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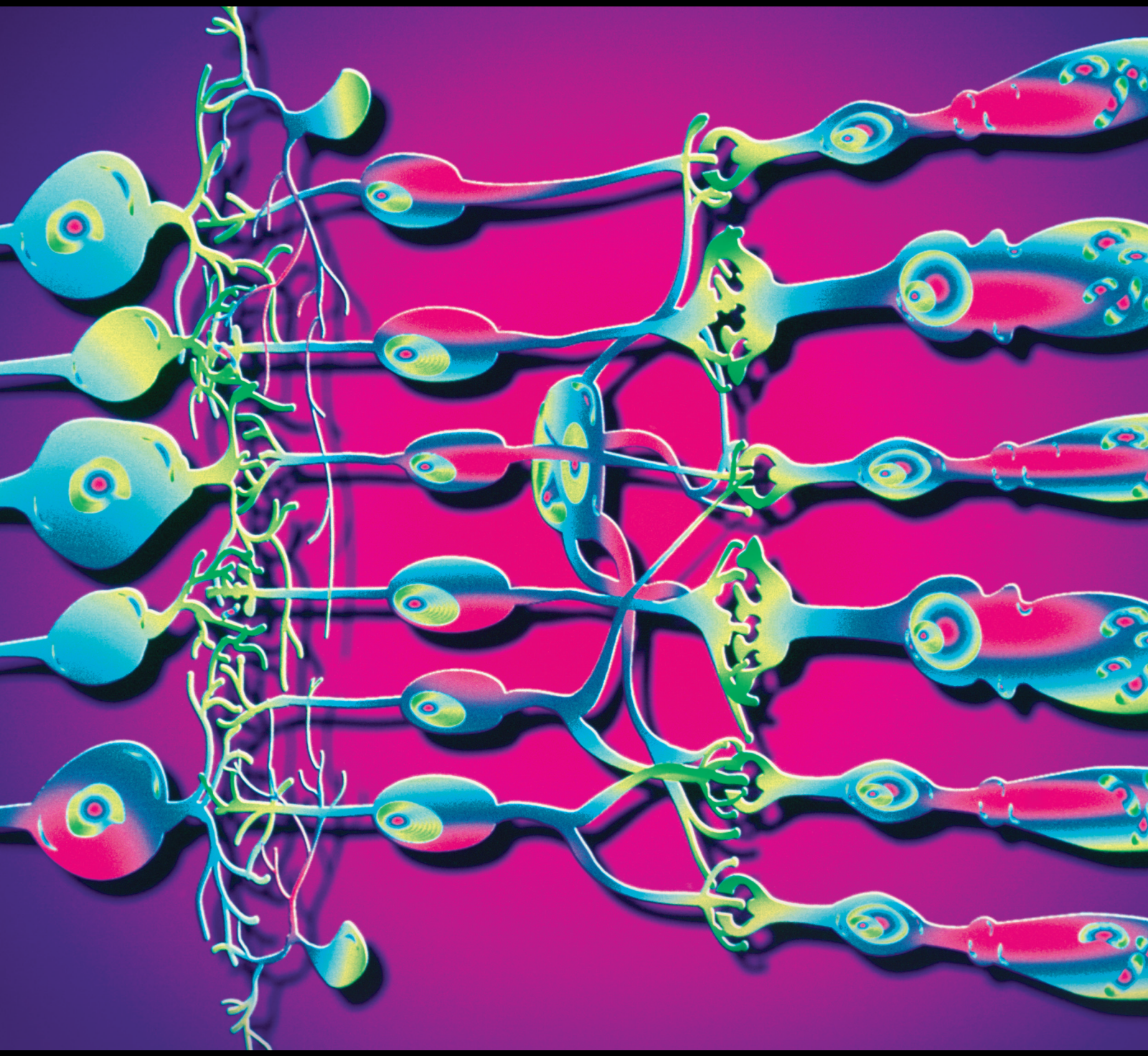
The Aging Eye

Guest Editors: Suddhasil Mookherjee, Ashima Bhattacharjee, and Mainak Sengupta



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Editorial Board

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Editorial

The Aging Eye

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With the advancement of medical science, average life expectancy of individuals is ever increasing. Percentage of elderly population has increased from 6.2% in 1990 to 8.2% in 2015 worldwide (http://www.unescap.org/resources/1-population). However, with increasing life expectancy, the prevalence of age related diseases will also increase, which will affect the quality of life in elderly population worldwide.

Eye is our window to the outer world and deterioration of this vital organ with age will definitely affect the lifestyle of the elderly people. According to WHO, approximately 65% of the population aged over 50 years has some forms of visual impairment (http://www.who.int/mediacentre/factsheets/fs282/en/). Therefore, understating and managing the age related changes in eye calls for significant effort and attention from the scientific world. This special issue focuses on the age related changes and diseases of eye as well as their management in elderly population. Eight meticulously chosen papers in this special issue focus on different aspects of vision problem and their management in elderly population.

Cataract is one of the major eye pathologies of elderly people. X. Yuan et al. reported the prevalence of astigmatism in eyes requiring cataract surgery. They found that prevalence of astigmatism also increases with age and discussed its implication in visual rehabilitation. L. Zuo et al. discussed the effect of unilateral or bilateral cataract surgery on visual acuity and quality of life in elderly patient.

Retinal pigment epithelium (RPE) is involved in various age related pathological changes in the eye including AMD. A. V. Kuznetsova et al. discussed the prospects of using RPE cell line in modelling various pathological changes in human disease and their potential use in retinal repair after ocular pathologies. They also discussed various signaling pathways in RPE which can be used as potential targets for different eye diseases.

L. Ottobelli et al. discussed the changes in ocular surface with increasing age and determined the frequency of ocular surface disease (OSD) with age. They concluded that dry eye disease (DED) is the most frequently occurring OSD and its frequency increases with age. A. Sharma and H. B. Hindman reviewed various aspect of DED with the increasing age.

Glaucoma is another major cause of vision loss especially in elderly population. Early detection and medical intervention are necessary to control vision loss due to glaucoma. Measurement of anterior chamber angle is an important parameter for diagnosis and management of glaucoma. M. Rigi et al., in this issue, have described a new parameter called TICV (trabecular-iris circumference volume) to detect the health of anterior chamber by optical coherence tomography. N. L. Pratt et al. discussed the relationship between bradycardia and Timolol, a widely used glaucoma medication, and concluded that patients' medical history should be reviewed before prescribing the medication. The study emphasizes the importance of considering full clinical information of patients for deciding treatment regimen taking into account other systemic ailments that the patient is already exposed to or might be predisposed to.

Finally, M. Oles and P. Oles discussed the issue of quality of lifestyle in people with low vision especially due to cataract and glaucoma. Their study highlights the importance of social support and task oriented coping to improve quality of life for individuals with low vision.

Age related eye diseases, being one of the most prevalent causes of blindness worldwide, demand attention as a global health problem. Research efforts must be concentrated on early detection and cost-effective methods of intervention accessible by people belonging to all economic strata globally. This issue is a small step towards such efforts for prevention of blindness and improving quality of human lives with progression of age.

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Research Article

The Impact of Unilateral or Bilateral Cataract Surgery on Visual Acuity and Life Quality of Elderly Patients

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In the current study, the CLVQOL was used to assess VRQOL before unilateral or bilateral cataract surgery and at the end of the follow-up period in order to determine the greater beneficial mode of surgery for patients, if one of the two surgical methods is more beneficial over the other. The patients were classified as receiving unilateral (group A) and bilateral cataract surgery (group B). There were no significant differences between groups A and B before the operation in terms of life quality scores, binocular weighted average LogMAR BCVA, age, educational level, gender, systematic and ocular comorbidities, and the complications of the operation. It was shown that visual acuity improved more significantly with bilateral cataract surgery than with unilateral surgery in elderly patients with a high preoperative disease burden in Shanghai city. However, the improvement in life quality was not different in patients receiving either bilateral or unilateral cataract surgery.

1. Introduction

Cataract is one of the common causes of visual impairment in people over 40 years old, which has a negative impact on their quality of life. Both unilateral and bilateral cataract surgeries have been shown to effectively improve the visual function of cataract patients. Therefore, it is important to elucidate the impact of unilateral and bilateral cataract surgeries on the improvement of visual acuity and quality of life of these patients and to determine whether bilateral cataract surgery has greater benefit over unilateral cataract surgery.

Visual acuity is commonly used to quantitatively measure the visual function of patients in clinical practice; however, it is the patient's self-perceived visual function and improvement in the life quality that are gradually recognized by the clinical practitioners and used as important factors to evaluate the outcomes of cataract surgery. The scale developed by Mangione et al. [1–3] has the advantage of effectively evaluating the impact of visual function on daily life and the alteration of life quality by the treatment. In the current study, the Chinese-version low vision quality-of-life questionnaire (CLVQOL) [4] was used to assess vision health-related quality of life (VRQOL) [5] before unilateral or bilateral cataract surgery and at the end of the follow-up period [6] in order to identify potential impact factors on the surgery outcome and to determine the greater beneficial mode of surgery for patients, if one of the two surgical methods is more beneficial over the other.

2. Methods

2.1. Patients. A total of 335 cataract patients underwent phacoemulsification surgery at the branch of Shanghai Jiao Tong University Affiliated First People's Hospital between January 2012 and February 2013, among which 37 patients were lost to follow-up. As a result, the complete follow-up records and the corresponding questionnaires were obtained from 298 patients. There were 165 female and 133 male patients enrolled in the study, with the average age of 73.53 ± 10.09 years (range, 43–96 years). The patients undergoing unilateral cataract surgeries were classified into group A (153 eyes from 153 patients), and those undergoing bilateral cataract surgeries were classified into group B (290 eyes from 145 patients). The CLVQOLs questionnaires were completed

by each patient before surgery and 3 months after surgery, and 30 patients received an additional questionnaire inquiry using the identical scale 2 weeks before the operation.

2.2. Cataract Surgery. Cataract surgery was defined as the absence of the crystalline lens in at least one eye of the subject [7], who received the phacoemulsification in combination with foldable intraocular lens (IOL) implantation. The IOL was foldable with single focus, and the patient paid 30% of the IOL cost. Bilateral cataract surgery was performed sequentially. Time interval was 2 to 3 weeks.

2.3. Assessment and Examinations. The demographic information of the patients was collected including gender, age, and educational level. The detailed ophthalmological examinations included the visual acuity test, anterior eye segment examination, and fundus examination before operation and 3 months after operation. At the same time, each patient was also required to complete the CLVQOL. The visual acuity was measured using an international standardized visual acuity chart. The best corrected visual acuity (BCVA) (subjective optometry) was converted into the minimum angle of resolution (LogMAR) vision. When Snellen visual acuity was less than 0.01, the visual acuity of "hand-motion" perception was defined as LogMAR2.2, that of "counting fingers" as LogMAR2.3, and that of "light perception" as LogMAR2.5 [8, 9].

2.4. The Assessment of Vision Health-Related Quality of Life. The CLVQOL questionnaire used in the current study was originally acquired from the low vision health-related quality-of-life questionnaire (LVQOL), which was developed by Wolffsohn and Cochrane [5], and translated into a Chinese version that was modified and culturally adapted for the Chinese patients [4]. The scale consists of 25 items, including four scales, namely, the Distance Vision (reading road signs or watching TV), Mobility and Lighting (outdoor activities and crossing a street with traffic), Adjustment (expectations on quality of life and perceived visual acuity), and Reading and Fine Work and Activities of Daily Living (reading the clock, reading one's own handwriting, and daily activities). Each item was scored using a numeric scale ranging from 0 (worst) to 5 (best). The total highest score was 125, and the score was correlated with the level of quality of life; the higher the score, the better the quality of life. The questionnaires were completed through face-to-face patient interviews conducted by two well-trained investigators. The VRQOL scores were calculated, and any complications due to cataract surgery [10] were also recorded for subsequent analysis.

2.5. Statistical Analysis. The software Statistical Package for the Social Science, version 11 (SPSS 11.0), was used in the current study for statistical analysis. $P < 0.05$ was considered statistically significant. The Spearman rank correlation method was used to analyze the correlation between the binocular weighted average LogMAR BCVA (with the weight of better eye and worse eye taken as 0.75 and 0.25, resp. [11]) and the VRQOL before surgery and at the end of follow-up. The correlation coefficient between the weighted average LogMAR BCVA and VRQOL of the patient before surgery and at the end of follow-up and that between the changed values of these two variables were calculated.

The score of VRQOL and the weighted average LogMAR BCVA were compared between the two groups by using Mann-Whitney test. t-test and Pearson X^2 test were used for the comparison of continuous data and categorical data, with respect to age, gender, educational level, systematic and ocular comorbidities, and surgery complications. Mann-Whitney test was used to investigate the impact of systematic and ocular comorbidities, gender, and surgery complications on the alteration of VRQOL scores at the end of the follow-up period.

The independent impact factors were identified by multiple linear regressions, with the improvement of VRQOL scores at the end of the follow-up period as an induced variable, and with the weighted average LogMAR BCVA before operation, VRQOL scores obtained before operation, the alteration of weighted average LogMAR BCVA after operation, age, and educational level as independent variables. The results were presented as standardized coefficients/P. The classified variables for the method of operation (1 for unilateral, 2 for bilateral), surgery complications (1 for yes, 0 for no), ocular comorbidities (1 for yes, 0 for no), and systematic complications (1 for yes, 0 for no) were recorded, and their influence on the alteration of the VRQOL score (1 for a score increase of no more than 19 and 2 for a score increase of more than 20) was analyzed by logistic regression. The results were presented as coefficients/P.

The reliability of the study was tested by Cronbach's α coefficient, and the repeatability of the study was tested by intraclass correlation coefficient (ICC) [12].

3. Results

3.1. Demographic Analysis. Table 1 compares the clinical characteristics of patients who underwent either unilateral or bilateral cataract extraction. There was no significant difference between the two groups with respect to age, educational level, gender, ocular comorbidities, systematic comorbidities, and surgery complications ($P > 0.05$). The detailed information of the ocular and systematic comorbidities and the surgery complications is listed in Table 2.

3.2. Visual Function and Quality of Life. The binocular weighted average LogMAR BCVA was significantly increased at the end of the follow-up period in group B compared with that in group A, although there was no significant improvement in the life quality between the two groups (Table 3).

3.3. Association between Visual Acuity and Quality of Life. The Spearman correlation coefficients between the preoperative weighted average LogMAR BCVA and the VRQOL score were 0.792 ($P = 0.000$), 0.700 ($P = 0.000$), and

Table 1: Clinical characteristics compared in unilateral and bilateral cataract extraction patients.

	Unilateral cataract extraction patients	Bilateral cataract extraction patients	P value	Statistical methods
Age (SD) (year)	74.38 (10.82)	72.57 (9.29)	0.477	Independent samples t-test
Educational time (SD) (year)	7.88 (3.80)	8.80 (3.60)	0.328	Independent samples t-test
Gender (male, female)	66, 87	67, 78	0.594	Pearson chi-square test
Ocular comorbidities (%)	84 (54.9)	80 (55.2)	0.963	Pearson chi-square test
Systemic comorbidities (%)	84 (54.9)	85 (58.6)	0.517	Pearson chi-square test
Surgical complications (%)	10 (6.5)	9 (6.2)	0.907	Pearson chi-square test

Table 2: Ocular comorbidities, systemic comorbidities, and surgical complications in patients receiving either unilateral or bilateral cataract extraction, $^{*}P < 0.05$ and $^{**}0.05 < P < 0.10$.

	Number (%)		χ^2/P (Pearson chi-square test)
	Unilateral cataract extraction patients	Bilateral cataract extraction patients	
	Ocular comorbidity		
Age-related macular degeneration	11 (7.2%)	12 (8.3%)	0.136/0.712
Pathologic myopia	20 (13.1%)	16 (11.0%)	0.291/0.590
Glaucoma	21 (13.7%)	31 (21.4%)	2.836/0.092**
Surgery history of scleral buckling and/or vitrectomy	13 (8.5%)	3 (2.1%)	6.054/0.014*
Pathologic myopia and surgery history of scleral buckling and/or vitrectomy	11 (7.2%)	10 (6.9%)	0.010/0.921
Diabetic retinopathy	2 (1.3%)	7 (4.8%)	3.150/0.076**
Other	6 (3.9%)	1 (0.7%)	3.390/0.066**
	Systemic comorbidity		
Hypertension	37 (24.2%)	37 (25.5%)	0.071/0.790
Diabetes mellitus	5 (3.3%)	11 (7.6%)	2.732/0.098**
Hypertension and diabetes mellitus	22 (14.4%)	18 (12.4%)	0.247/0.619
Cardiopathy	8 (5.2%)	11 (7.6%)	0.693/0.405
Respiratory	5 (3.3%)	3 (2.1%)	0.410/0.522
Other	7 (4.6%)	1 (0.7%)	4.302/0.038*
	Surgical complication		
Vitreous loss	5 (3.3%)	4 (2.8%)	0.066/0.797
Iris atrophy	3 (2.0%)	3 (2.1%)	0.004/0.947
Anisometropia	1 (0.7%)	2 (1.4%)	0.393/0.531
Opacification of anterior capsule	1 (0.7%)	0 (0%)	0.951/0.329

0.806 ($P = 0.000$) for patients who underwent the unilateral cataract surgery, for patients who underwent bilateral cataract surgery, and for total patients, respectively. The correlation coefficients between the weighted average LogMAR BCVA at the end of follow-up and the VRQOL scores were 0.664 ($P = 0.000$), 0.443 ($P = 0.014$), and 0.570 ($P = 0.000$) for patients who underwent unilateral cataract surgery, for patients who underwent bilateral cataract surgery, and for total patients, respectively.

The correlation coefficients between the postoperative improvement in the weighted average LogMAR BCVA and the improvement in the VRQOL score were 0.598 ($P = 0.000$), 0.707 ($P = 0.000$), and 0.739 ($P = 0.000$) for patients who underwent unilateral cataract surgery, for patients who underwent bilateral cataract surgery, and for total patients, respectively.

3.4. The Impact Factors for the VRQOL Score. Surgery complications and ocular comorbidities were found to be negative impact factors in the improvement of life quality, whereas gender and systematic comorbidities had little impact on the improvement of life quality (Table 4).

Table 3: Comparison of VRQOL score and weighted average LogMAR BCVA in patients undergoing either unilateral or bilateral cataract extraction, $^{*}P < 0.05$.

