, 60–0 mm). The longest filament length that resulted in a positive response was the corneal sensitivity threshold. Following the painful response, a drop of topical anesthetic (0.1% tetracaine and 0.4% oxibuprocaine) (Anestésico Doble Colirio; Alcon Cusí, El Masnou, Spain) was instilled onto each eye, and 2 min later the evaluation was repeated to assess the mechanosensitivity reduction. Scores <10 mm suggest that

pain would be peripheral or nociceptive and above or equal to 10 mm suggests neuropathic or centralized pain [33,34].

The *Anesthetic challenge test* was administered immediately after esthesiometry. Each patient rated the change in intensity of their current ocular symptoms post-anesthesia with the Global Rating of Change (GRC) scale. It measures enhancement or weakening of symptoms ranging from −5 (completely recovered), through 0 (unchanged), to +5 (much worse) [35]. Based on the interpretation of the GRC results peripheral pain was associated with a large reduction in the score (range −3 to −5); mixed pain with a slight reduction in the score (range, −2 to −1); and centrally mediated pain with unchanged or increased score (range, 0 to +5).

Basal tear production was determined by the Schirmer's test with topical anesthesia. Values ≤ 5 mm were abnormal [36].

2.5. Ocular pain-related definitions

The presence of ocular pain meant that both NRS and WFPRS scores were ≥2 [19]. According to the inclusion criteria, eye pain was considered to be chronic if it lasted ≥3 months [37]. Ocular pain frequency was evaluated with question number 3 of the OSDI questionnaire and the pain assessment of the mSIDEQ. The occurrence of pain radiating through the trigeminal nerve territory was also asked, and the presence of allodynia and hyperalgesia, highly suggestive of centralized neuropathic pain [38,39], were also recorded. Allodynia was defined as pain caused by an innocuous stimulus that does not normally elicit pain. Examples include pain caused by moving air around the ocular surface, such as air conditioning or windy conditions, by a light touch of the periocular skin, or pain caused by increased light sensitivity (photoallodynia) [40]. Hyperalgesia was defined as a long-lasting disproportionate pain from a stimulus that is normally only slightly painful.

"Neuropathic ocular pain" was defined following the definition of The International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory system" [41]. Based on the abundant published literature about neuropathic pain, and also following ophthalmology-based guidelines [42], it was considered present when at least 3 of the following 5 requirements were met: (1) evidence of damage or injury to the somatosensory nervous system [43]; (2) minimum corneal damage (Oxford score ≤1) [44]; (3) the presence of at least two typical descriptors (tingling, pins or needles, stabbing, shooting or electric shock-like pains) [33,38,45]; (4) abnormal corneal sensitivity including allodynia, hyperalgesia, and/or radiating pain [46]; and (5) persistence of symptoms after topical anesthesia (GRC scale between −2 and +5) [33]. Additionally, the diagnosis of neuropathic pain was corroborated by a medical doctor specializing in oculofacial pain (coauthor EO). Any ocular pain not classified as neuropathic was considered nociceptive.

2.6. Statistical analysis

Data were statistically analyzed using the SPSS software statistical package version 22.0 (SPSS Inc., Chicago, IL, USA) and R version 4.0.3 [47]. The variables assessed for each eye were expressed as the mean of both eyes, except when only one eye underwent RS or only one presented symptoms. Quantitative continuous data were summarized as means±standard deviations (SD), and ordinal values were described using medians and interquartile ranges [IQR], unless otherwise specified in the text. The normality assumption was checked by the Kolmogorov-Smirnov test. For quantitative variables, Student's t-tests for two independent samples were used to check differences between pairs of pain groups. Levene's test was used to check homogeneity of variance and Welch's test was used when this assumption was not valid. When the normality assumption was violated, the nonparametric alternative, Mann-Whitney *U* test, was performed. With qualitative variables, Chi-square tests were done to compare proportions. The Wilcoxon test was used to compare pre- and post-anesthetic Cochet-Bonnet values. Bonferroni correction was applied to adjust the experiment-wise error rates.

Relationships between quantitative variables were quantified by Pearson or Spearman's correlation coefficient depending on the assumption of data distribution normality. P-values ≤0.05 were considered statistically significant.

3. Results

3.1. General description of the included patients

A total of 104 patients (207 eyes) were recruited, with a mean age of 39.4 ± 9.5 (range, 23–63) years. There were more women (67.3%), and their age, 41.3 ± 9.9 (range, 25–63) years, was older ($p = 0.0069$) than that of the men, 35.4 ± 7.5 (range, 23–48) years. The mean time between the patients' RS and their visit to our institution was 7.3 ± 6.1 years with a large range, between 4.0 months and 25.7 years.

Most patients, 89 (85.6%, 177 eyes), had corneal RS and 67 (75.3%) underwent laser-assisted in situ keratomileusis (LASIK). The remaining 15 patients (14.4%, 30 eyes) had intraocular RS, most frequently lens phacoemulsification and multifocal intraocular lens implantation. Of these, 6 (5.8% of the total) had intraocular RS only and 9 (8.7% of the total) had an additional corneal retreatment. The age of the intraocular RS Group, 49.5 ± 10.5 years, was older than the corneal RS Group, 37.7 ± 8.3 years ($p < 0.0001$).

Globally, patients underwent 2.8 ± 1.4 surgeries, and all but one had bilateral RS. Thirty-four patients (32.7%) had more than one RS procedure in each eye. Of the 89 patients undergoing corneal RS, 25.8% had retreatment.

The preoperative spherical equivalent refractive error was −3.3 ± 4.5 (range, −19.00 to +8.50) diopters. Pre-RS, the vast majority (98.1%) of patients used eyeglasses to correct their refractive error, and 63.5% had used CLs for a mean of 119.5 ± 93.3 months.

Among the patients' pre- and post-RS reported medical history (Table 1), neurological disorders, anxiety, and depression, as well as the so-called central sensitization syndromes [42] were significantly more frequent after RS.

More than 90% of the patients used lubricants during the day, and half used them at bedtime. Around 15% were using topical cyclosporine, blood-derived products, and followed home-based lid hygiene protocols (Table 2).

DE-related symptoms and/or ocular pain arose 16.8 ± 42.8 months (range, 0–204 months) after RS. Most patients (71.2%) started their symptomatology immediately after RS. The mean time from onset of symptoms to our study was 5.9 ± 5.5 years (range, 4 months–25.7 years). Only 5 (4.8%) patients had unilateral symptoms, and one other patient underwent RS unilaterally.

3.2. Analysis of clinical questionnaires

Responding the *OSDI questionnaire*, most patients (86.5%) reported severe symptoms, while 9.6% had moderate symptoms, and only 3.8% reported mild symptoms. The global OSDI value was 60.7 ± 22.7 (range, 18.8–100.0), indicating severe symptomatology. Based on the analysis of OSDI questions by groups, for Group 1, 70.2% of the patients were sensitive to light most or all the time, and 69.2% had painful or sore eyes half of the time (Fig. 1). For Group 2, about half of the patients had difficulty while reading, driving, or working with computers most or all the time. For Group 3, most patients were noticeably affected by adverse environments.