	Unilateral cataract extraction patients	Bilateral cataract extraction patients	P value (Mann-Whitney test)
Preoperative VRQOL score (SD)	77.02 (30.08)	71.85 (25.24)	0.175
3-month postoperative VRQOL score (SD)	100.32 (20.95)	102.55 (17.65)	0.731
The improvement of VRQOL score (SD)	23.26 (17.89)	30.89 (25.78)	0.112
Preoperative weighted average LogMAR BCVA (SD)	0.76 (0.62)	0.86 (0.44)	0.137
3-month postoperative weighted average logMAR BCVA (SD)	0.36 (0.36)	0.26 (0. 24)	0.242
The improvement of weighted average LogMAR BCVA (SD)	0.40 (0.37)	0.59 (0.44)	0.024*

Table 4: Effects of systemic comorbidities, ocular comorbidities, surgical complications, and gender on the improvement of VRQOL score at the end of follow-up period ($^{*}P < 0.05$, $^{**}0.05 < P < 0.10$).

	Unilateral cataract extraction patients		Bilateral cataract extraction patients		All cataract extraction patients	
	Mean improvement in score (SD)	P value	Mean improvement in score (SD)	P value	Mean improvement in score (SD)	P value
With systemic comorbidities	25.00 (17.89)	0.671	47.64 (30.58)	0.158	35.83 (26.80)	0.149
Without systemic comorbidities	24.05 (18.89)		26.89 (28.18)		25.40 (23.49)	
With ocular comorbidities	21. 60 (19.31)	0.550	25.94 (35.07)	0.094**	24.33 (29.84)	0.135
Without ocular comorbidities	25.61 (18.07)		45.69 (18.45)		32.86 (20.44)	
With surgical complication	7.60 (10.60)	0.019*	11.00 (23.45)	0.094**	9.11 (16.30)	0.006*
Without surgical complication	27.39 (17.78)		38.12 (29.96)		32.56 (24.78)	
Female	25.12 (16.87)	0.763	30.93 (32.39)	0.412	27.84 (25.09)	0.655
Male	23.63 (20.13)		38.07 (28.75)		30.61 (25.34)	

The preoperative VRQOL score, the increase in the postoperative weighted average LogMAR BCVA, the preoperative weighted average LogMAR BCVA, ocular comorbidities, and systematic comorbidities were the important factors that were found to have a significant influence on improving the life quality of patients. The method used for cataract surgery (unilateral or bilateral) was also identified as an impact factor, although with less significance (Table 5).

The internal consistency of responses before and after surgery, measured by the Cronbach α, was 0.95 and 0.92, respectively. The intraclass correlation coefficient was 0.93.

4. Discussion

The current study focused on the impact of unilateral or bilateral cataract surgery on vision-related life quality of elderly patients in China, with the objective to investigate factors influencing the improvement in the postoperative quality of life.

It was previously reported that the therapeutic effect of bilateral cataract surgery is better than that of unilateral cataract surgery [13]; however, it was also demonstrated that cataract surgery on the fellow eye had no obvious clinical benefit in elderly female patients [14]. In the current study, we found that both unilateral and bilateral cataract surgeries can significantly improve both visual acuity and quality of life. Successful cataract surgery may not always lead to a significantly improved life quality of elderly patients, who usually have various comorbidities and relatively lower level of education [9, 15, 16].

We showed that cataract surgery complications significantly influenced postoperative quality of life. Our findings suggest that if preoperative examinations reveal a potential risk of complications [10, 17], such as hypermature cataract [18], microcoria, serious adhesions in the posterior of the iris, posterior scleral staphyloma, and/or corneal refractive operation history that cause difficulties in the prediction of IOL diopter [19], surgeons should make sufficient preoperative preparations to avoid surgical injury. Sufficient preoperative communication with the patients would be helpful to lower

Table 5: Multiple impact factors that influence the improvement in VRQOL score at the end of the follow-up period (3 months after cataract surgery) ($^{*}P < 0.05$, $^{**}0.05 < P < 0.10$).

	Unilateral cataract surgery patients	Bilateral cataract surgery patients	All cataract surgery patients
Preoperative VRQOL score	−0.367/0.030*	−0.823/0.000*	−0.679/0.000*
Preoperative weighted average LogMAR BCVA	−0.085/0.802	0.055/0.730	−0.554/0.001*
Weighted average LogMAR BCVA change	0.461/0.008*	0.278/0.053**	0.731/0.000*
Age	0.088/0.559	0.172/0.176	0.113/0.193
Educational time	0.196/0.116	−0.109/0.323	0.019/0.806
Unilateral or bilateral surgery	/	/	1.220/0.062**
With or without surgical complication	−2.015/0.098**	−1.802/0.237	−2.190/0.015*
With or without systemic comorbidities	−0.045/0.955	1.902/0.133	0.664/0.302
With or without ocular comorbidities	−1.049/0.211	−2.615/0.041*	−1.550/0.017*

their expectations about surgery outcome [20, 21], which will positively affect postoperative life quality.

In the present study, there was no significant difference in the improvement of life quality in patients with or without systematic comorbidities. In general, a comprehensive preoperative evaluation should be carried out, which includes obtaining a complete medical history and performing routine examinations. Unilateral cataract surgery should be usually preferred for those patients who have a poor general condition and are in a feared state of mind. The surgery should be based on sufficient communication between the clinicians and patients. Proper preoperative care [22] may pose lower risk of poor outcomes in elderly patients with systemic complications.

Based on the findings of the current study, cataract surgery on the fellow eye is associated with the type of ocular comorbidity being in the cataract patient [17, 23]. Primary angle-closure glaucoma is the major type of glaucoma in China [24], in which both of the eyes have similar anatomical pathology. Cataract surgery can improve the anatomical structure of the chamber angle [25]; therefore, bilateral cataract surgery is usually chosen based on the recommendation of the surgeon. The patients with diabetic retinopathy generally preferred bilateral cataract surgery. Diabetic retinopathy often affects both eyes of the patient, and bilateral cataract surgery is convenient for fundus inspection and laser photocoagulation treatment. Unilateral cataract surgery is often operated for patients who have ever undergone a retinal reattachment operation or vitrectomy. Because there is an increased need to adjust anisometropia in patients with pathological myopia and with a history of vitreoretinal operations, there is a corresponding increase in the number of patients undergoing bilateral cataract surgery.

Previous study [26] showed that the clinical outcomes and patient-rated satisfaction were similar whether bilateral cataract surgery was performed simultaneously or sequentially. In China, surgeons did not reach a consensus on option of simultaneous bilateral cataract surgery. We performed sequential bilateral cataract surgery in this study. With the development of cataract surgery techniques, there would be more doctors recognizing that simultaneous bilateral cataract surgery is safe and more economical than sequential [27], and it is very effective way to cut down waiting times in case there are long queues to surgery.

In summary, a greater improvement in visual acuity was observed in elderly patients of Shanghai city with a high preoperative disease burden and receiving bilateral cataract surgery, compared with those who received unilateral cataract surgery. However, there was no significant difference between the two groups in terms of improvement in vision-related quality of life.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Association between Ophthalmic Timolol and Hospitalisation for Bradycardia

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Introduction. Ophthalmic timolol, a topical nonselective beta-blocker, has the potential to be absorbed systemically which may cause adverse cardiovascular effects. This study was conducted to determine whether initiation of ophthalmic timolol was associated with an increased risk of hospitalisation for bradycardia. *Materials and Methods*. A self-controlled case-series study was undertaken in patients who were hospitalised for bradycardia and were exposed to timolol. Person-time after timolol initiation was partitioned into risk periods: 1–30 days, 31–180 days, and >180 days. A 30-day risk period prior to initiating timolol was also included. All remaining time was considered unexposed. *Results*. There were 6,373 patients with at least one hospitalisation for bradycardia during the study period; 267 were exposed to timolol. Risk of bradycardia was significantly increased in the 31–180 days after timolol initiation (incidence rate ratio (IRR) = 1.93; 95% confidence interval (CI) 1.00–1.87). No increased risk was observed in the first 30 days or beyond 180 days of continuous exposure (IRR = 1.40; 95% CI 0.87–2.26 and IRR = 1.21; 95% CI 0.64–2.31, resp.). *Conclusion*. Bradycardia is a potential adverse event following timolol initiation. Practitioners should consider patient history before choosing a glaucoma regime and closely monitor patients after treatment initiation with topical nonselective beta-blocker eye drops.

1. Introduction

The prevalence of glaucoma, a leading cause of vision loss [1], increases with age [2]. The number of people with glaucoma in Australia is predicted to increase from 208,000 in 2005 to 379,000 in 2025 [3]. The most common form of medical management of glaucoma is the use of topical eye drops that reduce intraocular pressure [4]. β-adrenergic antagonists (β-blockers) are the most commonly prescribed glaucoma medicines in a number of countries including the United Kingdom [5] and the United States [6]. In Australia, treatment options include prostaglandin analogues, which are now the most common treatment for glaucoma [4]. β-blockers still have substantial usage [4] and many combination products are available which contribute to their use.

Timolol is a potent nonselective β-blocker and was the mainstay of glaucoma therapy through the 1980s and 1990s [2, 7] because it is effective in lowering intraocular pressure [8], associated with few ocular side effects and does not affect pupil size [9, 10]. Although administered topically, when used in the eye timolol can reach the systemic circulation through the nasolacrimal duct, the conjunctival vessels, and gastrointestinal tract [11–13]. The systemic bioavailability and pharmacokinetics of ophthalmic timolol 0.5% are comparable to intravenous timolol [13]. A dose of one drop of 0.5% timolol solution to each eye is equivalent to a 10 mg oral dose [14, 15]. Systemic adrenergic β-blocking effects of ophthalmic timolol may therefore occur, including effects on cardiac, pulmonary, central nervous system, and endocrine functions [6, 16].

Change in heart rate is one of the effects of the systemically absorbed fraction of ophthalmic timolol [6, 17]. In the first seven years of commercial production of ophthalmic timolol in the United States, 450 serious adverse cardiopulmonary events were reported, and 32 deaths were attributed to the use of ophthalmic timolol. Preexisting cardiovascular disease was reported in 31% of the 212 persons for whom medical history was provided [18]. Ophthalmic

timolol is therefore contraindicated in patients with certain cardiovascular disorders, including bradyarrhythmias and atrioventricular block [2].

A number of studies have been conducted to confirm the systemic β-blocking effects of ophthalmic timolol on cardiovascular functions, including bradycardia, and results varied substantially across studies. Randomised controlled trials and crossover studies found a range in reduction of resting heart rate and in peak heart rate during exercise, from negligible to an 11 beat per minute (bpm) reduction and from 5 to 22 bpm reduction, respectively, depending on the types of ophthalmic timolol: 0.25–0.5% aqueous or 0.1–0.5% hydrogel formulations [13, 19–33].

Given these findings, we aimed to quantify the potential risks of hospitalisation for bradycardia following initiation of ophthalmic timolol in an elderly population.

2. Materials and Methods

2.1. Data Source. The Australian Government Department of Veterans' Affairs (DVA) administrative claims database was used in this study. Details of all prescription medicines, medical and allied health services, and hospitalisations for which DVA pays a subsidy are available. Data are available for a treatment population that in September 2011 was 242,147 people [34] and who had a median age of 80 years. DVA maintains a client file, which includes data on gender, date of birth, date of death, and family status. Medicines are coded in the dataset according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification [35] and the Schedule of Pharmaceutical Benefits Item Codes [36]. Hospitalisations are coded according to the International Classification of Diseases, version 10, Australian modification (ICD-10-AM) [37].

2.2. Study Design. The self-controlled case-series design [38, 39], which is a within person design, was used to compare the rate of hospitalisation for bradycardia during periods of exposure to timolol compared to unexposed periods. Eligible persons were those who were hospitalised for bradycardia (primary diagnosis ICD-10AM R001, I440, I441, I442, I443, and I495) between July 1, 2003, and June 30, 2009. Persons were included if they were aged 65 years or over at the start of the study, eligible for all health services subsidised by DVA and were dispensed at least one medicine in the year prior to the start of the study. To focus this analysis on new users of ophthalmic timolol, subjects who were dispensed ophthalmic timolol (ATC code S01ED01) or combination medicines with timolol (ATC code S01ED51) in the year prior to the start of the study were excluded. Subjects were followed until death or the end of the study period (June 30, 2009), whichever occurred first.

2.3. Statistical Analysis. As timolol eye drops are required to be discarded four weeks after opening, exposure duration for each dispensed ophthalmic timolol was defined as 35 days, allowing for an additional week to account for late prescription refill. Patients with repeat dispensings within 35 days were considered to be continuously exposed. The end of the exposure period was defined as 35 days after the last dispensing of timolol eye drops where no subsequent dispensing occurred. For those patients who had at least one timolol dispensing during the study period, their exposed time was partitioned into the following risk periods: 1–30 days, 31–180 days, and all remaining exposure time after timolol initiation (>180 days). A preexposure risk period of 30 days prior to initiating treatment with timolol was included to ensure the occurrence of the outcome was not altering the probability of subsequent exposure, a fundamental assumption of the self-controlled case series method. The actual day of prescription was excluded from this analysis as we were unable to define the temporal association between the exposure and a hospitalisation if they occurred on the same day. The incidence of outcomes in each of the exposure risk periods was compared to the incidence of outcomes in the unexposed reference period. Incidence rate ratios (IRRs) were calculated using conditional poisson regression adjusting for age at hospitalisation and calendar year.

Sensitivity analyses were performed by including additional adjustments for covariates including concomitant prescribing of oral beta-blockers (ATC code C07), calcium-channel blockers (ATC code C08), digitalis glycosides (ATC code C01AA), and antiarrhythmics (ATC code C01B). We also included patients who were hospitalised for bradycardia but not exposed to timolol during the study period to adjust for the possibility of increasing incidence of bradycardia hospitalisation with age. These patients contributed information on the impact of time varying covariates, including age, on the risk of the outcome [38, 39]. All person-time for the unexposed group was included in the unexposed reference period. We also stratified by concomitant use of oral beta-blockers. All analyses were performed using SAS version 9.12 (SAS Institute, Cary, NC).

3. Results

The demographics of the study population are presented in Table 1. There were 6,373 veterans with at least one hospitalisation for bradycardia during the study period, with 267 exposed to timolol and 6,106 never exposed. Of the study population, 59.6% were males. The mean age at first hospitalisation was 82.6 years.

There was no statistically significant increase in the risk of hospitalisation for bradycardia in the first 30 days after initiating timolol (incidence rate ratio (IRR) = 1.40; 95% confidence interval (CI) 0.87–2.26). The risk of bradycardia was significantly increased in the 31 to 180 days after timolol initiation (IRR = 1.93; 95% CI 1.30–2.87), but did not remain statistically significantly elevated thereafter (Table 2).

Results were similar after adjusting for other conditions and when including unexposed patients (Table 3). The stratified analyses also show similar risk estimates for patients not taking oral beta-blockers; however, the risk in the 31–180-day risk period was not statistically significant (IRR = 1.76; 95% CI 0.88–3.50) (Table 3).

Table 1: Demographics of the study cohort.

Demographics	Bradycardia hospitalisation cohort (n = 6,373)		
	Exposed (n = 267)	Never exposed (n = 6,106)	Whole cohort (n = 6,373)
Age, mean (SD), year	82.7 (4.8)	82.6 (4.8)	82.6 (4.8)
Male gender, No. (%)	154 (57.7)	3645 (59.7)	3799 (59.6)
Number of medicines used, median (IQR)[a]	12 (8–17)	12 (8–18)	12 (8–18)
Number of prescribers, median (IQR)[a]	12 (8–16)	12 (7–17)	12 (7–17)
Number of specialist visits, median (IQR)[a]	5 (2–8)	3 (1–8)	3 (1–8)
Number of hospitalisations, median (IQR)[a]	1 (0–2)	1 (0–2)	1 (0–2)
Number of comorbidities, median (IQR)[b]	5 (4–7)	5 (3–7)	5 (3–7)

SD: standard deviation; IQR: interquartile range; and No.: number.
[a]Values for 12 months prior to study entry.
[b]Value for time-varying every 4 months.

Table 2: Self-controlled case series results for patients with a hospitalisation for bradycardia and at least one dispensing of timolol.

Risk periods	N hospitalisations	Person-years	Adjusted rate[a] per 10 years (95% CI)	IRR[a] (95% CI)
Unexposed	161	1112	1.42 (1.17–1.71)	1.00 (1.00-1.00)
Before 1–30 days	2	22	0.82 (0.20–3.30)	0.58 (0.14–2.35)
After 1–30 days	25	127	1.98 (1.30–3.03)	1.40 (0.87–2.26)
After 31–180 days	58	234	2.73 (1.99–3.75)	1.93 (1.30–2.87)
After 180 days	17	121	1.72 (0.96–3.07)	1.21 (0.64–2.31)
Washout	4	63	0.60 (0.22–1.63)	0.42 (0.15–1.17)

CI: confidence interval; IRR: incidence rate ratio.
[a]Adjusted for age at hospitalisation and calendar year.

4. Discussion

Timolol is a nonselective β-blocker; thus it is a risk factor for cardiovascular functions. Most of the published evidence of the systemic β-blocking effects of ophthalmic timolol on cardiovascular functions was from randomised controlled trials (RCTs), cross-over studies, or case reports [13, 18–33]. Participants included in RCTs were often very selective (e.g., healthy people) and not representative of the real-world population. RCTs excluded the elderly in whom β-blockade has been found to be stronger and last longer. In addition, RCTs were limited to investigating the impact of timolol on resting heart rate and peak heart rate during exercise; however, the impact of timolol on the more serious outcome of hospitalisation for bradycardia was not assessed.

Using the DVA administrative claims database in this observational study, we found an increased risk of hospitalisation for bradycardia one month after initiation of timolol eye drops. The increased risk of hospitalisation for bradycardia was reduced and no longer statistically significant after six months of continuous treatment. One explanation for this finding may be that those patients who continue to take ophthalmic timolol for extended periods are those with better tolerance, thus being less likely to experience the adverse event. Our findings are in line with previous clinical trial evidence and case reports which suggested that ophthalmic timolol was associated with adverse cardiac effects [18, 40].

Despite evidence linking the use of topical β-blockers to bradycardia, codispensing of ophthalmic β-blockers with medicines which can cause or exacerbate bradycardia is common. We previously showed that 36% of those with glaucoma who were dispensed verapamil were also codispensed ophthalmic timolol [41], a contraindication which may worsen bradycardia [42]. Interventions raising awareness of these potential adverse events with prescribers are required. The majority of glaucoma medicines are initiated by ophthalmologists, while adverse events may be managed by general practitioners, raising challenges of how to address adverse events across the continuum of care. Cross-specialty cooperation is therefore needed to optimise patient care with improved communication among ophthalmologists, general practitioners, pharmacists, and patients regarding the history of cardiac diseases and glaucoma treatment.

The use of the self-controlled case series design where the patient implicitly acts as their own control adjusts for all confounders that remain fixed over the observation period, including sex, location, genetics, and underlying state of health [38]. The absence of diagnostic information in the DVA dataset means that disease severity could not be taken into account. However, sensitivity analyses were performed by adjusting for concurrent medications uses, which are the proxy for the presence of conditions that may impact on the risk of hospitalisation for bradycardia. These analyses made little difference to the risk estimates suggesting that the

Table 3: Sensitivity analyses.

Risk periods	*N* hospitalisations	Person-years	Adjusted rate per 10 years (95% CI)	IRR (95% CI)
Exposed patients only (adjusting for age, calendar year, and other conditions[a])				
Unexposed	161	1112	1.45 (1.20–1.75)	1.00 (1.00-1.00)
Before 1–30 days	2	22	0.86 (0.21–3.46)	0.59 (0.15–2.41)
After 1–30 days	25	127	2.02 (1.32–3.10)	1.40 (0.86–2.26)
After 31–180 days	58	234	2.78 (2.02–3.81)	1.91 (1.28–2.85)
After 180 days	17	121	1.75 (0.98–3.13)	1.21 (0.63–2.30)
Washout	4	63	0.62 (0.23–1.69)	0.43 (0.16–1.19)
Including unexposed patients (adjusting for age and calendar year)				
Unexposed	6267	36791	1.39 (1.33–1.46)	1.00 (1.00-1.00)
Before 1–30 days	2	22	0.74 (0.18–3.00)	0.53 (0.13–2.16)
After 1–30 days	25	127	1.77 (1.11–2.82)	1.27 (0.80–2.02)
After 31–180 days	58	234	2.47 (1.70–3.59)	1.77 (1.22–2.58)
After 180 days	17	121	1.58 (0.85–2.93)	1.13 (0.61–2.10)
Washout	4	63	0.54 (0.20–1.48)	0.39 (0.14–1.06)
Exposed patients only who were dispended at least one oral beta-blocker (adjusting for age and calendar year)				
Unexposed	97	690	1.43 (1.11–1.86)	1.00 (1.00-1.00)
Before 1–30 days	2	13	1.36 (0.34–5.46)	0.95 (0.23–3.88)
After 1–30 days	12	81	1.54 (0.85–2.80)	1.08 (0.55–2.09)
After 31–180 days	40	155	2.95 (2.03–4.31)	2.06 (1.26–3.36)
After 180 days	12	76	2.10 (1.06–4.15)	1.46 (0.68–3.15)
Washout	3	39	0.77 (0.24–2.43)	0.54 (0.16–1.75)
Exposed patients only who were not dispended oral beta-blockers (adjusting for age and calendar year)				
Unexposed	64	422	1.51 (1.11–2.05)	1.00 (1.00-1.00)
Before 1–30 days	0	88	—	0.95 (0.23–3.88)
After 1–30 days	13	46	3.04 (1.61–5.73)	2.01 (0.99–4.08)
After 31–180 days	18	79	2.65 (1.46–4.80)	1.76 (0.88–3.50)
After 180 days	5	45	1.18 (0.39–3.55)	0.78 (0.24–2.55)
Washout	1	24	0.42 (0.06–3.05)	0.28 (0.04–2.06)

CI: confidence interval; IRR: incidence rate ratio.
[a]Oral beta-blockers (ATC code C07), calcium-channel blockers (ATC code C08), digitalis glycosides (ATC code C01AA), and antiarrhythmics (ATC code C01B).

increased risk of hospitalisation for bradycardia is unlikely to be due to confounding because of changes in disease severity.

In Australia, ophthalmic timolol is registered for ocular hypertension and glaucoma, and the DVA dataset does not allow distinguishing which condition the exposed individuals had. In addition, dosage information is not available in the dataset, so we were unable to assess the dose-response relationship. The selection of the veteran population in this study may be seen as another limitation for the generalisation of our findings. However, previous research has shown that there was no difference in use of practitioners, health services, and pharmaceuticals between war veterans and nonveteran patients in both the primary and tertiary Australian care sectors after adjustment for age, service-related disability, and marital status [43]. Our results, which have consolidated scientific evidence on the risk of hospitalisation for bradycardia, are therefore likely to be applicable to the elderly Australian population and suggest that this adverse event is still occurring.

5. Conclusion

Bradycardia is a potential adverse event following timolol initiation. Practitioners should be reminded to carefully examine the patient history before choosing a glaucoma regime and closely monitor patients after treatment initiation with topical nonselective beta-blocker eye drops to minimise adverse events and potentially avoid hospitalisations.

Conflict of Interests

The authors declare that there are no conflict of interests regarding the publication of this paper.

Authors' Contribution

Elizabeth E. Roughead, Nicole L. Pratt, and Emmae N. Ramsay had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Elizabeth E. Roughead, Nicole L. Pratt, Emmae N. Ramsay, Lisa M. Kalisch Ellett, and Tuan A. Nguyen carried out study concept and design. Elizabeth E. Roughead carried out acquisition of data. Nicole L. Pratt and Emmae N. Ramsay carried out analysis of data. Nicole L. Pratt, Tuan A. Nguyen, Elizabeth E. Roughead, Emmae N. Ramsay, and Lisa M. Kalisch Ellett carried out interpretation of data and drafting of the paper. Elizabeth E. Roughead, Nicole L. Pratt, Lisa M. Kalisch Ellett, Emmae N. Ramsay, and Tuan A. Nguyen carried out critical revision of the paper for important intellectual content. Elizabeth E. Roughead carried out study supervision. All authors have approved the final version for submission.

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Research Article

Coping Style and Quality of Life in Elderly Patients with Vision Disturbances

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Purpose. This study aims at evaluating coping style and quality of life in patients with glaucoma and cataract. *Methods.* The participants were patients (N = 237, 130F; mean age: M = 67,8; SD = 9,5) with low vision caused by cataract (N = 188) and glaucoma (N = 49) who answered the Quality of Life Questionnaire (QOLQ) by Schalock and Keith. The participants were divided by means of cluster analysis (k-means) according to coping styles measured by CISS (Endler and Parker) into three groups: (1) high mobilization for coping, (2) task-oriented coping, and (3) low mobilization for coping. *Results.* In all the group, a general quality of life was moderately lowered; however, in task-oriented group it was relatively high. Moreover, task-oriented group had significantly lower level of anxiety (STAI), hopelessness (HS), and loneliness (UCLA LS-R) and higher level of self-esteem (SES) in comparison to the patients from high mobilization and low mobilization for coping. *Conclusions.* In an old age, adaptive coping with vision disturbances does not necessarily mean flexibility in combining all coping styles, but rather task-oriented coping and an ability to use social support. Extreme mobilization for coping seems not adaptive similarly like low mobilization for coping because it violates balance between environmental requirements and personal resources.

1. Introduction

Vision serves as a vital function ensuring the feeling of control over the immediate surroundings and creating a sense of contact with the world. Therefore, the fact does not render it peculiar that cases connected with vision disturbances and eyesight loss entail heightened anxiety and the fear for autonomy limitation [1–3]. Statistical data prove that the risk of developing cataract, glaucoma, and other ophthalmological disorders increases with age [4, 5]. Cataract affects almost 20% of people between the ages of 65 and 74 and for 50% of those who are between 75 and 84 years of age becomes the main factor leading to blindness [6, 7]. The risk of developing glaucoma, on the other hand, occurs in 2% population segment of forty-five-year-olds and older patients, increasing markedly in the case of people at an advanced age. Due to the fact that initial stages of the disease development are difficult to diagnose and since the diagnosis itself may lack precision, a strong feeling of anxiety can arise [8–10]. Low vision is one of the most important reasons of lowered quality of life, anxiety, and poor adaptation, especially in older patients who have two kinds of problems, relating to their health and age [11–13]. Thus, coping with stress seems especially important for adaptation to low vision [14].

The research projects on the patient groups focus predominantly on establishing the quality of life pattern and on examining changes both in the paradigm and in the vision-related functional status after the treatment. Only a fraction of these researches dealt with such variables as depression and anxiety, expectations concerning the future, the feeling of loneliness, or self-esteem [15, 16]. The importance of psychological variables such as strategies of coping or anxiety intensification factor has been duly underlined in glaucoma research due to the fact that the concealed development of the disease and the possibility of unfavourable prognosis may potentially lead to the development of the feeling of anxiety [8, 17]. According to current research results both socioeconomic factors and psychological variables influence quality of life in elderly patients with vision disturbances [2, 18–20].

This study has been intended to constitute a probe into coping styles in cases of patients with vision disturbances to

demonstrate interrelationships existing between the emerging pattern and quality of life assessment in cataract- and glaucoma-affected patients. The problem can be formulated in the following questions.

(1) What styles of coping do patients with vision disturbances adopt?

(2) What is the adaptive value of the styles of coping exhibited by elderly patients with vision disturbances who undergo cataract and glaucoma treatment?

Quality of life is defined as "an individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [21, p. 1405]. Quality of life evaluation was employed to designate the psychic adaptability coefficient. Additionally, the levels of self-esteem and such clinical variables as anxiety, depression, and loneliness were also diagnosed. The project was aimed at having a predominantly exploratory character. Its goal was to detect the styles of coping most frequently assumed in this group of patients and to test their adaptive value. In light of the literature on the subject, task-oriented coping and adaptive flexibility figure as having adaptive value. Therefore, it was postulated that H1: moderate mobilization of different styles of coping showing clear tendency towards employing task-oriented coping has adaptive value and that H2: coping based on emotion-oriented and avoidance-oriented coping has lesser adaptive value indicated by relatively low quality of life, low self-esteem, and a heightened level of anxiety, hopelessness, and loneliness.

2. Sample and Methods

The sample consisted of 237 patients (mean age: M = 67,8; SD = 9,5) including 188 cataract and 49 glaucoma patients. A time frame for the recruitment of the participants was one year, and they were consecutive patients, except those who refused to participate in this investigation due to their poor well-being or lack of motivation. Since there were no major differences regarding quality of life or coping styles, both glaucoma patients and cataract patients were treated as a unit irrespective of their sex.

Coping styles were investigated by means of the Coping Inventory for Stressful Situations (CISS) by Endler and Parker [22]. The inventory consists of three main scales: task-oriented coping (TOC), emotion-oriented coping (EOC), and avoidance-oriented coping (AOC), with the last one with two subscales: engagement in substitute activity (ESA) and seeking for social relationships (SSR). Cronbach alpha for three main scales checked in a sample of elderly patients with low vision (N = 50, 25 male and 25 female) is 0.81, 0.78, and 0.74, respectively, and for subscales it is 0.60 and 0.67.

Quality of life was measured with the help of The Quality of Life Questionnaire by Schalock and Keith [23]. The questionnaire consists of 40 items measuring the quality of life in four domains, each comprising 10 items: satisfaction, competence/productivity, empowerment/independence, and social belonging/community integration. The fifth domain was added to the present research: health related quality of life (5 items). The questionnaire is based on an interview containing 45 questions, each with 3 possible answers scored 1, 2, or 3—from low to high quality of life. Reliability of the Quality of Life Questionnaire (40 items), checked in cataract sample (N = 50, 25F and 25M), is Cronbach alpha = 0.86 and for each scale 0.81, 0.86, 0.58, 0.50, and 0.79, respectively.

The following scales were used to assess other variables indicating psychological functioning of the patients: Self-Esteem Scale (SES) by Rosenberg [24], State-Trait Anxiety Inventory (STAI) by Spielberger and Reheiser [25], Hopelessness Scale (HS) by Beck et al. [26], and Loneliness Scale Revised (UCLA LS-R) by Russell et al. [27].

3. Results and Discussion

In order to isolate subgroups of patients employing distinct styles of coping, cluster analysis based on k-means method and conducted on the standardized scores in three main scales of CISS by Endler and Parker was carried out. Three groups of patients exhibiting different coping styles were thus singled out:

(1) patients exhibiting high mobilization for coping with emotion-oriented and avoidance-oriented coping prevalent (N = 89, including 68 cataract patients and 21 glaucoma subjects);

(2) patients exhibiting task-oriented coping (N = 69, including 59 cataract patients and 10 glaucoma subjects);

(3) patients exhibiting low mobilization for coping (N = 79, including 61 cataract patients and 18 glaucoma subjects).

According to CISS scales, all of the differences emerging between the groups were significant ($P < 0.001$) (cf. Table 1). There are no major discrepancies in medical variables describing acuity and quality of vision.

Interestingly enough in all three groups three main coping strategies were used to a lesser or higher degree. In the first group, avoidance-oriented coping and emotion-oriented coping appear to be concurrent with each other. Furthermore, the patients belonging to this group achieved comparatively high scores as far as task-oriented coping is concerned, and this suggests flexibility of coping. The second group demonstrated task-oriented coping combined with the inclination to search for and employ social support. In the third group, the level of mobilization to cope was relatively low. The division of thus delineated groups with respect to quality of life revealed several crucial differences (Table 2).

The second group, namely, patients characterized by task-oriented coping, evidently reveals higher quality of life in contrast to the other two groups. This fact pertains not only to the overall result achieved on the Total Quality of Life Scale, but also to the results obtained in other two domains, that is, empowerment/independence and social belonging/community integration. It is also worth noting that, as for variables describing quality of life, there were no significant differences between the first group of patients with

Table 1: Coping styles in three groups of patients: comparison.

Group/CISS scales	Group 1 ($N = 89$)		Group 2 ($N = 69$)		Group 3 ($N = 79$)		Significant differences	
	M	SD	M	SD	M	SD	$F(3,234)$	$P<$
TOC	59,69	5,82	62,09	6,05	47,59	5,79	134,88	0,0001
EOC	50,98	6,66	34,57	6,14	42,11	7,09	119,68	0,0001
AOC	43,92	7,17	35,06	6,33	33,63	7,52	52,38	0,0001
ESA	15,76	4,44	11,65	3,27	12,18	3,63	27,65	0,0001
SSR	17,71	3,81	15,19	3,74	12,92	3,68	34,24	0,0001

TOC: task-oriented coping, EOC: emotion-oriented coping, AOC: avoidance-oriented coping, ESA: engagement in substitute activity, and SSR: seeking for social relationships.

Table 2: Quality of life in three groups: comparison.

Group/scale	Group 1 ($N = 89$)		Group 2 ($N = 69$)		Group 3 ($N = 79$)		Significance of differences	
	M	SD	M	SD	M	SD	$F(3,234)$	$P<$
QOL-TOT.	82,21	8,54	86,74	7,91	81,51	7,73	8,98[ab]	0,001
SATISF.	21,18	3,51	22,71	2,85	21,87	3,52	4,10[a]	0,05
COMPET.	13,61	3,85	13,77	4,70	12,51	2,86	2,49	—
INDEPEN.	26,38	2,41	27,43	2,00	25,99	2,93	6,57[ab]	0,01
INTEGR.	21,49	3,25	22,83	2,94	21,10	2,96	6,32[ab]	0,01
HRQOL	8,65	2,05	8,93	2,50	8,67	2,26	0,34	—

[a]Significant difference between groups 1 and 2, $P < 0,05$.
[b]Significant difference between groups 2 and 3, $P < 0,05$.

high mobilization for coping and the third group of patients with low mobilization for coping.

Further analysis aims at exploring the adaptive value of the styles of coping, respectively. On the basis of all the results presented so far, it transpires that task orientation can hold a higher adaptive value than the generally heightened as well as decreased mobilization for coping. Such an interpretation is plausible in light of higher quality of life in the majority of task-oriented patients in contrast to subjects belonging to the remaining two groups.

But why is it the case? In order to answer the question, the levels of anxiety (measured by means of State-Trait Anxiety Inventory (STAI)), of hopelessness (Hopelessness Scale (HS)), of loneliness (UCLA Loneliness Scale Revised (LS-R)), and of self-esteem (Self-Esteem Scale (SES)) were compared in the three selected groups. The juxtaposition of mean results in the scales measuring aforementioned clinical variables indicated that anxiety, hopelessness, and loneliness levels were markedly lower in the group of patients using mainly task-oriented coping (Table 3). From a statistical point of view, there existed no significant differences between the first group (with high mobilization and emotion-avoidance orientation) and the third group (with low mobilization for coping). For example, intensity of hopelessness (HS) reached a clinical level in both of the groups.

The level of self-esteem was higher in the group of task-oriented patients in comparison with the two remaining groups: with high and low mobilization for coping (there was no significant difference between the mean results in both groups). Both high and low mobilization for coping concurred with lowered self-esteem. Participants with high and low mobilization for coping had lower self-esteem than task-oriented patients and higher level of clinical variables such as anxiety, hopelessness, and loneliness. This implies that high mobilization for coping was not necessarily an adaptive orientation for patients with vision disturbances as well as the absence of mobilization in confrontation with stress. Research results seem to emphasize the fact that not only mobilization embodying all the styles of coping—which implies flexibility—has adaptive value. For adaptive functioning, two factors appear to be decisive: the effort put into the process of coping and the apt guiding of the process towards task-oriented coping. Moreover, the tendency towards searching for social support was also exhibited and it could be interpreted as task-oriented in the case of elderly persons with visual disturbances—to keep and develop social support seems a big challenge for the elderly and the sick [28].

The conducted studies once again attested to the adaptive value of task-oriented coping and in general an active life in old age [19, 29, 30]. Patients adhering to this style exhibit higher quality of life and a lower level of anxiety, pessimism, and loneliness unlike subjects adhering to coping style based on emotions or avoidance. Furthermore, it was discovered that, to a certain extent, task-oriented coping entails searching for and employing social support, which, on account of the patient age and vision disturbances involved, appears to show adaptive value [29, 31, 32]. This conclusion together with the interrelation between coping and its adaptive value, on the one hand, and self-evaluation, on the other hand, is not characteristic of persons with vision disturbances exclusively. Similar results were achieved in other groups of patients [33, 34].

However, the result suggesting that both high mobilization for coping and the absence of mobilization seem to be

Table 3: Clinical and social-cognitive variables in three groups. Comparison: state anxiety (X-1) and trait anxiety (X-2), hopelessness (HS), loneliness (UCLA LS-R), and self-esteem (SES).