The global *mSIDEQ score* was 18.6 ± 4.9 (range, 0–28). Dryness and photophobia were always felt by 80.8% and 71.2% of the sample, respectively (Fig. 2). Pain was always present in 53.8%.

Pain frequency assessed with mSIDEQ was positively correlated with the OSDI score ($r = 0.435$; $p < 0.001$), anxiety ($r = 0.429$; $p < 0.001$), and depression ($r = 0.388$; $p < 0.001$). It was also associated with higher

Table 1
Reported medical history, non-ocular surgeries, and systemic medication taken by patients (n = 104) having refractive surgery (RS) at least 3 months prior to the study evaluation.

Medical History	Onset before RS n (%)	Onset after RS n (%)	P-value
Neurological disorders	5 (4.8)	53 (51.0)	**<0.0001**
Migraines	5 (4.8)	48 (46.2)	**<0.0001**
Dizziness/Vertigo/Palypnosia	-/-/-	3 (2.9)/1 (1.0)/1(1.0)	0.2448/~1/~1
Atopic diseases	43 (41.3)	3 (2.9)	***<0.0001***
Allergic seasonal rhinitis/conjunctivitis*	18 (17.3)/4 (3.8)	-/1 (1.0)	***<0.0001***/0.3653
Food allergy	10 (9.6)	–	***0.0035***
Atopic dermatitis/Asthma	6 (5.8)/5 (4.8)	2 (1.9)/-	0.2794/0.0702
Psychiatric disorders	3 (2.8)	34 (32.7)	**<0.0001**
Anxiety and depression**/Psychotic episodes	3 (2.8)/-	33 (31.7)/1 (1.0)	**<0.0001**/~1
Metabolic- and hormonal-related disorders	9 (8.6)	15 (14.4)	0.2779
Autoimmune hypothyroidism	5 (4.8)	3 (2.9)	0.7184
Hypercholesterolemia/High blood pressure	1 (1.0)/2 (1.9)	8 (7.7)/3 (2.9)	**0.0409**/~1
Diabetes mellitus/Hematochromatosis	1 (1.0)/-	-/1 (1.0)	~1/~1
Central sensitization-related syndromes	5 (4.8)	16 (15.4)	**0.0214**
Bruxism/Temporomandibular disorders	-/-	3 (2.9)/2 (1.9)	0.2448/0.4774
Chemical sensitization syndrome	2 (1.9)	2 (1.9)	~1
Early amenorrhea	–	2 (1.9)	0.4774
Irritable bowel syndrome	–	2 (1.9)	0.4774
Chronic fatigue syndrome	–	2 (1.9)	0.4774
Fibromyalgia/Cervical dystonia	1 (1.0)/1 (1.1)	1 (1.0)/-	~1/~1
Sleep disorders (insomnia)	–	1 (1.0)	~1
Radial nerve sensitivity alteration	–	1 (1.0)	~1
Perineal pain (spinal neurostimulator)	1 (1.0)	–	~1
Dermatologic diseases	19 (18.3)	2 (1.9)	***0.0002***
Contact hypersensitivity (drugs, metals …)	14 (13.5)	–	***0.0003***
Rosacea/Psoriasis/Lichen planus	2 (1.9)/1 (1.0)/1 (1.0)	2 (1.9)/-/-	~1/~1/~1
Melanoma	1 (1.0)	–	~1
Gastro-intestinal disorders	4 (3.8)	10 (9.6)	0.1665
Hiatal hernia/Gastroesophageal reflux	1 (1.1)/1 (1.1)	2 (1.9)/3 (2.9)	~1/0.6136
Chronic gastritis/Helicobacter pylori	1 (1.0)/-	-/1 (1.0)	~1/~1
C Hepatitis/Celiac disease	1 (1.0)/-	-/4 (3.8)	~1/0.1299
Rheumatology-related disorders	2 (1.9)	6 (5.8)	0.2794
Arthralgias (unclassified)	2 (1.9)	5 (4.8)	0.4419
Sjögren's syndrome	–	1 (1.0)	~1
Hematologic disorders	4 (3.8)	1 (1.0)	0.3653
Immune thrombocytopenic purpura	1 (1.0)	-	~1
Raynaud syndrome	1 (1.0)	1 (1.0)	~1
Factor V Leiden thrombophilia	1 (1.0)	-	~1
Leukocytoclastic vasculitis	1 (1.0)	-	~1
Non-Ocular Surgeries – n (%)	**89 (85.6)**	**3 (2.9)**	***<0.0001***
Gastrointestinal surgeries	41 (39.4)	2 (1.9)	***<0.0001***
Orthopedic procedures	18 (17.3)	1 (1.0)	***0.0001***
Gynecologic-obstetric surgeries	16 (15.4)	–	*0.0001*
Ear, nose, throat and lung surgeries	8 (7.7)	–	*0.0116*
Urology or nephrology surgeries	6 (5.8)	–	*0.0383*
Systemic Medication – n (%)	**2 (1.9)**	**57 (54.8)**	**<0.0001**
Anxiolytics	1 (1.0)	20 (19.2)	**<0.0001**
Antidepressants	1 (1.0)	18 (17.3)	**0.0001**
	–	19 (18.3)	**<0.0001**
Analgesics (only those for ocular pain)			
Non-steroidal anti-inflammatory drugs	–	7 (6.7)	**0.0211**
Paracetamol (acetaminophen)	–	3 (2.9)	0.2448
Opioids	–	3 (2.9)	0.2448
Antiepileptics	–	3 (2.9)	0.2448
Metamizole (dipyrone)/Flunarizide	-/-	2 (1.9)/1 (1.0)	0.4774/~1
Miscellanea	10 (9.6)	33 (31.7)	**0.0002**
Vitamins, fatty acids/Antiacids	1 (1.0)/-	15 (14.4)/-	**0.0007**
Levothyroxine/Insulin/Contraceptives	4 (3.8)/1 (1.0)/-	2 (1.9)/-/5 (4.8)	0.6787/~1/0.0702
Anti-cholesterol drugs/Antihypertensives	1 (1.0)/1 (1.0)	3 (2.9)/3 (2.9)	0.6136/0.6136
Antihistamines/Bronchodilators/Steroids	1 (1.0)/1 (1.0)/-	1 (1.0)/-/2 (1.9)	~1/~1/0.4774
Pilocarpine/Hydroxychloroquine	–	1 (1.0)/1 (1.0)	~1/~1

*These patients were evaluated out of season. **All patients who developed depression after RS attributed it to their ocular complications after RS. Pre-RS data correspond to diagnoses collected from previous medical reports supplied by patients. Two-sample test for equality of proportions with continuity correction was done to calculate P-values. P-values in bold and in italics indicate significantly higher numbers after RS or before RS, respectively.

Table 2
Medications and other strategies used by patients (n = 104) either currently or in the past but abandoned for lack of efficacy.