Group/scale	Group 1		Group 2		Group 3		Significance of differences	
	M	SD	M	SD	M	SD	$F(3,234)$	$P<$
STAI: X-1	43,16	12,70	33,90	10,27	42,49	11,32	14,66[ab]	0,001
STAI: X-2	45,45	8,98	36,47	6,07	43,99	8,90	25,61[ab]	0,001
HS	9,07	4,63	6,16	4,46	9,25	5,19	9,64[ab]	0,001
LS	35,76	8,94	30,44	7,30	36,53	9,76	10,26[ab]	0,001
SES	27,38	3,08	30,45	3,46	27,41	3,94	16,82[ab]	0,001

[a]Significant difference between groups 1 and 2, $P < 0,05$.
[b]Significant difference between groups 2 and 3, $P < 0,05$.

equally nonadaptive becomes distinctive for the examined group of patients. The former case is often accompanied by noneffective exploitation of personal resources and the latter by passivity and the adoption of a resigned attitude which can be moderated by negative affectivity or depression [16, 35]; low quality of life cooccurring with an increasing level of anxiety, pessimism, loneliness, and lowered self-esteem is often generated in either of the cases [36]. Most probably, not so much the effort engaged as coping directed towards the task-oriented style and pertinent mobilization of the support of close persons, appropriate groups, and relevant institutions—which accords with positive self-evaluation and self-esteem—proves decisive in the process of adaptation throughout illness [17]. The ability of engaging oneself in substitute activities in place of disintegrated routine tasks appears to be equally important (e.g., concentrating on listening to the radio rather than watching television, involvement in gardening instead of reading papers, or going to the cinema).

Whenever the psychological corollary of disease symptoms developed due to cognitive functional disturbances—especially those related to visual perception—results in the loss of self-confidence, deterioration of social relations, poor performance of social or professional roles, the decline in the family status, and the development of negative emotions such as anxiety, tension, or lower self-esteem, the effectiveness of coping turns out to be vitally important [3, 15–17, 37–39]. However not all studies support the conclusion that visual impairment is necessarily linked to well-being or depression [40].

One should remember also about individual differences not only in effectiveness of given coping style but also in temperament [40] as well as in defining life domains which are important to the patients and which constitute their quality of life [41, 42]. At the same time, adaptive patterns in elderly persons may be affected by flexibility limitations. When faced with tense situations, they cope employing whatever methods are available or simply give up. The ability to retain self-esteem favours strengthening task-oriented coping and the ability to take advantage of social support, which, on its part, is conducive to lowering the anxiety, depression, and loneliness threshold.

There are some limitations of this study; first, this study, which is typical for questionnaire approach, based on self report data (and not verified, e.g., by objective observation), second, the research was conducted in one country (Poland), and, third, socioeconomic status of elderly people (rather low in most cases) could influence the results, especially assessment of quality of life, depression (i.e., hopelessness), or anxiety and loneliness.

While we have distinguished a few groups of patients different in coping with stress related to their illnesses, one can conduct similar analysis taking temperamental features as a criterion for division of the groups, providing also a relationship between coping, quality of life, and temperament. In fact, empirical data suggest that patients differ also in their psychological functioning due to specific temperamental features [40]. Moreover, temperamental factors can underline different coping strategies. It seems to be an interesting topic for further research, especially when such a study would be focused on how the patients face the illness as well as on more practical issue, namely, how to organize and propose better care for elderly people with vision disturbances.

4. Conclusions

The conclusions to be drawn from the presented study are as follows.

(1) Patients who follow the pattern of task-oriented coping and who take advantage of social support are characterized by higher quality of life, higher self-esteem, and comparatively lower level of anxiety, pessimism, and loneliness. This proves task-oriented coping to be of greater adaptive value than passivity in stress exposure situations and a generally heightened mobilization for coping in emotion-avoidance pattern, in particular.

(2) The results hint at the significance of social support and at the value of interpersonal relationships for quality of life in elderly persons with vision disturbances such as glaucoma or cataract, provided that task orientation is involved. The tendency towards searching for interpersonal interactions as a way of coping detected in the task-oriented group of patients can be plausibly accounted for. In the case of elderly persons coping with their illnesses, seeking and employing the support of other people are not exclusively of adaptive value, but they also appear to constitute a definite task enabling them to function on a daily basis.

(3) Both demobilization and high mobilization for coping appear to be nonadaptive styles of functioning which entail lowered quality of life, lowered self-esteem, and increased level of pessimism, loneliness, and anxiety.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Trabecular-Iris Circumference Volume in Open Angle Eyes Using Swept-Source Fourier Domain Anterior Segment Optical Coherence Tomography

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Purpose. To introduce a new anterior segment optical coherence tomography parameter, trabecular-iris circumference volume (TICV), which measures the integrated volume of the peripheral angle, and establish a reference range in normal, open angle eyes. *Methods*. One eye of each participant with open angles and a normal anterior segment was imaged using 3D mode by the CASIA SS-1000 (Tomey, Nagoya, Japan). Trabecular-iris space area (TISA) and TICV at 500 and 750 μm were calculated. Analysis of covariance was performed to examine the effect of age and its interaction with spherical equivalent. *Results*. The study included 100 participants with a mean age of 50 (±15) years (range 20–79). TICV showed a normal distribution with a mean (±SD) value of 4.75 μL (±2.30) for TICV500 and a mean (±SD) value of 8.90 μL (±3.88) for TICV750. Overall, TICV showed an age-related reduction ($P = 0.035$). In addition, angle volume increased with increased myopia for all age groups, except for those older than 65 years. *Conclusions*. This study introduces a new parameter to measure peripheral angle volume, TICV, with age-adjusted normal ranges for open angle eyes. Further investigation is warranted to determine the clinical utility of this new parameter.

1. Introduction

Evaluation of the anterior chamber angle is essential to diagnose and manage eyes with glaucoma. Evaluating angle anatomy and monitoring changes in angle configuration after treatment, such as laser peripheral iridotomy (LPI) or lens extraction (LE), depend on the accuracy and precision of angle measurements. Several anterior segment optical coherence tomography (ASOCT) devices have been developed in the last decade [1] and have been shown to provide repeatable and reproducible measurements of the angle [2–5]. Although early generations of ASOCT instruments were able to assess angle measurements, their relatively slow scan rate did not capture adequate numbers of images in a feasible time frame, allowing for imaging of only 2 meridians (4 angles) in one scan.

The commonly used quantitative measures to characterize angle structures are angle opening distance (AOD) and trabecular-iris space area (TISA) [6] (Figure 1). These measurements have been used to monitor changes in the anterior chamber angle morphology after LPI [7] or LE [8]. However, extrapolation of these measurements over the entire angle may be flawed because most ASOCT devices can only image 2 meridians in one scan.

The CASIA SS-1000 (Tomey Corporation, Nagoya, Japan) using Fourier domain (FD) swept-source technology can image 128 meridians (256 angles) in less than 5 seconds [1, 6].

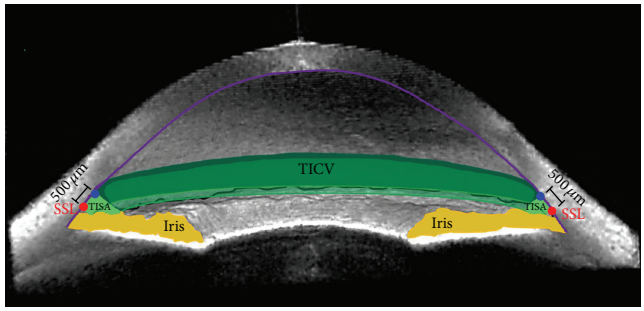

Figure 1: Trabecular-iris circumference volume (TICV). 3D anterior segment optical coherence tomography (ASOCT) image exhibiting TISA500 (light green space) and TICV500 (darker green spaces), along with the scleral spur landmark (red circle), iris (yellow), and cornea (violet line).

This allows a 3D reconstruction of the anterior chamber angle and, therefore, more precise quantification of the angle structures. Trabecular-iris circumference volume (TICV; Figure 1) is the integrated volume of the peripheral angle derived from TISA taken at 256 locations in the angle. With any newly developed measurement, there is a need to establish the reference distribution. This study evaluates the normative distribution of TICV in open angle eyes using the CASIA SS-1000 FD ASOCT.

2. Participants and Methods

This prospective study was conducted at the Robert Cizik Eye Clinic of the Ruiz Department of Ophthalmology and Visual Science at The University of Texas Medical School at Houston. Institutional review board approval was obtained from The University of Texas Health Science Center Committee for the Protection of Human Subjects. All research was HIPAA compliant.

2.1. Participants. Participants 18 years of age or older were recruited between December 2012 and December 2013. One hundred and six participants distributed among 5 age groups (18–35, 36–45, 46–55, 56–65, and 66–79) met eligibility criteria. After obtaining informed consent, participants underwent slit lamp examination, intraocular pressure measurement, and gonioscopic examination performed by a glaucoma specialist (RMF, NPB, LSB, or DAL). Eyes with open angles (open to the ciliary body band or the scleral spur) were included. Lens grading was done using a scale of 0–4. Eyes were excluded if there was a history of intraocular surgery (such as LE or LPI), penetrating trauma, or any anterior segment abnormality that affected visualization of the angle or its measurements (i.e., significant corneal opacity). Participants were also excluded if they used any medication that may have affected angle anatomy within a month prior to imaging. When both eyes of the participant were eligible, one eye was randomly selected by coin flip. Although refraction was not performed, spherical equivalent data, where available, was recorded.

Table 1: Baseline ocular characteristics.

Ocular Characteristics	Statistics
Iris Color, *N* (%)	
Blue	22 (22%)
Brown	70 (70%)
Hazel	8 (8%)
Cornea, *N* (%)	
Normal	88 (88%)
PEK	8 (8%)
Others (EBMD, KP)	4 (4%)
Presence of cataract, *N* normal (%)[1]	49 (51%)
Glaucoma, *N* (%)[2]	
Normal	60 (61%)
POAG suspect	26 (26%)
POAG	13 (13%)
IOP, mm Hg (±SD)[2]	14.94 (±3.04)
Number of IOP-lowering Medications, *N* (%)[2]	
0	81 (81%)
1	11 (11%)
2	6 (6%)
3	2 (2%)
Gonioscopy, *N* (%)	
Open to posterior trabecular meshwork	1 (1%)
Open to scleral spur	41 (41%)
Open to ciliary body band	58 (58%)
Spherical Equivalent, *D* (±SD)[3]	−1.93 (±3.64)

[1]3 missing data points.
[2]1 missing data point.
[3]12 missing data points.
PEK = punctuate epithelial keratopathy; EBMD = epithelial basement membrane dystrophy; KP = keratic precipitates; IOP = intraocular pressure; POAG = primary open angle glaucoma.

2.2. ASOCT Instrument. Instrumental details have been previously described [6]. For 3D image reconstruction, the CASIA SS-1000 obtains a series of 128 cross-sectional images (512 A-scans each) across the whole anterior chamber in less than 5 seconds. Each image dimension is 16 mm (length) × 16 mm (width) × 6 mm (depth).

2.3. Acquisition of ASOCT Images. Participant procedures for image acquisition have been previously described [6]. For 3D image reconstruction, eyes were scanned in 3D mode using the anterior analysis scan type with the autoalignment function.

2.4. Analysis of ASOCT Images. The images were exported from the CASIA SS-1000 and read by an experienced reader using customized software, Anterior Chamber Angle and Interpretation (ACAI, Houston, TX). The reader (AZC) was masked to the gonioscopy grade. The ACAI software divides 128 images into 8 panels, 16 images per panel (11.25 degrees between 2 consecutive angles). The reader marks the scleral spur landmarks (SSLs) [6] on each image in the first panel (this panel includes horizontal and vertical meridian images),

Table 2: Angle measurements [mean (SD)] for all eyes and for eyes in each age group.

		Age (years)				
	All ($N = 100$)	≤35 ($N = 20$)	36–45 ($N = 21$)	46–55 ($N = 21$)	56–65 ($N = 19$)	>65 ($N = 19$)
TISA500 (mm^2)						
Temporal	0.153 (0.070)	0.201 (0.074)	0.168 (0.057)	0.119 (0.044)	0.147 (0.080)	0.127 (0.061)
Nasal	0.160 (0.091)	0.208 (0.097)	0.172 (0.065)	0.122 (0.071)	0.154 (0.081)	0.143 (0.117)
Superior	0.109 (0.066)	0.158 (0.061)	0.130 (0.064)	0.073 (0.048)	0.092 (0.055)	0.090 (0.065)
Inferior	0.148 (0.080)	0.214 (0.081)	0.162 (0.065)	0.107 (0.066)	0.131 (0.082)	0.126 (0.064)
TISA750 (mm^2)						
Temporal	0.286 (0.115)	0.369 (0.125)	0.313 (0.094)	0.227 (0.075)	0.280 (0.128)	0.239 (0.095)
Nasal	0.296 (0.144)	0.378 (0.152)	0.321 (0.113)	0.236 (0.117)	0.288 (0.146)	0.254 (0.159)
Superior	0.221 (0.113)	0.306 (0.105)	0.260 (0.113)	0.161 (0.083)	0.196 (0.101)	0.179 (0.100)
Inferior	0.281 (0.136)	0.391 (0.136)	0.311 (0.115)	0.212 (0.114)	0.253 (0.140)	0.235 (0.098)
TICV500 (μL)	4.751 (2.304)	6.568 (2.432)	5.309 (1.810)	3.491 (1.640)	4.339 (2.085)	4.028 (2.316)
TICV750 (μL)	8.896 (3.880)	11.934 (4.018)	9.966 (3.113)	6.808 (2.826)	8.257 (3.701)	7.461 (3.627)

TISA = trabecular-iris surface area; TICV = trabecular-iris circumference volume.

and then the ACAI software automatically detects corneal edges and iris edges. If the edges of cornea and iris are not accurate, the reader manually adjusts intensity and, if not successful, manually adjusts the edge margins. Once the reader has completed and saved the interpreted result of the first panel, ACAI interpolates the SSLs in the remaining panels using the first panel result and detects edges. It should be noted that a previous study showed that 16 read images is sufficient to estimate TICV (within 5% mean absolute percent error) [9].

ACAI provides AOD and TISA at 500 and 750 μm for each angle as well as radius (R), which is the distance from the midpoint of 2 SSLs to the centroid of each TISA. TICV500 and TICV750 are defined as bounded by the posterior corneal surface, anterior iris surface, scleral spur landmark ring, and 500 or 750 μm centrally from scleral spur landmark ring, respectively. TICV500 and TICV750 were calculated using Pappus's centroid theorem formula:

$$\text{TICV} = 2\pi \sum_{i=1}^{256} \text{TISA}_i \times \frac{R_i}{256}. \quad (1)$$

2.5. Statistical Analysis. Demographics were summarized by mean and standard deviation (SD) for continuous variables or by frequency (%) for discrete variables. TISA at each quadrant (nasal, temporal, superior, and inferior) was summarized for all eyes and each age group. Comparing TISA among quadrants was performed using a mixed effect model. In this model, eye was the random effect, and quadrant was the fixed effect.

Histograms for TICV500 and TICV750 were plotted, as well as descriptive summary statistics, including mean, SD, median, range, and 2.5 and 97.5 percentile. Normality testing was performed to investigate whether TICV was normally distributed. Linearity between TICV500 and TICV750 was examined using regression analysis. TICV was summarized for each age group and compared using one-way analysis of variance (ANOVA). Mean and standard deviation of TICV measurements for each gonioscopic grade were calculated and compared using the two-sample t-test for validation. Furthermore, stepwise regression analysis was used to investigate the factors that affected TICV. The factors investigated were age, gonioscopic grade, gender, race, IOP, presence or absence of open angle glaucoma/suspect, lens grade (0 to 4, with 0.5 = trace), and spherical equivalent (sphere +1/2 cylinder). Analysis of covariance was used to compare TICV among age groups after adjusting for spherical equivalent.

All statistical analyses were performed using SAS for Windows v9.3 (SAS, Inc., Cary, NC). $P < 0.05$ was considered statistically significant for all comparisons.

3. Results

A total of 106 eyes of 106 participants were recruited. There were approximately 21 participants in each of the 5 age groups: 18–35, 36–45, 46–55, 56–65, and 65–79 years. Six eyes

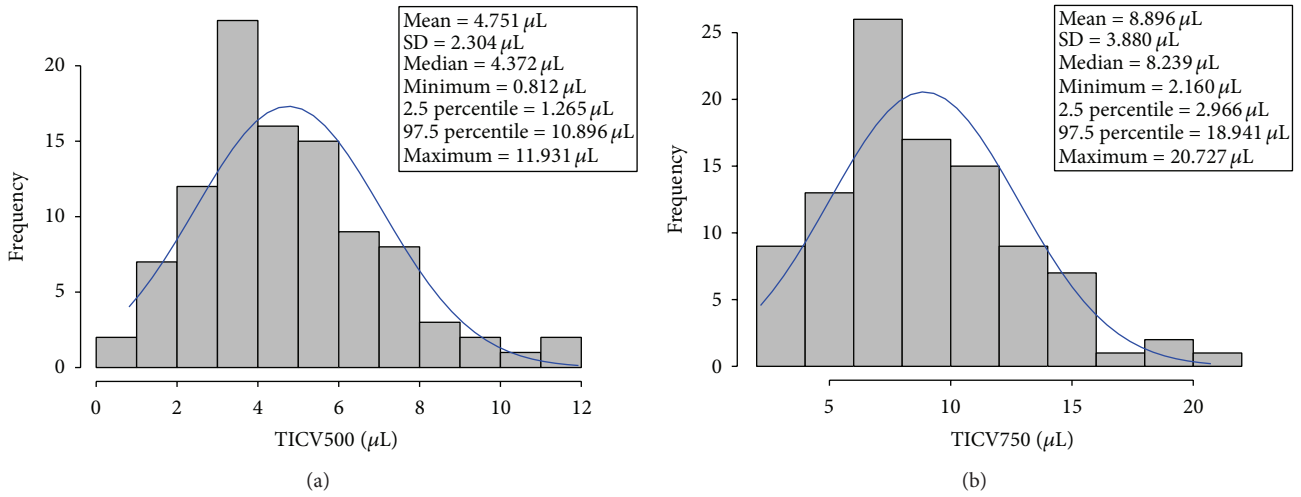

Figure 2: (a) Histogram and estimated density function for TICV500. (b) Histogram and estimated density function for TICV750.