Therapeutic strategies	Current use n (%)	Past use n (%)
Lubrication during the day	97 (93.3)	7 (6.7)
Lubrication at bedtime	46 (44.2)	12 (11.5)
Topical cyclosporine (>3 months)[a]	16 (15.4)	12 (11.5)
Blood derivatives	15 (14.4)	11 (10.6)
Lid hygiene: home-based/in-office procedures	15 (14.4)/-	1 (1.0)/1 (1.0)
Punctal plugs	3 (2.9)	8 (7.7)
Topical corticosteroids (>1 month)[a]	3 (2.9)	11 (10.6)
Oral doxycycline (>1 month)[a]	3 (2.9)	–
Topical antibiotics	–	3 (2.9)
Topical tacrolimus (>3 months)[a]	–	1 (1.0)

[a] The current use of these medications was discontinued 1-3 months before enrollment, as per the inclusion/exclusion criteria.

use of analgesics, (r = 0.222; p = 0.024) and antidepressants (r = 0.248; p = 0.011).

Among the chief symptoms, dryness was chosen as the most bothersome by 62.5% of the patients with a score of 7.3 ± 1.7 and 7.1 ± 2.1, in NRS and WFPRS scales respectively (Fig. 3). Severe or unbearable dryness was reported by 46.2% and 53.8% based on these scales.

Ocular pain was chosen by 29.8% of the patients as the most bothersome symptom. The NRS and WFPRS scores were 6.9 ± 2.4 and 7.3 ± 2.2, and 48.4% and 58.1% reported severe or unbearable pain, respectively.

Ocular pain questionnaires for all 104 patients showed an pain intensity of 5.2 ± 3.2 and 5.2 ± 3.1, with NRS and WFPRS scales respectively (Fig. 3). Pain was present in 78.8% of the patients with a mean of 6.5 ± 2.3 on the NRS and 6.4 ± 2.3 on the WFPRS. Based on both scales, scores ≥5 and ≥ 6, were reported by 67.0% and 71.9%, respectively. The severity of pain was correlated with higher use of analgesics (r = 0.242; p = 0.014).

The overall score for the HADS questionnaire was 18.9 ± 9.6, and for the anxiety subscale it was 10.5 ± 5.0, indicating a clinical problem. Pathological anxiety values were present in 48.1% of the patients, and 21.1% had borderline values. The depression subscale was 8.4 ± 5.1, meaning "borderline". Pathological depression was present in 33.7%,

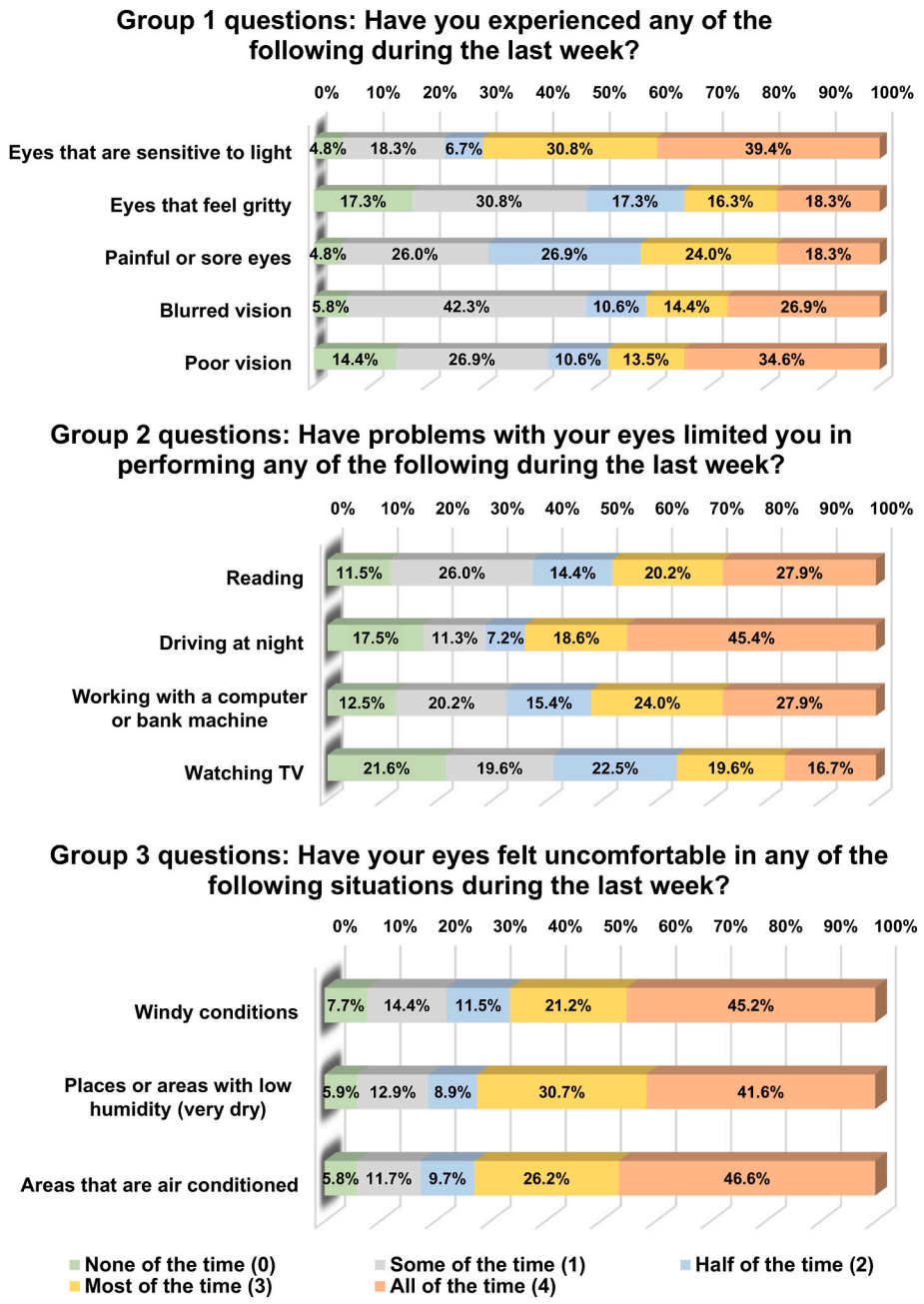

Fig. 1. Percentage of patients that express each frequency answer for each OSDI questionnaire item.
Questions in group 1 correspond to ocular surface symptoms. Questions in group 2 correspond to vision-related tasks. Questions in group 3 correspond to effect of environmental factors on common tasks. OSDI, Ocular Surface Disease Index.

and 20.2% had borderline depression. The NRS pain severity was positively correlated with the level of anxiety ($r = 0.298$; $p = 0.002$) and depression ($r = 0.295$; $p = 0.002$) and with a higher use of antidepressants ($r = 0.280$; $p = 0.004$).

3.3. Visual assessment

The uncorrected and corrected distance high contrast VAs were 0.16 ± 0.29 and 0.09 ± 0.22 LogMAR, respectively. The uncorrected and corrected distance low contrast VAs were 0.60 ± 0.31 LogMAR and 0.54 ± 0.27 LogMAR, respectively.

3.4. Clinical tests

The tear osmolarity for the study group was 315.2 ± 17.1 mOsm/L (range, 286–373 mOsm/L), and most patients, 66.3%, had increased values.

The median [IQR] conjunctival hyperemia was 1.5 [1.0–2.0], and 60 (57.7%) patients had a score >1. The Meibomian gland disfunction median score was 1.0 [0.5–1.5], and 36.5% of the patients had a score of >1. The TBUT value was 4.1 ± 2.5 (range, 0.9–15.8) seconds, and 89.4% had shorter values.

The median corneal fluorescein staining was 1 [0.5–1.5] (range, 0.0–3.5) on the Oxford scale and 0.8 [0.4–1.3] on the CCLRU scale. Only 1 patient had severe staining (≥3). The median for conjunctival staining was 0.5 [0.0–1.0].

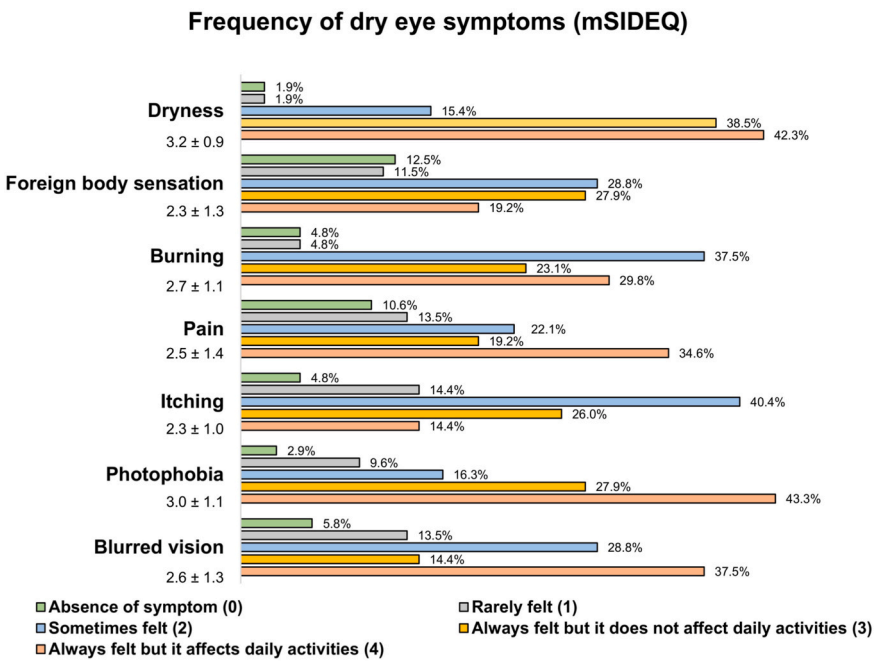

Fig. 2. Percentage of patients having dry eye symptoms and the frequency of occurrence.
The mean ± standard deviation of each mSIDEQ score, representing the frequency of occurrence, is shown under each symptom. mSIDEQ, Modified Single Item Dry Eye Questionnaire.

The corneal mechanical sensitivity before topical anesthesia was 55.4 ± 7.0 mm (range, 25.0–60.0 mm). After topical anesthesia, the sensitivity decreased to 6.0 ± 10.4 mm (range, 0.0–50.0 mm; $p < 0.0001$). The post-anesthesia value was ≥10 mm in both eyes of 25.0% of the patients (20.5 ± 12.2 mm) and for 33.7% of the patients, it was ≥10 mm in only one eye.

For the anesthetic challenge test, the GRC score after topical anesthesia was −0.6 ± 2.4, meaning no relief of symptoms in general. Twenty-four percent of the patients reported a great improvement of symptoms; 20.2% reported a slight improvement; 31.7% reported no change; and 24.0% reported worsening symptoms. Based on this test alone, these data suggest that 55.7% of the patients had centralized symptoms.

The value of the Schirmer test with topical anesthesia was 7.3 ± 7.3 mm. Although 47.1% of the patients had values of ≤5 mm, only 10.6% were <2 mm.

3.5. *Classification of patients according to their ocular pain characteristics*

According to the NRS and WFPRS, 82 (78.8%) patients had chronic ocular pain. The characteristics of the pain suffered by patients having corneal RS were similar to those of patients having intraocular RS (Table 3). Of the patients with pain, (a) all had obvious evidence of injury to the somatosensory nervous system due to the RS; (b) 67 (64.4%) had only a small amount of corneal damage (Oxford score ≤1); (c) 70 (67.3%) had at least two descriptors of neuropathic pain; (d) 37 (35.6%) had one or more of the three symptoms of abnormal corneal pain, i.e., 12 (11.5%) with abnormal corneal sensitivity, 12 (11.5%) with hyperalgesia, and 29 (27.9%) with radiating pain; and (e) 79 (76.0%) reported persistence or the absence of improvement of symptoms after the anesthetic challenge test.

Thus, 66 (80.5%) of the 82 patients with chronic pain had neuropathic pain. This represents 63.5% of the study patients. The remaining 16 of the 82 (19.5%) patients were then classified as having nociceptive pain. All 16 patients had corneal staining >1; 13 of the 16 (81.2%) had Cochet-Bonnet values after topical anesthesia <10 in both eyes; the anesthetic test evaluated by GRC scale showed reduction of symptoms in 11 of the 16 (68.7%) patients, and none of them had radiating pain, hyperalgesia, or allodynia.

The severity of pain assessed with NRS was significantly higher in the neuropathic pain group compared to the nociceptive pain group (Table 4). In contrast, the scores of the DE-related questionnaires were significantly higher for the nociceptive pain group than for neuropathic pain group. Patients in both pain groups had anxiety, depression, and headaches; however these symptoms were significantly greater in the neuropathic pain group. Corneal sensitivity was similar in the three groups, but after topical anesthesia, it was significantly higher in the neuropathic group compared to the no pain group.

Corneal staining was significantly higher in the nociceptive pain group, as expected, according to the classification criteria (Table 4). Conjunctival staining was moderately correlated with the OSDI ($r = 0.509$, $p = 0.044$) and pain NRS ($r = 0.579$, $p = 0.019$) in the nociceptive group, but not in the neuropathic pain group.

4. Discussion

In this study, we characterized a large cohort of patients who developed persistent DE symptomatology after undergoing RS. We also recorded and analyzed the types of chronic ocular pain and other variables. For RS patients, the persistent DE-related symptoms assessed by the different validated measurements and scales provided results that encompassed the severity ranges, while the clinical signs were within normal limits or only mildly altered (i.e., staining, osmolarity). Chronic ocular pain was present in 78.8% of all patients, and it was classified as neuropathic in 73.2% of them, representing 57.7% of the total cohort.

Almost 70% of the recruited patients were women, as in other studies of similar pathologies [19,48]. This is consistent with the finding by others that female sex is associated with increased risk of developing post-RS chronic symptomatology [5,11,49].