(5.7%) were excluded due to poor image quality, leaving a total of 100 eyes included in the study. Of those, 61% (61 eyes) were women. The mean (±SD) age was 50 (±15) years (range 20–79 years). Forty-three (43%) were right eyes. The study included 55 White (55%), 25 Black (25%), 10 Hispanic (10%), and 10 Asian (10%) participants. Gonioscopic findings included 58 eyes (58%) open to the ciliary body band, 41 eyes (41%) open to the scleral spur, and one eye (1%) open to the posterior trabecular meshwork. Thirteen eyes (13%) had primary open angle glaucoma without visible structural abnormalities. Two eyes (2%) had undergone laser-assisted in situ keratomileusis (LASIK) in the past. Forty-nine eyes (51%) showed presence of cataract. Eighty-eight (88%) eyes had documented spherical equivalent data. Baseline ocular characteristics are given in Table 1.

3.1. Trabecular-Iris Space Area. The cross-sectional iridocorneal angle parameters for all eyes and for each age group are summarized in Table 2. TISA500 and TISA750 were significantly smaller superiorly than in the other quadrants ($P < 0.0001$ for both TISA500 and TISA750). Differences between the other quadrants were not found to be statistically significant. The linear correlations between TISA500 and TISA750 were $R^2 > 0.96$, and the slopes ranged from 1.56 (nasal) to 1.70 (superior).

3.2. Trabecular-Iris Circumference Volume. Figures 2 and 3 show the distribution of TICV500 and TICV750. The summary statistics for TICV500 and TICV750 are shown in Table 2. The means (±SD) were 4.751 μL (±2.304) and 8.896 μL (±3.880) for TICV500 and TICV750, respectively. TICV500 was normally distributed ($P = 0.0873$, Kolmogorov-Smirnov normality test), but TICV750 was not ($P = 0.0385$, slightly skewed to the right). A linear relationship, $R^2 = 0.99$, between TICV750 and TICV500 was observed, and the slope was 1.67. The mean (±SD) TICV500 was 3.246 μL (±1.761) for eyes open gonioscopically to the scleral spur and 5.841 μL (±2.028) for eyes open to the ciliary body band ($P < 0.0001$). The mean (±SD) TICV750 was 6.337 μL (±5.407) for eyes open to the scleral spur and 10.749 μL (±9.860) for eyes open to the ciliary body band ($P < 0.0001$). It should be noted that one eye gonioscopically open to the posterior trabecular meshwork was included in the group of eyes open to the scleral spur.

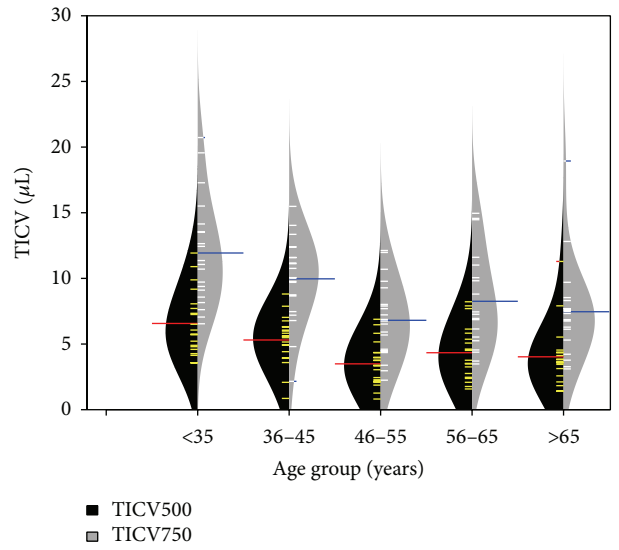

Figure 3: Observed TICV500 (yellow) and TICV750 (white), estimated normal density functions (black for TICV500 and grey for TICV750), as well as means (red for TICV500 and blue for TICV750) for each age group.

The 46–55-year-old group showed the smallest TICV (mean (±SD) 3.5 μL (± 1.6) for TICV500 and 6.8 μL (±2.8) for TICV750), which was significantly different from 18–35 and 36–45 age groups (Table 2), but not significantly different from the 56–65 and 65–79 age groups (one-way ANOVA with *post hoc* Duncan multiple comparison).

Age ($P = 0.03455$), lens grade ($P = 0.0170$), and spherical equivalent (SPE; $P = 0.0402$) influenced TICV500,

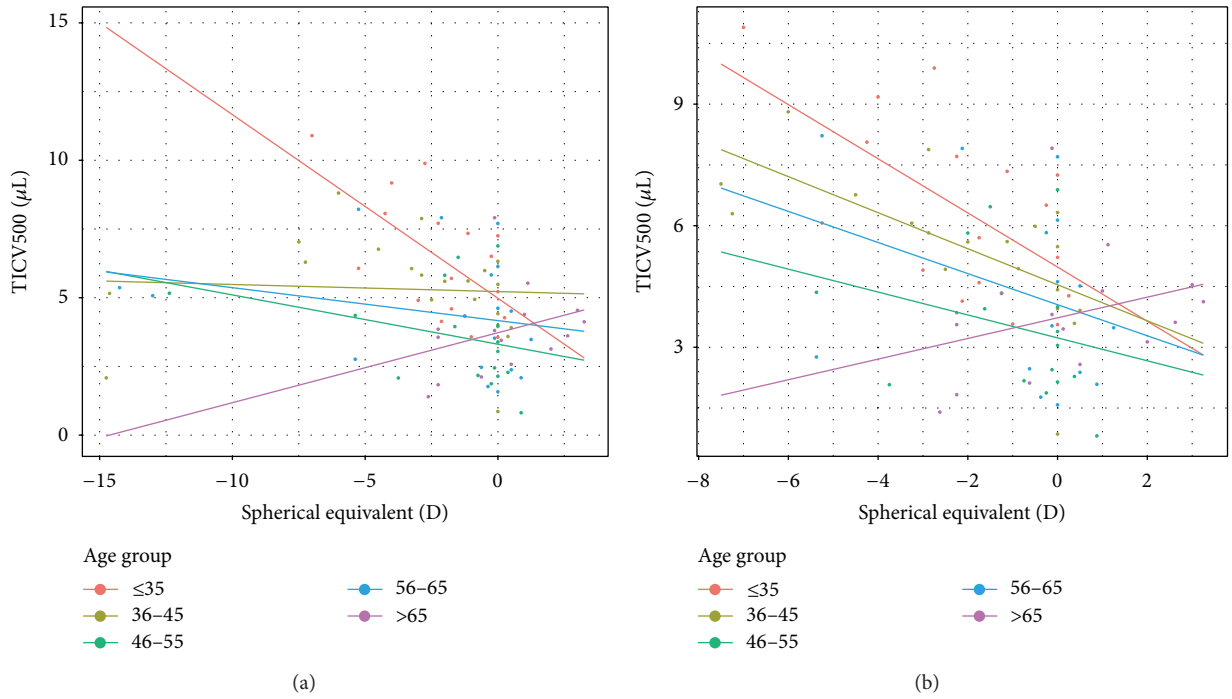

Figure 4: (a) TICV500 versus spherical equivalent scatter plot with estimated regression line for each group (with outliers). (b) TICV500 versus spherical equivalent scatter plot with estimated regression line for each group (without outliers).

using stepwise regression analysis. TICV500 decreased with age at the mean (±SD) rate of −0.37 μL (±0.17) per decade, after adjusting for lens grade and SPE. Adjusted TICV500 decreased at a mean (±SD) rate of −0.89 μL (±0.37) per grade of lens. TICV500 increased at a mean (±SD) rate of 0.12 μL ± 0.06 per diopter of myopia. Similar results were obtained for TICV750.

In addition, to examine whether an interaction effect of age and SPE had any influence on TICV, a scatter plot of 88 eyes, where SPE data was evaluated, revealed that 5 eyes with high myopia (myopic refractive error > 12 diopters) skewed the estimates of slopes in the 36–45, 46–55, and 56–65 age groups (Figure 4(a)). After excluding those 5 highly myopic eyes, the results showed that the angle deepens as the degree of myopia increases ($P = 0.0034$ for TICV500 and $P = 0.0012$ for TICV750) for all groups except the oldest group (65–79 age group) (Figure 4(b)).

4. Discussion

This is the first study reporting a novel quantitative parameter, trabecular-iris circumference volume (TICV), and it establishes initial normal, age-adjusted reference values for open angle eyes. We found that TICV500 decreased with age at a rate of −0.37 μL per decade, after adjusting for lens grade and SPE. This correlates with anatomic findings previously reported using other measurement techniques [10, 11]. Age affected TICV750 in a similar fashion. TICV500 and TICV750 showed a linear correlation, which indicates that both are equally suitable to quantitatively describe peripheral angle volume.

Previously, anterior chamber depth (ACD) estimation has been used to infer peripheral angle volume. The relationship between central ACD and peripheral angle volume has not been established, because until now peripheral angle volume could not be measured. In glaucoma, the overall anterior chamber depth is probably not as clinically relevant as the configuration of the peripheral angle. Estimates that use anterior chamber depth or volume as a marker for peripheral angle configuration may not be sensitive enough to detect small but clinically significant differences in the peripheral angle volume. The strength of TICV lies in determining peripheral angle volume, which accounts for only 2–2.5% of the anterior chamber volume [10].

TICV appears to have a normal distribution, when considering all age groups as well as within each age group, except within the oldest group (>65 years). We observed a similar range of TICV500 in both men and women. The age group 46–55 showed the smallest TICV500, which was significantly different from younger age groups (18–35 and 36–45), but not significantly different from older groups (56–65 and 65–79). The lowest volumes measured in the 46–55 age group may reflect subject selection bias, as eyes with progressively larger lenses causing clinically significant angle narrowing in the older age groups would be more likely to have undergone LE for vision reasons and not have been included in our study population (as pseudophakic eyes were excluded). Alternatively, lens enlargement may peak in the 46–55 age group and remain stable thereafter. It is also possible that the lens continues to enlarge but not in an anterior direction.

Overall, the results showed that TICV increased as the degree of myopia increased for all groups, except in the 65–79

group. This likely reflects the etiology of myopia in younger versus older age groups. In general, myopia in the former is typically caused by longer axial length or steeper corneal curvatures and in the latter by increasing lens power (cataract formation). This finding is also consistent with the selection bias mentioned above in that, as the population gets older, they are more likely to have visually significant cataracts that would undergo extraction, excluding them from our study population. It should be noted that the SPE was taken from habitual refractions, which may have overestimated myopia in younger patients with a masking of latent hyperopes prior to age 46.

We also observed that TISA in the superior angle was significantly smaller than other quadrants in all eyes ($P < 0.0001$). These results concur with the earlier studies showing that superior angle is the narrowest [3, 6]. We did not find a statistically significant difference between TISA measurements in the other quadrants.

There are several limitations to this study. Our results may not extrapolate to patients with anterior segment abnormalities or pseudophakia because this population was not included in our study. Also, we did not initially consider the effect that spherical equivalent would have on TICV. To better assess this relationship, further investigation is required. This sample may not be representative of the population as participants were recruited from patients, family members, and staff of a tertiary eye clinic. Results may not be generalizable outside of our inclusion and exclusion criteria.

In summary, this study describes a novel quantitative parameter, TICV, for measuring the peripheral angle and establishes a preliminary normal range of age-adjusted values. The reference range may require refinement adjusting for spherical equivalent. This deserves further study. With the introduction of normal values in open angle patients, further investigation is warranted to determine the clinical utility of this new parameter.

Conflict of Interests

No author has any conflicts of interests.

Acknowledgments

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Review Article

Aging: A Predisposition to Dry Eyes

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Dry eye syndrome is a disease of the ocular surface and tear film that is prevalent in older adults. Even though the degree of visual acuity loss in dry eye patients is commonly mild-to-moderate, in the aging population, this minimal change in visual status can lead to a significant decrease in visual function and quality of life. A healthy ocular surface is maintained by appropriate tear production and tear drainage, and deficiencies in this delicate balance can lead to dryness. In the aging eye, risk factors such as polypharmacy, androgen deficiency, decreased blink rates, and oxidative stress can predispose the patient to developing dry eye that is frequently more severe, has higher economic costs, and leads to worse consequences to the well-being of the patient. Understanding why elderly patients are at higher risk for developing dry eyes can provide insights into the diagnosis and management of the growing number of older adults struggling with dry eye and minimize the burden of disease on our aging population.

1. Introduction

Dry eye syndrome, or keratoconjunctivitis sicca, is a multifactorial disease of the tear film and ocular surface resulting in eye discomfort and compromised visual quality. Dysfunction of any component of the lacrimal gland, ocular surface, eyelids, and nervous system can cause dry eyes. Dry eye is especially common in the elderly, occurring in approximately 5–30% of the general elderly population, and affects women more commonly than men [1]. The prevalence disparity by age ranges from 8.4% in subjects younger than 60 years old to 15% in patients 70–79 years old and 20% in those older than 80 years [2, 3]. Various factors predispose older adults to dry eyes including higher rates of systemic and topical medication use, lid laxity, hormonal changes (menopause), inflammatory systemic conditions, and oxidative stress. With greater life expectancy, a growing number of people are expected to join the over-60 age group and the prevalence of dry eye disease is therefore expected to increase even more.

Patients with dry eye experience blurred vision, foreign body sensation, pain, injection, epiphora, and, in severe cases, loss of vision. While high-contrast visual acuity may not be affected or may be only minimally reduced, individuals with dry eye can suffer from discomfort and/or functional vision changes that can be debilitating. In a study assessing the impact of severe dry eye disease (DED) on patients' lives, subjects with severe dry eye reported an impact similar to that reported in other studies for moderate to severe angina or dialysis [4]. Quality of life is affected since even with mild vision loss, such as that which most commonly occurs with DED, the risk of falling is increased 2-fold, the risk of depression is increased 3-fold, and the risk of hip fracture is increased 4-fold [5–7]. Hip fractures, known to cause significant morbidity among the elderly, are more common amongst individuals with lower vision; 8.5% of hip fractures occur in elderly patients with mild-to-moderate vision loss (VA between 20/30 and 20/80) which can result from dry eyes. In contrast, only 3% of hip fractures occur in older patients with a VA of 20/25 or better [8]. Hip fractures can lead to decreased independence, functional status, and quality of life.

Along with the physiologic toll on patients, DED also generates a significant economic burden on this population. A study by Yu et al. determined the average annual direct medical cost per DED patient to be $678 for mild dry eye, $771 for moderate dry eye, and $1267 for severe dry eye [9].

In light of higher DED prevalence in patients over 50 years of age, this amounts to $3.84 billion for the health care system to support cost of ocular lubricants, cyclosporine, punctal plugs, nutritional supplements, and professional healthcare visits as well as loss of workplace productivity. In indirect costs, the average annual cost to society per patient was $11,302 and the overall societal burden was $55.4 billion [9].

It is important to bear in mind that even seemingly benign impairments from dry eyes, such as impaired reading, can lead to errors in medication administration [10] which can be life-threatening. Quality of life can be severely affected—with DED being likened to chronic pain syndromes [11], being associated with poorer general health [12], and leading to greater problems in daily activities by factors 2-3x over those of normal [13]. In light of the susceptible state of the aging population for developing dry eyes, early screening, prompt attention, and targeted cost-effective treatment can make a difference in a patient's mental health, self-confidence [14], and functional status.

2. Pathophysiology of Dry Eyes and Implications for the Aging Eye

The tear film consists of the following 3 main layers: the lipid layer secreted by the meibomian glands, the aqueous layer produced by the lacrimal gland, and the mucin layer secreted by conjunctival goblet cells. Homeostasis of the ocular surface environment is maintained by a fine balance of tear production and appropriate tear drainage. Tear production is orchestrated by multiple components including the lacrimal gland that secretes the aqueous component of the tears, which comprises the thickest layer of the tear, and the corneal nerves which provide a reflex loop that modulates tear production in response to different conditions [15]. Appropriate tear drainage is maintained by the physical apposition of the eyelids to the globe that minimizes tear evaporation, meibomian glands that contribute to tear-film stability [16, 17], the blink mechanism that adequately distributes the tear film across ocular surface, and the orbicularis muscle that drives the flow of tears medially, maintains the thickness of the tear film over the cornea, and directs closure of the lacrimal punctum [18]. The Dry Eye Workshop (DEWS) classification divides dry eye into two major pathophysiologic categories—aqueous tear deficiency and evaporative dry eye—with older adults being more susceptible to both categories [19].

3. Aqueous Tear Deficiency Changes with Aging

Decreased tear production as a consequence of lacrimal gland dysfunction, altered reflex secretion, diminished corneal sensation, or inflammatory destruction of lacrimal glands lead to tear deficiency—a major cause of dry eye. Older adults are particularly susceptible to inadequate tear production because they have a higher prevalence of autoimmune diseases (Sjögren's syndrome and rheumatoid arthritis), decreased corneal sensitivity, and medicamentosa (polypharmacy), which contribute to the etiologic mechanisms and can, in severe cases, have vision threatening consequences. Inadequate aqueous tear film drives tear hyperosmolarity that induces an inflammatory cascade, leaving epithelial cells dead or devitalized [20]. Goblet cells produce mucin which bears a protective function by clearing debris, preventing bacterial adhesion, promoting boundary lubrication, and maintaining the epithelial barrier function [21]. In the setting of inflammation, the goblet cell number and secretory function are decreased and inflammatory cytokines such as interferon gamma and TNF alpha induce goblet cell apoptosis—further diminishing mucin production [22–24]. Corneal epithelial cells with inadequate mucin protection are left vulnerable to cell damage. The loss of goblet cells from injury induced by the inflammatory response further perpetuates the loss of corneal epithelial cells. A spectrum of ocular surface disease can then result—ranging from mild dry eye, to particularly painful symptoms associated with filament and mucous plaque formation. With aging, the number of goblet cells remains unchanged; however, the cell functions decline [25]; in addition, the aging conjunctival cells are more prone to apoptosis [26]. In the setting of dry eyes in older adults, a cumulative higher loss of functional goblet cells and increased level of goblet cell apoptosis occur which can lead to advanced DED. At the advanced stages of the disease spectrum, corneal keratinization, corneal ulceration, and band keratopathy can arise from repeated or severe insults over time.