Most patients underwent corneal RS, and of them, most had LASIK. However, 5.8% had intraocular RS, indicating that it can trigger problems similar to those experienced following corneal RS. The present work included 9 of 15 patients who had an intraocular lens (usually

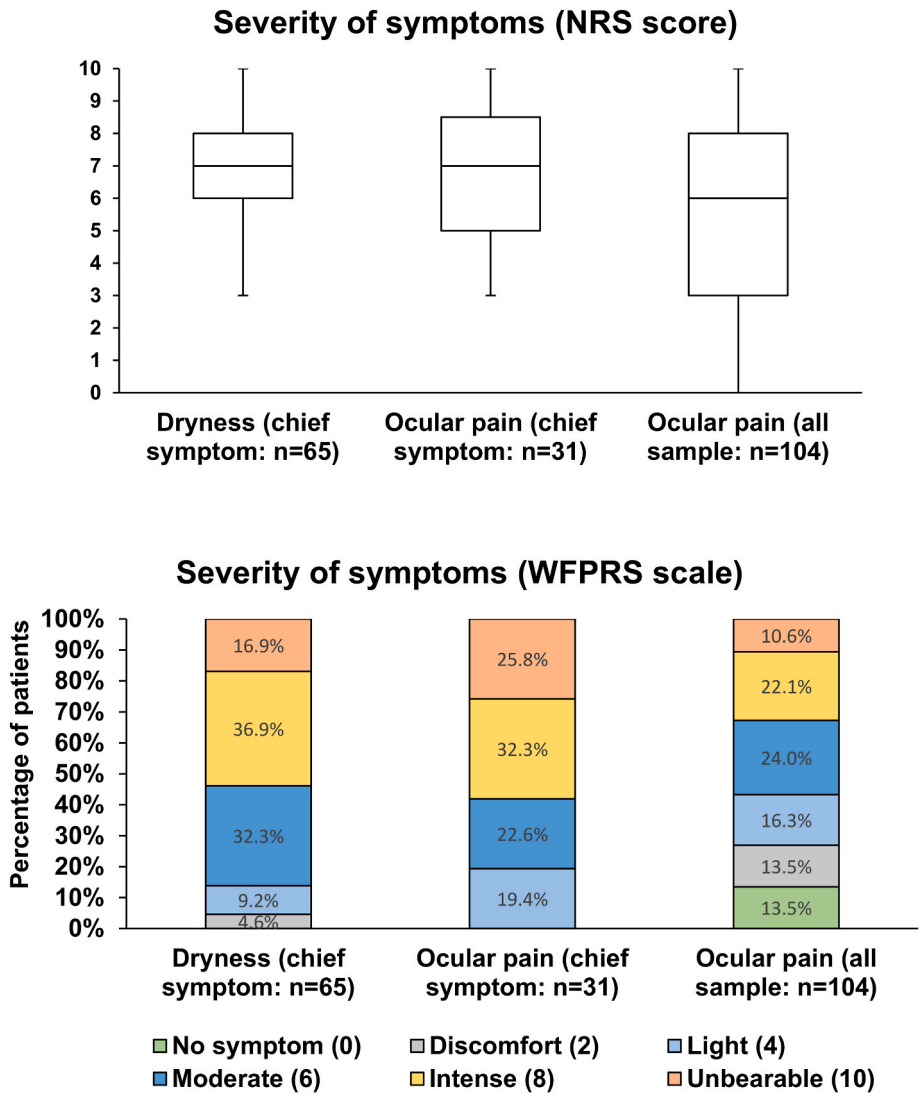

Fig. 3. Severity of chief symptoms and ocular pain.
Top: Numerical Rating Scale (NRS) score for each symptom. Boxes, 25th to 75th percentiles; central black horizontal lines, median values; Whiskers, minimum and maximum values. Bottom: Percentage of patients suffering each symptom as classified by the Wong-Baker Faces Pain Rating Scale (WFPRS) categories.

multifocal) and an additional keratorefractive retreatment procedure. These patients represented 8.7% of the study sample. This is in concordance with the data reported by *Gurdersen* et al. [50] who found that after multifocal intraocular lens implantation, a retreatment was necessary in 10.8% of the study eyes (12.4% of the study patients). In addition, these authors observed that residual astigmatism after multifocal intraocular lens implantation was the main cause for corneal retreatment in their sample.

Although our patients developed their symptoms between 0 and 204 months post-RS, more than half of them began having symptoms in the immediate postoperative period. For some, the symptoms began as soon as the first day after surgery, and for many, the symptoms were out of proportion to what was expected, and they never went away. *Moshirfar* et al. reported the onset of symptoms at 9.6 months in a case series with only 18 LASIK patients [48] In contrast, *Sobas* et al. reported that almost all of their patients undergoing surface ablation surgery had noticeable pain immediately after surgery, but the pain disappeared in 2–3 days [51,52]. Although most of them started with immediate postoperative symptoms, for some there was a long delay of about 5 years between the onset of symptoms and their visit to our institution. By then the symptomatology was severe, and a large proportion had centralized neuropathic pain. We hypothesize that the symptomatology worsened with time, but this aspect was not specifically asked. We also presume that the main reason for this delay was the absence of sufficient medical knowledge of these complications after RS at the time these patients were recruited. We are now observing that patients are coming to be evaluated sooner, usually within the first year after RS. We also hypothesize that early and effective treatment is crucial to avoid central sensitization.

The prevalence of post-RS DE-related symptomatology is approximately 95% in the immediate post-operative period, 50% at one week, 40% at one month, and persisting in 20–35% of the patients for 6 months or more [49,53–55]. Patients with severe DE also report specific symptoms of persistent and disabling pain, sometimes accompanied by hyperalgesia and allodynia. This set of symptoms is known as neuropathic ocular pain, corneal neuralgia, or keratoneuralgia [34], and there is a paucity of data regarding its prevalence and incidence. *Levitt* et al. [56] reported that 20–55% of their LASIK patients had at least mild symptoms of DE or persistent ocular pain; whereas *Moshirfar* et al. reported that only one patient per 900 undergoing LASIK developed corneal neuralgia [48].

Because the presence of persistent DE-related symptoms was one of the inclusion criteria, we cannot report the prevalence of DE after RS in this study population. However, among the patients, the prevalence of

Table 3
Characteristics of ocular pain in patients who had corneal or intraocular refractive surgery.

Ocular Pain Characteristics	C-RS (n = 89) n (%)	I-RS (n = 15) n (%)	p-value
Presence of pain			
No pain	21 (23.6)	1 (6.7)	0.147
Nociceptive pain	13 (14.6)	3 (20.0)	0.592
Neuropathic pain	55 (61.8)	11 (73.3)	0.391
Severity of pain (scale 0–10)			
NRS scale - all patients (n = 104)	5.1 ± 3.2	5.9 ± 3.0	0.4104
Patients with pain (n = 82)	6.5 ± 2.1	6.2 ± 2.8	0.7184
Patients with nociceptive pain (n = 16)	7.8 ± 1.8	5.6 ± 2.3	0.521
Patients with neuropathic pain (n = 66)	7.5 ± 1.9	7.7 ± 1.5	0.781*
WFPRS scale - all patients (n = 104)	5.0 ± 3.2	6.3 ± 2.6	0.1937
Patients with pain (n = 82)	6.4 ± 2.3	6.6 ± 2.4	0.809
Patients with nociceptive pain (n = 16)	7.5 ± 1.8	6.6 ± 3.0	0.364
Patients with neuropathic pain (n = 66)	7.3 ± 1.9	8.1 ± 1.4	0.353
Frequency of pain			
Most or all of the time (OSDI 3–4)	39 (43.8)	15 (14.4)	0.724
Always felt (mSIDEQ, 3–4)	47 (52.8)	9 (60.0)	0.576
Onset of pain (months post-RS)	18.9 ± 45.6	4.2 ± 15.4	0.317
Pain Radiation			
Peri-ocular	17 (19.1)	4 (26.7)	0.7432
Retro-ocular (orbit)	5 (5.6)	–	0.7729
Forehead	9 (10.11)	–	0.4282
Temporal regions	5 (5.6)	1 (6.7)	~1
Parietal and occipital areas	4 (4.5)	3 (20.0)	0.0969
Associated headaches	40 (44.9)	9 (60.0)	0.4231
Hyperalgesia	10 (11.2)	1 (6.7)	0.595
Allodynia	10 (11.2)	1 (6.7)	0.595
Harmful activities			
Computer use and electronics displays	69 (77.5)	12 (80.0)	~1
Air conditioning	74 (83.1)	10 (66.6)	0.2526
Visual tasks	39 (43.8)	8 (53.3)	0.6859
Others			
Stress	2 (2.2)	–	~1
Lack of sleep	3 (3.4)	–	~1
Intense lights	4 (4.5)	1 (6.7)	~1
Air currents	8 (9.0)	–	0.4934
Electronic displays	5 (5.6)	–	0.7729
Indoors and dry environments	2 (2.2)	–	~1
Seasonal or circadian variations			
Worse in summer	20 (22.5)	4 (26.7)	0.9797
Worse in autumn	5 (5.6)	–	0.7729
Worse in spring	7 (7.9)	–	0.5702
Worse in winter	12 (13.5)	1 (6.7)	0.7516
Worse in the morning	30 (33.7)	6 (40.0)	0.8567
Worse in the evening	49 (55.1)	9 (60.0)	0.9397
No variation	12 (13.5)	1 (6.7)	0.7516
Others	9 (10.1)	2 (13.4)	~1

C-RS: Corneal Refractive Surgery; I-RS: Intra-ocular Refractive Surgery; mSIDEQ: Modified Single Item Dry Eye Questionnaire; NRS: Numerical Rating Scale; OSDI: Ocular Surface Disease Index; SD: Standard Deviation; WFPRS: Wong-Baker Faces Pain Rating Scale; OSDI and mSIDEQ pain questions assess the frequency of pain. * Student's test was performed. All other comparisons were by Mann-Whitney *U* test.

severe DE symptomatology was 86.5%. Further, the prevalence of ocular pain in our series was 78.8%, and of these, the pain in 63.5% (57.7% of the initial 104 included patients) was classified as neuropathic in origin.

Among the risk factors identified for developing post-RS neuropathic pain are neuropsychiatric conditions and central sensitization syndromes [48,57–59]. While these conditions and syndromes were evident in our study population, in most instances they began after and as a consequence of the ocular issues, not before. Before RS, only 4.8% of our patients reported having neurological disorders (i.e., migraines), 2.8% reported having psychiatric comorbidities (i.e., anxiety and depression), and 4.8% reported having central sensitization syndromes. However, the prevalence of these not only increased significantly post-RS to 51.0%, 32.7%, and 15.4%, respectively, but the patients directly attributed these disorders to their ocular problems. Accordingly, the consumption of anxiolytics, antidepressants, and analgesics was significantly higher post-RS. In Spain, 11.0% of the population is reported to have neurological disorders [60], 6.5% have anxiety and depression [61], and 3.0% have central sensitization syndromes [62]. These percentages are closer to and actually higher than the incidence described in our series before RS. A limitation in this regard is the possible existence of recall bias with respect to the pre-RS data, as they were obtained while taking the medical history, and not all patients had medical records supporting their statements.

It is possible that the comorbidities of neuropsychiatric conditions and central sensitization syndromes facilitate post-RS neuropathic pain. However, our data support the role of the post-RS ocular issues as a trigger that induces a higher incidence of these neuropsychiatric conditions and central sensitization syndrome comorbidities [58]. The higher prevalence of depression in DE patients is more closely associated with DE symptoms than DE signs [58]. These results are in perfect accord with ours because our patients showed severe symptoms that were unsupported by the classical equivalent signs [42,63].

Only osmolarity, which increased, and TBUT, which decreased, were significantly altered in our patients, regardless of the presence of pain. Osmolarity values above the cut-off point are generally present in DE [27,64], in CL wearers [65], and in RS eyes at 6 months after surgery [66]. *It has been* reported that patients with short TBUTs and persistent severe DE had higher corneal pain sensitivity than healthy patients, even though they had similar tactile sensitivity [67,68]. Our DE patients had a decreased TBUT of around 4 s regardless of whether or not pain was present.

DE symptoms have a large negative impact on the quality of life, especially if accompanied by neuropathic pain [69]. Thus, patients with severe DE are more likely to experience psychological stress, depression, and/or anxiety [70,71]. Also, severe DE has previously been associated with higher degrees of ocular pain and with the development of neuropathic pain. In our study, most patients (86.5%) had severe DE-related symptoms, according to the OSDI questionnaire.

The main and most bothersome symptom reported after RS in our study was dryness, which is consistent with previous studies [72,73]. This was followed by pain and, to a lesser degree, by stinging, foreign body sensation, burning, and photophobia. In previous studies, these symptoms were grouped together and referred to as "discomfort" [51], but increasingly, the literature suggests that these ocular discomfort manifestations are better understood as corneal pain [56]. We do not agree with the concept that everything is now pain. In fact, our patients could perfectly distinguish between pain, especially when it had neuropathic characteristics, and all other symptoms, although most of them reported that pain and dryness worsened usually in parallel.

Pain was reported by 78.8% of our patients, and 74.4% had a moderate or severe pain. We further analyzed this pain in an attempt to discern the incidence of neuropathic pain. Thus, we followed a strict combination of published criteria [38,41–44,46,74,75], and additionally, the diagnosis had to be endorsed by a physician expert in these matters. Our aim was to avoid overestimation of the presence of neuropathic pain.

In 43.9% of the 66 patients suffering from neuropathic pain, the pain signals radiated from the eye following the neuroanatomically plausible distribution of the trigeminal nerve, with symptoms of trigeminal neuralgia. This pattern of pain radiation did not occur in patients with nociceptive pain. Also, some patients reported hyperalgesia and allodynia that manifested as pain upon eyedrop instillation, when applying makeup, when cutting onions, by cold wind, by light, or even their own tears evoked the pain. Although there are no standard scales for

Table 4
Characteristics of patients who had neuropathic or nociceptive postsurgical chronic pain or the absence of pain.