Systemic and topical medications are a key risk factor predisposing the over-60 population to sicca from deficient tear production. The CDC reported that greater than 76% of Americans 60 years or older used two or more prescription drugs and 37% used five or more between 2007 and 2008. Only 10.8% of younger adults (18–44 year olds) take 5 or more drugs, whereas 41.7% of middle aged adults and up to 47.5% of older adults take 5 or more medications [27, 28]. Systemic medications including antidepressants, diuretics, dopaminergic drugs for Parkinson's disease, and antimetabolites frequently used in treating rheumatoid arthritis are all prescription drugs that cause or exacerbate dry eyes and are used commonly in older patients. Drug clearance also changes with aging as hepatic and renal function decline. Reduced clearance of drugs such as diuretics [29] leads to increased plasma half-life and increased sensitivity to drugs [30]. The Beaver Dam Eye Study found an overall 10-year dry eye incidence of 21.6% among individuals aged from 43 to 84 years, with an increase in incidence from 17.3% in subjects in the 48- to 59-year-old age group, to 28.0% in those 80 years or older [31]. This study also showed that patients using decongestants, antihistamine, and vitamins have a higher incidence of dry eyes [31]. With increasing use of such over-the-counter (OTC) medications and supplements in the elderly, the prevalence of medication induced dry eye is expected to be even higher than that among younger age groups. In the elderly, the underlying systemic disease for which they are taking systemic medications is often more severe or has persisted for a longer duration, making the long-term use of dry eye-inducing systemic medications more likely and increasing the likelihood of developing medication-induced sicca. Dry eye, for example, is frequent in patients

using antidepressant medications. Older patients are particularly at risk for developing antidepressant-induced dry eye because they tend to have longer duration of depression and take antidepressant medications for a longer period of time [32].

The use of topical medications, such as topical glaucoma medications, can also increase the risk of development of dry eye relative to age matched controls [33]. Glaucoma is more prevalent in the elderly [34], with increasing numbers of people on more than one topical medication. Sixty-one percent of patients using one or more pressure lowering drops have decreased tear production (<5 mm) on Schirmer's test indicating tear deficiency dry eye [35]. In adults using glaucoma drops, 63% developed signs and symptoms consistent with dry eye and did so at a mean age of 55. In patients not using glaucoma drops, only 23% developed symptoms and signs of dry eye but did not do so until a mean age of 70 [36]. Earlier disease onset translates into a longer course of ocular discomfort, higher cumulative healthcare burden, and more severe morbidity. Ocular surface disease due to glaucoma medications correlates with the number of medications containing preservatives such as benzalkonium chloride (BAK), which can cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues even at low concentrations [37]. More severe ocular surface disease has also been seen with preservative containing eye drops. Schwab et al. showed that long-term glaucoma medications with preservatives can cause conjunctival foreshortening with shrinkage including conjunctival scarring [38, 39]. Furthermore, a significant foreshortening of the inferior conjunctival fornix was found with aging independent of medication use [38]. Since more elderly patients use glaucoma eye drops, many of which contain preservatives, the older adults on glaucoma medications with preservatives are at an even increased risk of severe dry eye sequelae.

Another common disease causing aqueous dry eye in the elderly, especially older women, is lacrimal gland dysfunction. Notably, older men and women are almost twice as likely to have dry eyes compared with their younger counterparts. The dry eye prevalence is 3.90% among men aged from 50 to 54 years compared to 7.67% among men 80 years and older [40]. Similarly, dry eye prevalence is 9.8% among women aged 75 years or older compared to only 5.7% among women less than 50 years old [41]. Secretory function of the lacrimal gland is known to be regulated by androgens [42, 43]. Dehydroepiandrosterone sulphate (DHEAS) is one of the main adrenal androgens. Serum levels of DHEAS are lower in women with Sjögren's syndrome, older men, and older women [44]. Decreased DHEAS levels in older men correlate with dry eye symptoms and decreased Schirmer's test (<5 mm) due to insufficient lacrimal gland function; however, the association is weak ($r = 0.13$) [45]. Since women have lower levels of androgens compared to the levels in men, further age-related decreases in androgen levels may diminish the androgen levels below the critical amount needed for optimum eye health [46]. Along with a decrease in androgen levels, postmenopausal women develop lower levels of estrogen—a hormone that is known to stimulate meibomian glands and help regulate ocular surface homeostasis [42]. Together, androgen deficiency and estrogen decrease lead to inadequate lacrimal gland secretion with superimposed tear-film instability in older women and higher risk of developing dry eye.

4. Tear Evaporation Changes with Aging

The second major component of dry eye pathophysiology is the rate of tear film evaporation. Multiple features are at play to effectively conserve tears over the ocular surface. Eyelid apposition to the globe minimizes exposure, appropriate frequency of blinking ensures constant renewal of the tear film across the corneal surface, lipid production from meibomian glands stabilizes the tear film, and the orbicularis portion of the eyelid directs tear outflow at a controlled rate [47]. Abnormalities in eyelid positioning (laxity, floppy eyelid syndrome, retraction, and lagophthalmos), meibomian gland dysfunction, rosacea, abnormal corneal sensation, and decreased blink reflex are significant contributors to rapid tear film break-up and are seen increasingly in older adults [48–50]. Horizontal lid laxity, for example, is notable in elderly patients and is the most common cause of involutional eyelid malposition. Eyelid malposition, in turn, leads to corneal exposure, poor tear-film distribution, and abnormal tear outflow that induce sicca. Prevalence of involutional entropion in patients 60 or older has been reported as 2.1% and of involutional ectropion as 2.9% [48]. Patients with malpositioned lids can subsequently develop chronic blepharitis, chronic conjunctivitis, superficial punctate keratopathy from abnormal meibomian gland secretory function, mechanical injury, and exposure. As many as 50–70% of patients with malpositioned lids develop dry eye syndrome [48].

Conjunctivochalasis is another notable contributor to poor tear outflow and is characterized by a redundant bulbar conjunctiva interposed between the globe and the eyelid [51]. The prevalence of conjunctivochalasis increases dramatically with age from less than 71.5% in patients 50 years or younger, to greater than 98% in patients above 61 years of age [52]. Pathogenesis of conjunctivochalasis is under investigation; however, elastotic degeneration from cumulative sun exposure and inflammatory degeneration from delayed tear film clearance have been proposed [51, 53, 54]. Once formed, the redundant folds interfere with the inferior tear meniscus and, in some cases, cause occlusion of the inferior punctum. Elderly patients often have higher collective sun exposure that can predispose to development of conjunctivochalasis and often have aqueous tear deficiency that can be exacerbated by disruption of the tear meniscus. Older adults with coexisting eyelid malpositioning can have worsening of appropriate tear flow medially that can cause further pooling of inflammatory cytokines and reinforce conjunctival degeneration.

5. Corneal Sensitivity Changes with Aging

A gradual reduction in corneal sensitivity has been shown to occur with increasing age that predisposes older adults

to dry eyes [50]. Roszkowska et al. reported that mechanical sensitivity of peripheral cornea decreases gradually throughout life, whereas central corneal sensitivity remains stable until age 60 and then decreases sharply subsequently [55]. The role of corneal sensitivity in dry eye patients, however, is conflicting. Some studies show decreased sensitivity in dry eyes compared with controls on noncontact esthesiometer measurements [56, 57]. Other groups demonstrate hypersensitivity in patients with dry eyes that may result from compromised epithelial barrier function [58, 59]. A characteristic change in dry eye patients that is generally agreed upon is a beadlike transformation of the nerves that is thought to represent nerve damage due to inflammatory processes in DED [60, 61]. Regardless of the direction of change in corneal sensitivity, elderly patients with DED are placed at higher risk of developing sicca signs and symptoms due to corneal nerve alterations. Older adults with corneal hypersensitivity experience increased ocular surface discomfort, while those with decreased sensitivity are prone to complications of exposure keratopathy.

6. Neurodegenerative Disease Contributes to Dry Eye among Older Adults

Neurodegenerative diseases can also predispose the aging population to evaporative dry eye. Parkinson's disease, for example, has an incidence of 13.4 per 100,000; only 4% of the cases occur in patients younger than 50 years [62]. Patients with Parkinson's disease have lower blink rates compared with controls [63]. In Parkinson's patients, dopaminergic dysfunction is thought to play a role in decreasing the blink reflex that leads to dry eyes. In addition to lower blink rates, Parkinson's patients with DED also exhibit decreased corneal sensation. Mean corneal sensitivity is shown to be decreased in some studies even in otherwise healthy patients with DED and correlates negatively with age [64]. The decreased corneal sensitivity exacerbates the risk of exposure keratopathy in DED patients and can be especially severe in a patient with a neurodegenerative disease. Parkinson's disease patients, for example, are relatively asymptomatic when compared to sicca counterparts without neurodegenerative disease. These patients may be brought in for evaluation when their family members identify a significant decline in visual function or obvious ocular change. Despite being relatively asymptomatic, these patients frequently have exam findings consistent with the advanced sequelae of chronic dry eye.

7. Inflammation and Oxidative Stress

Inflammation and oxidative stress, which increase in aging [65], may play a key role in dry eye development in the elderly. Increased levels of osmolarity and inflammatory cytokines have been detected in the tears of dry eye patients [66]. Tear concentrations of IL-6, IL-8, and TNF-α have been shown to be significantly higher in DED and can further amplify inflammation by recruiting activated immune cells [67]. Other inflammatory markers, such as IFN-γ, can promote goblet cell loss and stimulate keratinization of conjunctival epithelium [68]. Healthy adults acquire a baseline chronic low-grade inflammation with advancing age that is precipitated by constant antigenic load [69]. Older adults with DED, hence, bear damage via inflammatory cytokines from normal aging as well as from sicca. Oxidative stress, a counterpart of inflammation, occurs when antioxidants are unable to counteract reactive oxygen species (ROS) that are generated in normal metabolic processes. Production of aggressive oxygen species such as free radicals and peroxides leads to DNA damage over time, inducing cell necrosis. In younger, healthy human bodies, low levels of ROS are counteracted by antioxidant enzymes. With accumulation of radical species over time such as that which occurs in aging, oxidative stress activates cell regulatory pathways that can alter the regenerative capacity of cells such as the corneal epithelial cell layer under dry eye conditions [65]. Furthermore, inflammatory conditions such as rosacea and blepharitis, commonly seen in the aging population, are characterized by release of cytokines and chemokines which can induce further free radical production [70, 71]. Poorly healing epithelium in the setting of inflammation in the elderly can thus cascade into severe corneal conditions such as erosions, keratitis, or ulcers.

8. Treatment from the Aging Perspective

Standard of care therapy with artificial tears, cyclosporine, punctal plugs, steroids, or antibiotics can be effective in the elderly population. For mild dry eye, lubrication with artificial tear drops and gels is a key initial step to address patient symptoms. Environmental factors contributing to tear deficiency or evaporation should be minimized. Cigarette smoking, for example, has been found to adversely affect the lipid layer of the tear film and thus can negatively affect tear-film stability [72]. Dry eye inducing medications such as antihistamines or diuretics should be avoided if possible, and evaporative forces such as air conditioners or ceiling fans and low-humidity environments should be minimized [73]. For mild-to-moderate dry eye, treating the underlying diseases—blepharitis, rosacea, autoimmune disease, and others—with topical or oral antibiotics, low-dose steroids, warm compresses, or lid hygiene is necessary. Cyclosporine is an immunosuppressive that inhibits T-cell activation [74] and can be effective in cases of dry eye associated with inflammation [75]. Low dose corticosteroids can help decrease ocular irritation symptoms, decrease corneal fluorescein staining, and improve filamentary keratitis [76].

Punctal plugs can be efficient means to decrease the drainage of tears and prolong the retention time of tears on the ocular surface. They can, thus, improve tear volume and have similar efficacy with upper or lower tear duct occlusion [77]. In severe dry eyes, oral cholinergic agonists such as pilocarpine and cevimeline may improve symptoms by stimulating lacrimal gland secretion [78, 79]. Autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with Sjögren's syndrome [80]. Though the role of hormone replacement therapy in dry eye treatment remains controversial [81–83], postmenopausal women with dry eyes

may benefit from phytoestrogen supplementation. Phytoestrogen is a naturally occurring nonsteroidal with estrogenic effects that has been shown to decrease tear osmolarity and improve tear production [84]. Additionally, androgen supplementation for older women may help stimulate lacrimal gland function and reduce ocular discomfort. In a pilot study by Nanavaty et al., androgen patching for 3 weeks resulted in an increase in tear-film break-up time and improved Schirmer's test scores [85]. In addition, all 14 subjects reported improvement in "painful or sore eye" symptom.

A few caveats, however, are warranted for the aging population. Many of the artificial tear products, though affordable, contain preservatives, including BAK. With increased susceptibility to tear film instability, loss of goblet cells, and poor epithelial healing from oxidative stress, the addition of toxic ingredients can potentially exacerbate patient symptoms. Preservative-free artificial tears may therefore be better alternatives for older adults but do come at an increased cost. Other treatment options can also be expensive; punctal plugs plus cyclosporine had the highest annual direct expenditure in the study by Yu et al.—with costs close to 3 thousand dollars [9, 73]. Additionally, cyclosporine use has been associated with ocular burning in 17% of the patients [48] and eyelid malposition may alter the efficacy of punctal plugs if poor globe apposition, lid ectropion, or orbicularis weakness is present. Furthermore, in patients with underlying inflammatory conditions, delayed tear clearance can lead to accumulation of significantly high concentrations of inflammatory cytokines, such as interleukin 1, which can exacerbate epithelial cell damage and goblet cell loss [22, 86]. Ongoing advances in tear substitutes and secretagogues may be especially helpful in this population in addressing specific deficiencies of tear components induced by polypharmacy, menopause, or inflammatory disease. Combination therapy in severe disease may be necessary, especially if the patients are predisposed to microbial keratitis such as in patients with high risk nosocomial infections (frequent hospitalizations, nursing home residents, and diabetics) or exposure keratopathy. In summary, treatments must be individualized to most effectively target the disease process while matching the needs and the resources of the patient. Treatment strategies should be developed in partnership with the patient. It is helpful to communicate to the patient that cures are rare and that your goal is to engage them in developing a management strategy that will work for them.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Age-Related Changes of the Ocular Surface: A Hospital Setting-Based Retrospective Study

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Purpose. To investigate the effects of age on the prevalence of ocular surface diseases (OSD), adherence to treatment, and recovery rates. *Patients and Methods*. Retrospective analysis of 3000 clinical records from a first-level general ophthalmology clinic. Patients with OSD were prospectively submitted a questionnaire to assess compliance and recovery rates. *Results*. OSD prevalence was 10.3%. Patients with OSD were significantly older than patients without it: 67.5 ± 20.3 versus 57.0 ± 22.0 years ($P = 0.036$). No significant difference in season distribution was shown. Dry eye disease (DED) represented 58% of OSD; its prevalence increased with age until 80 years old and suddenly decreased thereafter. Asymptomatic DED was 37%. Adherence to treatment in OSD was very high (94%); recovery rates were lower in patients aged 21–40 and 61–80 (resp., 65.5% and 77.8%) and this was associated with higher OSDI scores. Tear substitutes represented 50% of all prescribed medications; their use increased with age. *Discussion*. In a "real-life" low-tech setting, OSD showed a prevalence of 10.3%. DED was the most prevalent disease, and it was asymptomatic in more than 1/3 of cases.

1. Introduction

The ocular surface system (OSS) is defined as the wet-surfaced epithelia of the cornea, conjunctiva, lacrimal gland, accessory lacrimal glands, nasolacrimal duct, meibomian gland, and their apical and basal matrices, linked as a functional system by both continuity of epithelia, by innervation, and the endocrine and immune systems. Several age-related changes occur in most components of the OSS: meibomian glands decrease in density and their ducts may keratinize causing occlusion and consequent alteration in lipid secretion; lacrimal gland secretion diminishes and its composition changes; corneal nerve density decreases [1–5]. These changes are frequently associated with inadequate volume of tears, tear film instability, increased evaporation, and abnormal immune responses. Tear film impairment is therefore associated with a number of different ocular surface diseases (OSD), which may range from dry eye disease (DED) to infections and immune diseases [6].

All these conditions negatively impact quality of life (QoL). Assessment of the vision-related QoL is important in the management of patients suffering from OSD: it reflects the burden of disease experienced by the patient, overall assessing the impact of OSD on the individual and it helps monitor the changes occurring in patients with OSD. The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of OSD consistent with chronic dry eye, its severity, and its impact on vision-related functioning.

OSDI has been shown to have a high reliability, reproducibility, and validity [7]. It correlates weakly but positively with objective markers of OSD such as tear film break-up time, Schirmer test, and lissamine green surface staining. It has been validated with good sensitivity and specificity to detect normal subjects and patients with a value of ≤12; scores 13 or greater indicate OSD [8, 9].

Epidemiology studies of OSD are available only for DED and allergic conjunctivitis. DED has an extremely variable prevalence, as it is reported to affect 5 to 34% of the population, lying close to the higher bound of the range in subjects 50 years old or more. Females are more affected than males (17.0% versus 11.1% [10]), having nearly a 3-fold higher risk of DED [11–13]. Allergic conjunctivitis has been reported to range from 10 to 20% of the population [14].

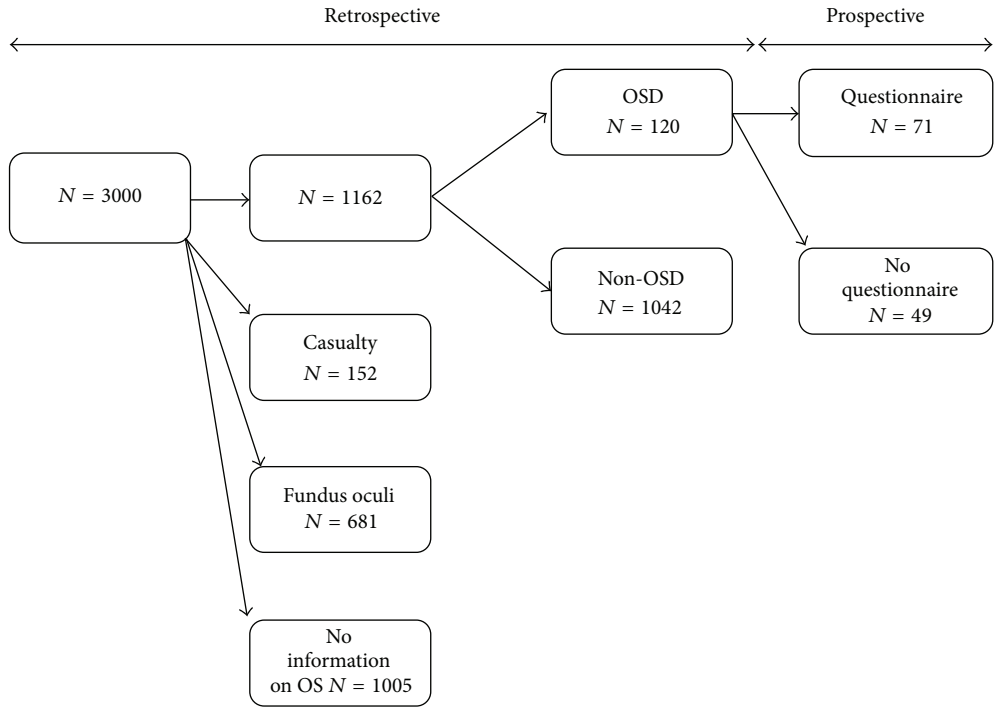

Figure 1: Flow chart of the events of the study.