Characteristic	Neuropathic pain[1] (n = 66)	Nociceptive pain[2] (n = 16)	No pain[3] (n = 22)	P-value (1 *vs* 2)	P-value (1 *vs* 3)	P-value (2 *vs* 3)
Age – mean ± SD	38.5 ± 9.8	43.9 ± 10.0	38.8 ± 7.5	0.135	0.921	0.307
Female/male – n (%)	45 (68.2)/21 (31.8)	11 (68.8)/5 (31.3)	14 (63.6)/8 (36.4)	0.965	0.694	0.743
Type of surgery – C-RS/I-RS – n (%)	55 (83.3)/11 (16.7)	13 (81.3)/3 (18.7.)	21 (95.4)/1 (4.5)	0.843	0.151	0.159
Number of surgeries – mean ± SD	2.7 ± 1.3	3.1 ± 2.7	2.8 ± 1.2	0.501	0.567	0.895
Previous spherical equivalent – mean ± SD	−3.8 ± 4.6	−1.6 ± 4.2	−3.1 ± 4.1	0.060	0.603	0.212
Previous contact lens use – n (%)	42 (63.6)	9 (56.3)	15 (68.2)	0.585	0.699	0.452
Months of previous CL use – mean ± SD	82.5 ± 77.3	53.6 ± 98.1	73.6 ± 95.9	0.161	0.123	0.510
Refractive correction needed – n (%)	28 (42.4)	6 (37.5)	10 (45.4)	0.720	0.804	0.624
Visual acuity – mean ± SD						
High contrast (100%)	0.2 ± 0.3	0.2 ± 0.3	0.1 ± 0.2	0.902	0.282	0.421
Low contrast (10%)	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	~1	~1	~1
OSDI (0–100) – mean ± SD	63.6 ± 21.1	74.4 ± 17.2	41.9 ± 20.0	0.070	**<0.001**	**<0.001**
Symptoms (questions 1–5, score 0–20)	11.7 ± 4.3	14.1 ± 3.7	8.3 ± 4.3	**0.046**	**0.002**	**<0.001**
Vision (questions 6–9, score 0–16)	9.5 ± 4.6	11.1 ± 4.4	5.5 ± 4.1	0.220	**<0.001**	**<0.001**
Environment (questions 10–12, score 0–12)	8.9 ± 3.3	10.2 ± 2.5	6.3 ± 3.7	0.147	**0.003**	**<0.001**
mSIDEQ – mean ± SD	19.5 ± 4.1	21.9 ± 4.7	13.6 ± 3.8	**0.030**	**<0.001**	**<0.001**
Onset of symptoms (months) – mean ± SD	12.9 ± 37.0	15.1 ± 40.7	29.8 ± 57.9	0.859	0.538	0.651
Months with symptoms – mean ± SD	69.6 ± 70.1	78.5 ± 63.5	71.2 ± 54.4	0.386	0.500	0.849
Level of pain, NRS scale – mean ± SD	6.8 ± 2.1	5.2 ± 2.5	0.5 ± 0.5	**0.018**	**<0.001**	**<0.001**
No pain (0–2) – n (%)	–	–	22 (21.1)	–	–	–
Mild pain (2–4) – n (%)	15 (22.7)	6 (37.5)	–	0.225	–	–
Moderate pain (5–7) – n (%)	23 (34.8)	6 (37.5)	–	0.842	–	–
Severe pain (8-10) – n (%)	28 (42.4)	4 (25.0)	–	0.200	–	–
Level of pain, WFPRS scale – mean ± SD	6.6 ± 2.2	5.4 ± 2.5	0.7 ± 1.0	0.064	**<0.001**	**<0.001**
No pain (0) – n (%)	–	–	14 (63.6)	–	–	–
Discomfort (2) – n (%)	3 (4.5)	3 (18.8)	8 (36.4)	**0.050**	0.0648	**0.0165**
Light pain (4) – n (%)	12 (18.2)	5 (31.3)	–	0.247	–	–
Moderate pain (6) – n (%)	22 (33.3)	3 (18.8)	–	0.256	–	–
Intense pain (8) – n (%)	19 (28.8)	4 (25.0)	–	0.762	–	–
Unbearable pain (10) – n (%)	10 (15.2)	1 (6.3)	–	0.349	–	–
Dissatisfaction (NRS 0–10) – mean ± SD						
With current visual quality	7.1 ± 3.0	6.4 ± 4.0	5.7 ± 3.4	0.083	**<0.001**	0.284
With current symptoms	8.6 ± 2.1	8.3 ± 1.3	6.2 ± 3.3	0.857	**0.049**	0.078
HADS questionnaire – mean ± SD	19.8 ± 8.2	20.9 ± 11.8	14.6 ± 10.8	0.865	**0.015**	0.122
Anxiety subscale – mean ± SD	11.2 ± 4.3	11.3 ± 5.9	7.8 ± 5.3	0.907	**0.005**	0.108
Anxiety subscale (≥8) - n (%)	52 (78.8)	11 (68.7)	9 (40.1)	0.393	**<0.001**	0.090
Depression subscale - mean ± SD	8.6 ± 4.5	9.6 ± 6.4	6.8 ± 5.9	0.606	0.088	0.181
Depression subscale (≥8) - n (%)	39 (59.0)	10 (62.5)	7 (31.8)	0.803	**0.027**	0.060
Osmolarity mOsm/L – mean ± SD	314.5 ± 17.5	315.8 ± 21.2	316.9 ± 12.3	~1	~1	~1
Ocular surface integrity – mean ± SD						
Corneal staining (Oxford scale, 0–5)	0.8 ± 0.7	1.9 ± 0.6	1.2 ± 0.7	**<0.001**	**0.041**	**0.003**
Corneal staining (CCLRU, 0–4)	0.8 ± 0.6	1.7 ± 0.7	0.9 ± 0.5	**<0.001**	0.398	**<0.001**
Conjunctival staining (Oxford scale, 0–5)	0.6 ± 0.7	1.3 ± 1.1	0.8 ± 0.8	**0.012**	0.232	0.212
MGD (Efron scale, 0–4)	1.1 ± 0.6	1.6 ± 0.6	0.9 ± 0.6	**0.048**	0.243	**0.011**
TBUT ≤ 7 s – n (%)	59 (89.4)	12 (75.0)	20 (90.9)	0.234	0.984	0.314
TBUT - mean ± SD	4.1 ± 2.3	4.2 ± 2.4	4.2 ± 3.0	0.808	0.826	0.981
Corneal mechanosensitivity – mean ± SD						
Without topical anesthesia	55.5 ± 7.0	55.9 ± 7.2	54.9 ± 7.0	0.826	0.948	0.944
With topical anesthesia	8.3 ± 12.2	2.5 ± 4.6	1.7 ± 2.4	0.063	**0.042**	0.895
Anesthetic challenge test (GRC) – mean ± SD	−0.3 ± 2.3	−1.6 ± 2.8	−0.9 ± 2.2	**0.037**	0.351	0.942
Improvement (−3 to −5) - n (%)	12 (18.2)	7 (43.8)	6 (27.3)	**0.030**	0.360	0.290
Minimal improvement (−2 to −1) - n (%)	13 (19.7)	4 (25.0)	4 (18.2)	0.639	0.876	0.611
No change (0) - n (%)	24 (36.4)	2 (12.5)	7 (31.8)	0.066	0.699	0.167
Worsening (+1 to +5) - n (%)	17 (25.8)	3 (18.8)	5 (22.7)	0.558	0.776	0.767
Tear production (Schirmer test) – mean ± SD	7.9 ± 8.5	3.9 ± 2.7	7.8 ± 4.8	**0.047**	0.757	**0.007**
Pain Radiation - n (%)	29 (43.9)	0 (0.0)	–	–	–	–
Peri-ocular	21 (31.8)	0 (0.0)	–	–	–	–
Retro-ocular (orbit)	5 (7.6)	0 (0.0)	–	–	–	–
Forehead	9 (13.6)	0 (0.0)	–	–	–	–
Temporal regions	6 (9.1)	0 (0.0)	–	–	–	–
Parietal and occipital areas	7 (10.6)	0 (0.0)	–	–	–	–
Associated headaches – n (%)	35 (53.0)	9 (56.2)	5 (22.7)	0.817	**0.013**	**0.034**
Hyperalgesia – n (%)	12 (18.2)	0 (0.0)	–	–	-	–
Allodynia – n (%)	12 (18.2)	0 (0.0)	–	–	-	–
Seasonal or circadian variations – n (%)						
Worse in summer	21 (31.8)	0 (0.0)	3 (13.6)	**0.009**	0.097	0.124
Worse in autumn	2 (3.0)	1 (6.3)	2 (9.1)	0.538	0.237	0.748
Worse in spring	3 (4.5)	3 (18.8)	1 (4.5)	**0.050**	~1	0.159