To the best of our knowledge there are no studies exploring the effect of age on the prevalence of OSD. Therefore, through a hospital setting-based review of first-level general ophthalmology visits, we investigated the association of OSD and age as well as either patient's adherence to treatment and recovery rates or therapy and eye-drop instillation procedure efficacy based on patient's age.

2. Materials and Methods

This was a retrospective cross-sectional study with a prospective part consisting of the administration of a questionnaire on the group of patients with OSD. It was conducted at the Eye Clinic of San Paolo Hospital of Milan between January and December 2012.

3000 clinical records obtained from a first-level general ophthalmology clinic (the first 250 per month) were analysed and divided into 4 groups based on the type of visit (Figure 1): 1010 first ophthalmic visits (33.7%), 1157 control visits (38.6%), 152 access from emergency department (5%), and 681 fundus oculi examinations (22.7%).

Included were patients undergoing first ophthalmic visits and control visits. Exclusion criteria were emergency department visits, fundus oculi examinations, and inability to retrieve information of the ocular surface from the medical chart. The presence of ocular or systemic comorbidities was not an exclusion criterion as well as the medical prescriptions received at the end of the visit.

After applying exclusion criteria, the original dataset was restricted to 1162 patients, whose main characteristics are summarized in Table 1.

Table 1: Demographic and ophthalmic characteristics of study participants.

	Overall	OSD	NO OSD
Number of patients	1162	120	1042
Age, years (SD)	61.3 (21.2)	67.5 (20.3)	57.0 (22.0)
Sex, F/M	616/546	64/56	552/490
Refraction, diopters (SD)	−1.20 (1.9)	−1.13 (1.7)	−1.31 (2.1)
IOP, mmHg (SD)	15.6 (4.2)	15.5 (3.9)	15.7 (4.4)

OSD was diagnosed in the presence of one or more of the following:

(1) one or more of the following symptoms related to OSD: dryness, grittiness, burning, foreign body sensation, and visual disturbance;

(2) tear film abnormalities (Schirmer I test results $\leq$ 5 mm/5 minutes or tear film break-up time $<$ 10 seconds);

(3) any ocular surface abnormality.

The prevalence of OSD was calculated, and sex, age, seasonality, diagnosis, and therapeutic prescriptions were recorded.

Within one month after the visit, patients with OSD were contacted by phone and submitted a questionnaire to assess their adherence to the therapy, the persistence/disappearance of symptoms, and their OSDI score. OSDI was normal (0–12 points) or showed mild (13–22 points), moderate (23–32 points), or severe (33–100 points) disease.

With the questionnaire, we inspected the adherence to treatments; the ability to self-administer treatments and to

Table 2: Prevalence and distribution of OSD etiology by age group.

Age (y)	Overall	OSD	F/M	Infection	Allergy	Eyelid pathology	Trauma	Dry eye	OSDI < 12
1–10	27	4	2/2	1	0	1	0	2	1
11–20	87	6	3/3	0	2	0	0	4	1
21–30	53	10	6/4	3	1	1	1	4	2
31–40	82	14	6/8	0	5	0	2	7	2
41–50	148	18	10/8	3	2	1	0	12	3
51–60	143	17	9/8	3	4	0	0	10	3
61–70	205	23	13/10	5	2	0	0	16	9
71–80	277	24	13/11	6	3	1	1	13	5
81–90	132	4	2/2	2	0	0	0	2	0
91–100	8	0	0	0	0	0	0	0	0
	1162	120	64/56	23	19	4	4	70	26

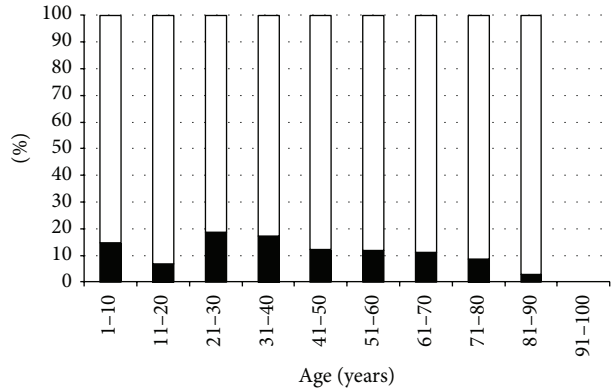

Figure 2: Percentage of subjects suffering and not suffering from OSD by age group. Black bars: presence of OSD; white bars: absence of OSD.

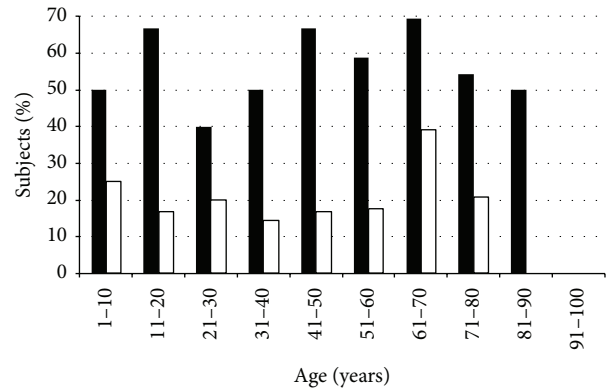

Figure 3: Percentage of overall and asymptomatic dry eye in OSD patients by age group. Black bars: overall dry eye; white bars: asymptomatic dry eye (OSDI ≤ 12).

instill the proper dosage into the eyes; treatment-related satisfaction; and the management of persistent symptoms. 71 out of 120 subjects suffering from OSD answered the questionnaire, 9 refused, 4 did not understand Italian and English language, 1 had died, 29 patients could not be contacted, and 6 patients were not called because they were recommended a surgical treatment.

3. Results

The prevalence of OSD was 10.3% (120/1162).

The mean age for subjects without OSD was 57.0 ± 22.0 years (range: 1–100) and for OSD 67.5 ± 20.3 years (range: 3–84; $P = 0.01$), the ratio between females and males was 64/56.

OSD prevalence was equally distributed from childhood to the middle old age, decreasing after 80 years old (Table 2, Figure 2), without significant differences in seasonal distribution.

We classified OSD patients in 5 categories: DED (58.3%), infections (19.2%), allergies (15.8%), eyelid pathologies (3.3%), and trauma (3.3%). The distribution of the etiologies was different at varying ages: infections showed a constant distribution across all age groups; about 75% (14/19) of the cases of allergy affected subjects younger than 60; and eyelid pathologies equally affected both the young and the elderly, but the causes were different (hordeolum and chalazion were more prevalent under 40 years of age, whereas blepharitis was progressively increasing from 30 years of age). Few traumas were reported, and they also occurred in two age groups based on different etiologies: foreign bodies in the class of 21–40 years; falls in the classes of 71–100 years.

DED represented 58% (70/120) of OSD in the population. The number of cases with DED increased with age until 80 years old, and it suddenly decreased for patients with 81 years old or more (Figure 3). DED was distinguished in two groups: asymptomatic (OSDI ≤ 12) and symptomatic (OSDI > 13); in our dataset, 37% of subjects had asymptomatic DED, with a percentage apparently increasing over 60 years of age (Figure 3). Female/male ratio for DED was 38/32.

Recovery rates for OSD ranged from 60 to 100% depending on age (Figure 4).

Compliance was high among the 71 patients submitted to the questionnaire, as 67 (94%) followed the medical therapy as prescribed by the ophthalmologist. Lack of resolution occurred in 11/67 patients (16.4%); these patients asked a second opinion (39%), required further control visits (21%), underwent surgical treatment (11%), modified the therapy

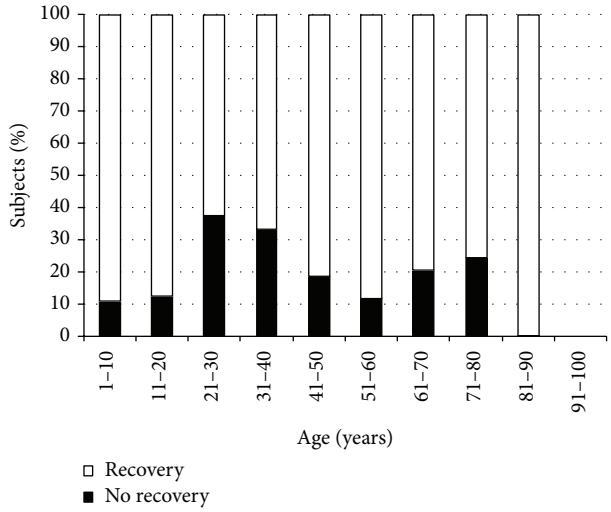

Figure 4: Percentage of OSD recovery rates by age group.

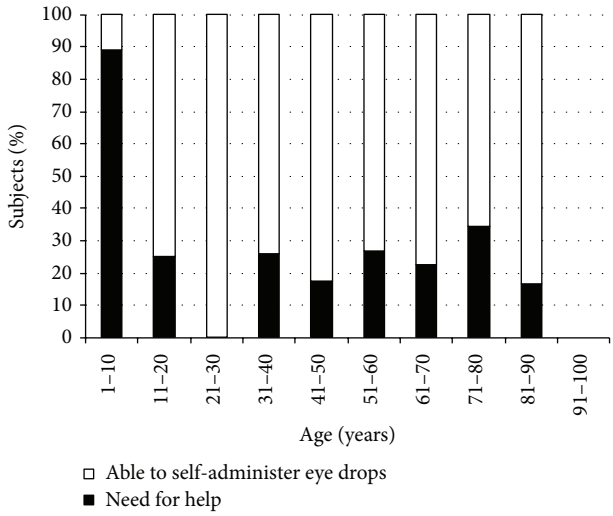

Figure 5: Percentage of subjects able and not able to self-administer eye drops by age group.

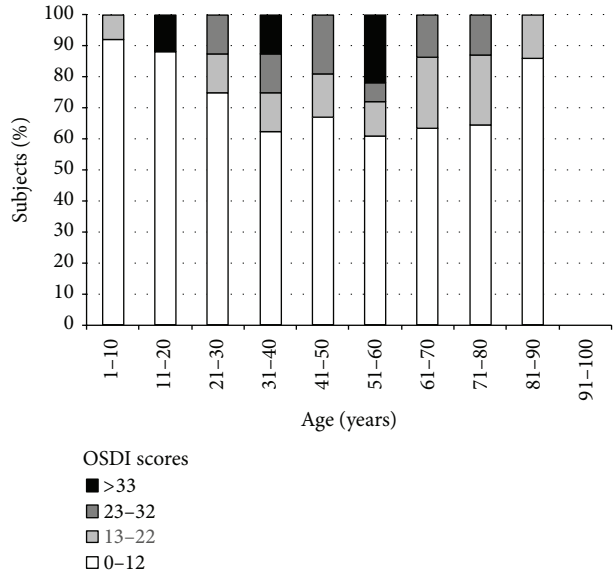

Figure 6: Percentage of OSDI scores by age group.

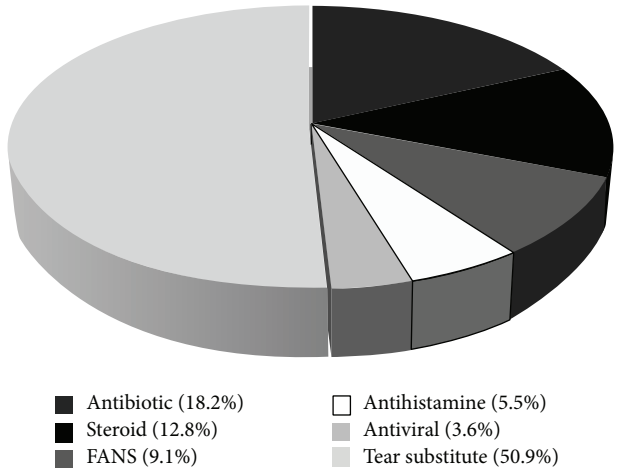

Figure 7: Therapy distribution.

without consulting the doctor (7%), tolerated symptoms (4%), or recovered without any medical therapy (18%). Only 4 patients (6%) did not adhere to the prescribed treatment either because they spontaneously recovered (50%) either because of the onset of an allergic reaction (25%) or a lack of faith in the doctor (25%). Unexpectedly, most of the nonadherent patients were graduated (95.9%); no correlation between age and adherence to treatment was found.

Patients were also asked if they were able to self-administer eye drops: 28.4% needed to be helped—especially subjects younger than 10 and aged 71–80 years old (88.9% and 34.3%, resp.)—and most of them reported a difficulty in aiming a drop onto their eye (Figure 5). Nevertheless, 92% patients never forgot to put eye drops in.

OSDI scores were usually ≤12, but the higher percentages of OSDI scores >13 were found in subjects aged 31–80 years old (Figure 6).

Therapy prescription in OSD was considered: tear substitutes represented 50.9% of the topical medications, followed by antibiotics (18.2%), steroids (12.8%), FANS (9.1%), antihistamines (5.5%), and antivirals (3.6%) (Figure 7). Tear substitutes were increasingly prescribed with increasing age, with a peak for patients aged 61–80 years old (Figure 8).

4. Discussion

The results of studies on epidemiology of a disease depend mostly on two factors: the features of the population and the diagnostic criteria and instruments used for diagnosis.

This paper included a relatively small sample of 1162 patients, representative of the population of subjects seen on a first-level general ophthalmology clinic. We collected a similar number of consecutive cases per month over a 1-year interval, so that the dataset is not influenced by seasonal

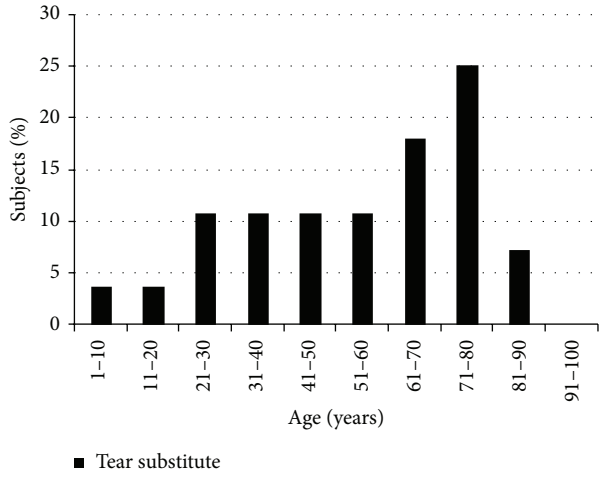

Figure 8: Percentage of tear substitutes by age group.

variations of diseases. The study was a retrospective evaluation of routine visits performed using slit-lamp examination and, at discretion of the physician, dying with fluorescein to evaluate parameters related to dry eye (break-up time, epithelial staining, and clearance of fluorescein). Due to the use of low-tech methods, underestimation of conditions such as DED, particularly in asymptomatic cases, is extremely likely; moreover, the population of this study is not fully representative of the whole population, as in our clinic, patients with glaucoma or corneal pathologies (who have a very high prevalence of OSD [12, 15, 16]) are directly referred to tertiary services. Nevertheless, we found a prevalence of OSD of about 10%, which is confirmatory of the literature. Patients with OSD were significantly older than patients without it [6, 12, 13].

Unexpectedly, the distribution of OSD per decade was different than reported in the literature, as we found that the prevalence of OSD was higher in patients with 20 to 40 years. This data is influenced by the different prevalence of allergy over age [14, 17], the effect of working activity (the study included patients with foreign body), and the relatively higher-than-expected prevalence of DED in young patients [13, 18]. This prevalence is possibly due to the large prevalence of video-terminalists and users of contact lenses [19–22], a fact that is also linked to the lower rate of recovery rate shown in Figure 4.

The prevalence of OSD suddenly decreased after 80 years of age, a fact that may be explained considering that patients tend to consider this problem as "minor" when compared to general diseases and may not require ophthalmic evaluation. Eye doctors might also tend to overlook mild cases on this group of patients (as a matter of fact, the prevalence of asymptomatic DED, which peaked in the interval of 60–80 years of age, was reported as null over 80 years).

The major cause of OSD was, as expected, DED, which affected about 60% of patients with OSD, and a mild but constantly higher prevalence was found for females of age between 20 and 80 years. OSD influence on QoL was indirectly estimated through OSDI score: the higher the score, the worse the QoL [23, 24]. OSDI had a peak of severity in the decade 51–60, even if data in the range of ages of 31–80 were overall similar.

The adherence to treatment and the recovery rates found in this paper were higher than previously reported [25, 26]. The lack of adherence in graduated patients with OSD is possibly linked to the awareness that OSDs are frequently benign and self-limiting.

Eye drops prescription increased with age, with a peak for patients aged 61–80 years old. Tear substitutes were the most frequently administered treatment (more than 50% of all treatments): formulations containing sodium hyaluronate and/or carboxymethylcellulose were the most commonly prescribed, thus reflecting efficacy data from several studies [27–29]. Preservative-free eye drops were introduced to reduce toxic or allergic reactions when applied to the injured ocular surface; treatment with topical coenzyme Q10 also improved ocular surface stability [30].

In conclusion, this paper reported the prevalence of OSD in a group of patients visited with low-tech instruments in a "real-life" setting. The prevalence found was about 10%, with DED being the most prevalent disease (60% of cases). We investigated the distribution of different OSDs at varying ages, the prevalence of asymptomatic disease, and the implications on the efficacy and distribution of treatments as well as the adherence to them.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Cell Models to Study Regulation of Cell Transformation in Pathologies of Retinal Pigment Epithelium

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The retinal pigment epithelium (RPE) plays a key role in the development of many eye diseases leading to visual impairment and even blindness. Cell culture models of pathological changes in the RPE make it possible to study factors responsible for these changes and signaling pathways coordinating cellular and molecular mechanisms of cell interactions under pathological conditions. Moreover, they give an opportunity to reveal target cells and develop effective specific treatment for degenerative and dystrophic diseases of the retina. In this review, data are presented on RPE cell sources for culture models, approaches to RPE cell culturing, phenotypic changes of RPE cells *in vitro*, the role of signal pathways, and possibilities for their regulation in pathological processes.