(*continued on next page*)

Table 4 (*continued*)

Characteristic	Neuropathic pain[1] (n = 66)	Nociceptive pain[2] (n = 16)	No pain[3] (n = 22)	P-value (1 *vs* 2)	P-value (1 *vs* 3)	P-value (2 *vs* 3)
Worse in winter	6 (9.1)	3 (18.8)	4 (18.2)	0.267	0.245	0.964
No seasonal variation	34 (51.5)	9 (56.25)	12 (54.5)	~1	~1	~1
Worse in the morning	22 (33.3)	5 (31.3)	9 (40.9)	0.874	0.519	0.542
Worse in the evening	39 (59.1)	8 (50.0)	11 (50.0)	0.510	0.456	~1
No circadian variation	5 (10.6)	3 (18.8)	3 (13.6)	0.372	0.698	0.670

C-RS = corneal refractive surgery; CCLRU = Cornea and Contact Lens Research Unit grading scale; GRC = global rating of change; HADS = hospital anxiety and depression subscale; I-RS = intra-ocular refractive surgery; mSIDEQ = modified single item dry eye questionnaire; MGD = Meibomian gland dysfunction; NRS = numerical rating scale; OSDI = ocular surface disease index; SD = standard deviation; WFPRS = Wong-Baker Faces pain rating scale; TBUT = tear break-up time. For parametric variables, Student's t-test was used. Levene's test was used to check homogeneity of variance and Welch's test was used when this assumption was not valid. For no-parametric variables, Mann-Whitney *U* test, was performed and for qualitative variables, equality of proportions hypothesis. Bonferroni correction was applied to adjust the experiment-wise error rate.

measuring neuropathic pain, an objective way to assess hyperalgesia was defined recently by *Tagawa* et al. as pain sensitivity ≥40 mm with the Cochet-Bonnet esthesiometer [67].

In both pain groups, activities that worsen ocular pain were computer use and visual tasks such as reading. Furthermore, patients with nociceptive pain reported that seasonal variation was highest during the springtime of year, which is consistent with previous DE studies that reported seasonal variations under outdoor conditions where allergen exposure would be greater [76]. Conversely, our patients in the neuropathic group reported summertime worsening that was probably associated with photoallodynia, e.g., pain evoked by light. Such limitations could result in impaired social functioning and frustration [77]. OSDI results revealed that photophobia severity was correlated with the level of pain, and patients often cited this symptom in their medical history.

Corneal sensitivity is one way to assess the function of sensory nerves. Both corneal hypo- and hypersensitivity in DE patients have been reported. In some cases, corneal sensitivity was reduced immediately after RS and did not return to preoperative levels by 6 months [78]. *Spierer* et al. reported that patients with more severe signs of DE and pain had decreased mechanical corneal sensitivity [46]. On the other hand, increased mechanical sensitivity was observed in patients with evaporative DE [67,79,80]. In patients with a central sensitization syndrome and fibromyalgia, corneal sensitivity was significantly higher compared with a control group [80,81]. In our study, the groups with and without ocular pain had similar results in terms of corneal sensitivity. However, after topical anesthesia, the neuropathic pain group had significantly higher values than patients with no pain. There are no standard criteria establishing whether sensory testing can determine if a pain syndrome is peripherally mediated or is centralized. Nevertheless, it is widely believed that if topical anesthesia eliminates pain and symptoms in general, it is peripherally mediated [33,38,82]. In contrast, if pain persists after topical anesthesia, it suggests that the pain is centrally mediated [33,38].

This study has some limitations. First, Belmonte's gas esthesiometry and *in vivo* confocal microscopy of the corneal nerve plexus were not done. These studies are now underway by our group, as the presence of microneuromas is being studied as an objective biomarker of corneal neuropathic pain [83]. Another limitation is the possibility that some patients had both neuropathic and nociceptive pain. However, based on our strict adherence to the criteria for identifying patients who had neuropathic pain, we are confident in the assignments that we made to the neuropathic group. Finally, recall bias is likely to be present when obtaining data based on a medical history reported by the patient, and it can be a source of data uncertainty and variability.

In conclusion, persistent severe DE symptoms and ocular pain can be disabling complications of ocular surgical procedures. Although it is a problem that is increasingly studied, it is not possible to predict yet which individuals will develop these symptoms. Thus, it is extremely important to identify the risk factors for susceptible people. Individuals who generally opt for RS are usually young and healthy, and the onset and chronicity of these symptoms can drastically affect their quality of life, especially emotionally with the inherent consequences. Until the predisposing factors are known, a thorough clinical history of the patients who will undergo this surgery is warranted. The final goal is to fully understand which patients could be predisposed to develop these complications so that they could be excluded as candidates for surgery or at least fully informed. Considering the high percentage of central sensitization in these patients, eye care providers should consider the symptomatology of DE and post-RS pain as a chronic postoperative syndrome and address it in this way to prevent centralization.

Disclosure/conflict of interest statement

No conflicting relationship exists for any author. Disclosures of Dr. Margarita Calonge are the following: Research/clinical trials contracts, consultantships, advisory boards and/or lectures for Novartis, Santen Pharmaceutical, Johnson & Johnson, Horus Pharma, Fidia Farmaceutica, UrsaPharm GmbH, and Thea Laboratories. Disclosures of Dr. María J. González-García are the following: Esteve Pharmaceuticals. The remaining authors have no relationship to disclose.

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