1. Introduction

The retinal pigment epithelium (RPE) has a number of important physiological functions, including the maintenance of the structure and functions of photoreceptors and the blood-retinal barrier. Although RPE forms a dense monolayer of nonproliferating cells, it is capable of transformation into other cell types, with this capability varying in the series of vertebrates. In adult newts, for example, central RPE cells and low-differentiated cells of the peripheral growth zone account for regeneration of the retina [1–4]. After the surgical removal of the retina, RPE cells dedifferentiate, lose pigment, and proliferate; thereafter, part of cells recover RPE differentiation, while another part transdifferentiate into neural retinal cells [5]. Unlike in lower vertebrates, in which the ability to regenerate the retina via transdifferentiation is lifelong, its regeneration in some mammals is possible only during the embryonic period [6], whereas RPE plasticity retained in adults is responsible for a variety of ocular pathologies. Thus, RPE damage in humans initiates processes similar to its transdifferentiation in urodeles: RPE cells lose pigment, proliferate, migrate, and differentiate into different cell types, expressing appropriate markers (atypical of RPE) [7], but fail to produce a new functional retina. In pathological cases, RPE cells often transdifferentiate not into neural retinal cells but into fibroblast-like cells, which, in the "wet" (exudative) form of age-related macular degeneration (AMD), are involved in the formation of subretinal (choroidal) neovascular membrane [8–10]. In pathologies such as proliferative vitreoretinopathy (PVR) and proliferative diabetic retinopathy, transformed RPE cells contribute to the formation of epiretinal membranes [10–12], with consequent visual impairment.

There is no universally accepted term for what occurs with RPE cells *in vivo* under pathological conditions. Thus, phenotypic changes observed in RPE cells are referred to as "metaplasia" [13], "transformation" [9, 10, 14], "epithelial-mesenchymal transdifferentiation" [9], or "epithelial-mesenchymal transition" (EMT) [15].

The problem of control over RPE cell differentiation is of major significance to both biologists and specialists in clinical medicine. In particular, long-standing questions concern the causes of phenotypic changes in the human RPE and ways to regulate fibrotic changes in certain pathological states. A promising way to find the answers is to use well-characterized cell models, provided reliable protocols for effective cell isolation and culturing are available.

Table 1: Human RPE cell lines (according to Mannermaa [31], modified).

Cell line	Source	References
	Spontaneously transformed cell lines	
H80HrPE-6	Created by Goro Eguchi using primary RPE cells from an 80-year-old person	Tsonis et al. [32]
ARPE-19	Derived in 1986 by Amy Aotaki-Keen from the normal eyes of a 19-year-old male who died from head trauma in a motor vehicle accident	Dunn et al. [33]; ATCC CRL-2302
D407	Derived from the eye of a 12-year-old male child	Davis et al. [34]
RPE-340	Derived in 1989 from the eye of a 1-year-old female child who died from trauma	Matsunaga et al. [35]; Rambhatla et al. [36]
	Immortalized cell lines	
hTERT RPE-1	Generated by transfecting the RPE-340 cell line with a plasmid expressing the human telomerase reverse transcriptase subunit (hTERT)	Rambhatla et al. [36], ATCC CRL-4000
h1RPE-7	Generated by transfecting primary RPE cells from a 50-year-old female donor with a plasmid encoding the SV40 large T antigen	Lund et al. [37]
h1RPE-116		Kanuga et al. [38]

2. Sources of RPE Cells for Culturing

There are two main sources of RPE cells for model *in vitro* experiments: primary cells and continuous cell lines obtained as a result of spontaneous transformation and immortalization of cells.

2.1. Primary Cells. In countries where eye banks are maintained, specialists usually make use of human RPE cells either isolated directly from the initial material (as a rule, cadaver eyes) or available from certain research laboratories. Thus, ScienCell Research Laboratories (USA) offers primary RPE cells (HRPEpiC) isolated from normal human retina and cryopreserved at passage 1 (http://www.sciencellonline.com), and Lonza Walkersville Inc. (USA) offers Clonetics human primary RPE cells (H-RPE) cryopreserved at passage 2 (http://www.lonza.com/).

In countries where no human eye banks exist, primary RPE cells are obtained from the eyes of cows, pigs, rabbits, rats, and other animals [16–19].

Researchers in different laboratories use essentially the same procedure to isolate RPE cells from an adult human eye. The eyeball is cut along the perimeter about 6 mm posterior to the corneal limbus, and its anterior part is discarded [20]. The posterior part is turned upside down to dislodge the vitreous together with the neural retina, and the remains of the retina are then cut off at the optic disc. The resulting cup-shaped segment with RPE on the inner surface is filled with a cell dissociation reagent and incubated at 37°C or room temperature for 8 min to 1 hour. Suitable dissociation reagents include solutions of pronase, papain, trypsin, hialuronidase/collagenase, or dispase [20–24] or of nonenzymatic substances such as EDTA [25, 26]. The solutions are usually prepared in calcium- and magnesium-free Hank's balanced salt solution (HBSS), and the incubation regime depends on the reagent used. The dissociated fragments of RPE are collected with a pipette, pelleted by centrifugation, and resuspended in a complete medium.

To isolate RPE cells from a fetal human eye, the eyeball is cut about 1-2 mm posterior to the corneal limbus to remove the anterior segment, vitreous, and retina [27, 28]. The posterior segment is transferred to a Petri dish with silicone coating and dissected into four quadrants, which are then incubated in dispase solution at 37°C for 30 min. After dispase treatment, sheets of RPE cells are peeled off with forceps under a microscope and collected in tubes with a complete medium [27, 28].

Unlike continuous cell lines, primary RPE cells are relatively heterogeneous, exhibit donor-to-donor variability, and can be expanded for a limited number of passages. Rawes et al. [29] reported that a subculture of adult RPE cells reached replicative failure after 15 population doublings. It is known that aging cells cease to divide, which is explained by alterations in gene expression [30].

2.2. Continuous Cell Lines. To date, a variety of continuous RPE cell lines have been produced. They include both human lines listed in Table 1 and, for example, rat cell line RPE-J, which are available from biotechnological companies, in particular, the American type culture collection (ATCC). A major advantage of such lines is that they can be subcultured over more than hundred of passages. Another important feature is that they have a uniform cell composition, although this may be evidence that these lines have lost certain properties essential to the initial cell material.

3. Properties of Cell Lines

3.1. H80HrPE-6. This dedifferentiated RPE cell line, created by Eguchi et al. from the eye of an 80-year-old man, may form lentoid structures expressing crystallins [22, 32]. This cell line may be a useful system for investigating the regeneration of the lens by human RPE cells [39].

3.2. ARPE-19. During the past decade, the ARPE-19 cell line has become most popular in RPE cell research. It has a visually normal karyotype and expresses RPE-specific markers, the retinal pigment epithelium-specific 65 kDa protein (RPE65) and cellular retinaldehyde-binding protein (CRALBP), as has been shown at the mRNA and protein levels, respectively [33]. The properties of ARPE-19 cells

depend on culture conditions and the way the cells are maintained and subcultured [40]. Thus, original ARPE-19 cells at passages 15 to 20 in tissue culture flasks produce a uniform epithelial monolayer with typical cobblestone morphology [33], but ARPE-19 strains upon further subculturing change into a heterogeneous mixture of elongate and polygonal cells [40]. In long-term culture on Transwell membranes, ARPE-19 cells have been shown to form a polarized monolayer (see below). ARPE-19 cells have been widely used in studies on oxidative stress, retinal pathogenesis, and signaling pathways and also in research related to drug and toxicity testing [10, 31, 41, 42].

3.3. D407. This cell line has typical features of RPE, including cobblestone morphology, phagocytosis of photoreceptor outer segments, and expression of CRALBP protein and cytokeratins (8 and 18) characteristic of RPE [34]. The D407 cells at early passages have a modal chromosome number of 44 ± 2, but by passage 52 they may become almost triploid (71 ± 4 chromosomes) [34]. Unfortunately, D407 cells do not polarize in filter culture and do not synthesize pigment [31, 43].

3.4. RPE-340. These cells originally have epithelial morphology in culture, but their replicative ability upon serial passages is limited, and they senesce after 50–60 population doublings by assuming two doublings per passage [35]. RPE-340 cells transfected with hTERT have an extended life span [30, 36].

3.5. hTERT RPE-1. This is a near-diploid cell line of female origin with a modal chromosome number of 46 in 90% of the cells counted (http://www.atcc.org/). hTERT RPE-1 cells have been used in studies on the inactive X chromosome (Xi), which provides an excellent model of epigenetic regulation [44, 45].

3.6. h1RPE (-7 and -116). These cells have epithelial morphology with apical microvilli but fail to develop transepithelial electrical resistance (TER) above 30–40 $\Omega \cdot cm^2$ under normal culture conditions. This cell line has been used in few studies. For example, subretinal transplantation of hRPE cells in Royal College of Surgeons (RCS) rats proved to result in photoreceptors rescue for 5 months after grafting [37]. These cells were found to express P-glycoprotein, but its activity could not be detected [46].

4. Cell Culture Conditions for RPE Cells

Cell differentiation in culture depends on a number of factors, including the composition of the medium and growth substrate. A variety of culture conditions have been used in studies on RPE cells.

4.1. Growth Media. The range of media used in RPE cultures includes Iscove's modified Dulbecco's medium (IMDM) [47, 48], Chee's essential medium (CEM) [49], alpha modified Eagle's medium (MEM) [27, 43], Dulbecco's modified eagle medium (DMEM) high glucose [43], and DMEM/F12 [33, 42, 43]. For example, the base media for D407 and ARPE-19 cell lines are DMEM high glucose and DMEM/F12, respectively. Moreover, different supplements to basic media are used to improve the growth and other properties of RPE cells. The proportion of serum added to the base medium varies from 1 to 20%. Chang et al. [17] consider that serum contains a factor that inhibits the formation of tight junctions. The effects of some media supplements on the improvement of barrier properties of the ARPE-19 cell monolayer are described in detail in the study by Mannermaa [31]. Typical supplements used in primary RPE cell cultures include basic fibroblast growth factor (bFGF) and optimized commercial mixtures such as N1 Supplement (containing transferrin, insulin, putrescine, progesterone, selenium, and biotin) or N2 Supplement (based on N1 Supplement without biotin) [25, 26, 28, 49]. Other supplements and different glucose concentrations have also been tested, but there still are no systematic data or any definitive conclusions on the role of media supplements in the properness of cultured RPE-derived cells [31].

4.2. Growth Substrate. It has been shown that the presence of the basement membrane is essential for the polarization of RPE cells. Since Bruch's membrane contains laminin and collagens, specialists have widely used growth matrices with these proteins [17, 31]. The same is also true of various biological membranes, such as the amniotic membrane [19].

5. Advantages and Disadvantages of Cell Culturing

The culturing of human RPE cells provides the possibility to analyze in detail their morphology, functions, and molecular and genomic properties under normal and pathological conditions, which is hardly possible *in vivo*. On the other hand, cell culture, as any artificial system, obviously has certain disadvantages [50]. Unlike cells *in vivo*, cultured cells are devoid of their native 3D microenvironment. RPE cells *in vitro* may activate the cell cycle, alter differentiation and behavior, senesce, and undergo apoptosis [7, 14, 51], with culture conditions and certain media components having an effect on their differentiation and viability [27, 52, 53]. Additional limitations on the use of RPE cell cultures arise due to genetic instability of continuous cell lines, which results from their unstable aneuploid chromosome constitution, and heterogeneity of short-term cultures in terms of growth rate and capacity for intrapopulation differentiation, with consequent variation in their properties between passages [54]. Despite all these circumstances, however, cultured cells retain many specialized functions, and cell lines have become an important tool in studies on RPE. The advantage of cell lines is that they maintain their characteristics over a number of passages and have longer survival times, compared to primary cultures. Moreover, many cell lines are homogeneous to a large extent, while primary cultures exhibit heterogeneity and individual donor variability [55]. A noteworthy fact is

that RPE cells are not uniform even *in situ,* forming a heterogeneous mosaic of similar but not identical cells [56]. It is important to take into account these features of cultured RPE cells. Anyway, there is no alternative to this approach in studies on cell behavior and molecular mechanisms underlying pathological processes. Currently, both sources of RPE cells for model *in vitro* experiments—primary cells and continuous cell lines—are used in fundamental and applied research, including the development of new approaches to treatment of ophthalmological disorders.

6. Approaches to Human RPE Cell Culturing

Depending on research purposes, human RPE cells are cultured so as to obtain either a highly polarized, functional monolayer of differentiated cells or an adhesive monolayer of dedifferentiated cells on a solid substrate.

6.1. Human RPE Cell Culturing under Conditions of a Highly Polarized, Functional Monolayer. This approach is aimed at producing a culture of RPE cells with properties characteristic of the native tissue, including morphological features (apical microvilli, basal invaginations, well-defined tight junctions, and prominent melanocytic pigmentation), expression of specific proteins (CRALBP, RPE65, MITF, Otx2, ZO-1, occludin, claudin, ezrin, Na^+/K^+-ATPase, bestrophin, and cytokeratins 8/18), and physiological parameters, TER in particular. To this end, it is expedient to use special culture inserts (e.g., Transwell permeable supports) with a membrane coated with a certain component of extracellular matrix (ECM). The RPE cells are plated onto the membrane at a high density (e.g., 1×10^5 cells per 12 mm diameter insert [28] or 3×10^5 cells per 24 mm diameter insert [57]) and cultured to form a confluent monolayer, which takes 30–60 days. It is only in such a monolayer that epithelial cells produce tight junctions, which provide for a high electrical resistance between electrodes placed in the inner and outer chambers. Cultures derived from the RPE of fetuses at weeks 16–22 of gestation make it possible to obtain a polarized RPE cell monolayer with a high TER (over 500 $\Omega \cdot cm^2$) [27, 28, 49]. For comparison, this parameter in the human RPE *in vivo* is only 150 $\Omega \cdot cm^2$ [28].

Polarized monolayer cultures are used as a model for analyzing properties and functions characteristic of native RPE. Moreover, since disturbances of RPE polarization play a major role in the pathogenesis of various retinal diseases, simulation of RPE dysfunction in such cultures provides the possibility to evaluate the ability of RPE to recover under pathological conditions and to test *in vitro* the effects of new medicines. In particular, RPE cells cultured in Transwell inserts are highly suitable for analyzing the transport of various substances and their distribution relative to the insert membrane; polarized secretion of growth factors [33, 48], cytokines [47], and retinoids [58]; and drug toxicity [42].

A polarized functional monolayer can be grown not only from fetal cells but also from human ARPE-19 cell line [33, 43, 47, 59]. For example, Dunn et al. [33] confirmed the ability of ARPE-19 cell line to form polarized monolayers and evaluated their properties, showing, in particular, that FGF5 is secreted from the basolateral surface of ARPE-19 cells. Unlike fetal cells, adult RPE cell lines usually form polarized monolayers with a low TER (<50 $\Omega \cdot cm^2$) [33, 59]. However, Fragoso et al. [42] managed to obtain ARPE-19 cell monolayers with a TER of about 150 $\Omega \cdot cm^2$. This is evidence that optimization of protocols for obtaining polarized human RPE cultures from an adult donor is a difficult task that nevertheless should be attempted in view of the special clinical significance of such cultures.

Polarized human RPE cultures derived from donors aged 9–24 years have been used to study polarized secretion of interleukins IL-6 and IL-8 [47], vascular endothelial growth factor (VEGF), and pigment epithelium-derived factor (PEDF) [48, 60]. The level of TER recorded in these cultures is similar to that in monolayers formed by continuous cell lines. The main difficulty in experiments with cultures of adult human RPE is that there is a high probability of change in the morphology of these cells in the course of culturing. Compared to fetal cells, RPE cells from an adult donor are less capable of proper assembly/disassembly of cytoskeleton and cell-to-cell contacts in the course of proliferation, which may eventually result in EMT. However, Blenkinsop et al. [61] have developed an optimized protocol where the growth medium is supplemented with several factors used for culturing fetal RPE cells (taurine, hydrocortisone, and triiodothyronine), which makes it possible to obtain a functional monolayer of adult RPE cells with a TER of about 200 $\Omega \cdot cm^2$.

6.2. RPE Cell Culturing as an Adhesive Monolayer on a Solid Substrate. This approach has been used in the majority of studies on phenotypic changes in RPE cells evaluated by morphological and molecular genetics methods. It has been shown that RPE cells in such cultures gradually lose polarity and specialized cell-to-cell contacts characteristic of epithelia and acquire certain features of mesenchymal cells, including migration behavior [15]. Similar changes take place *in vivo* during EMT in the embryonic neuroectoderm, with RPE being one of its derivatives. In particular, cells from the roof plate of the neural tube undergo EMT and delaminate from the neuroepithelium to form a migratory population of multipotent mesenchyme-like neural crest cells [62, 63].

One of the early events in EMT is the disassembly of tight junctions, with consequent redistribution of zonula occludens (ZO) proteins, claudins, and occludin, the disruption of the polarity complex, and the initiation of cytoskeletal reorganization [64]. Experiments with the ARPE-19 cell line have shown that these cells gradually lose tight junctions but continue to express ZO-1 and occludin proteins [40]. In primary cultures of human RPE cells and in rat RPE-J cell line, the loss of polarity in the expression of Na^+/K^+-ATPase has been observed [65], with this enzyme being revealed not only on the apical but also on the basolateral surface of RPE cells [66].

Subsequent EMT events include disassembly of adhesion contacts and reorganization of the polarized epithelial actin cytoskeleton into actin stress fibers anchored to the focal

adhesion complexes [64]. The attachment of actin microfilaments to the cytoplasmic membrane in cultured human RPE cells is facilitated due to the synthesis of vinculin, which contributes to the binding of cell surface integrin receptors to ECM adhesion molecules [67].

A basic factor of cytoskeletal reorganization is the cessation or reduction of E-cadherin expression, which is also observed in RPE cells *in vitro.* This is accompanied by increased expression of N-cadherin, a marker of neural cell contacts [25, 68–70], which is evidence for the loss of epithelial cell organization [71]. As a result of aforementioned rearrangements, the cells undergoing EMT acquire a mesenchyme-like phenotype characterized by the expression of corresponding cytoskeletal proteins (namely, vimentin) and increased deposition of ECM proteins, including collagen and fibronectin [62, 72]. All these events also take place in RPE cells grown in culture flasks. Thus, human RPE cells grown *in vitro* show distinct positive staining for vimentin [73] and synthesize various ECM molecules such as tissue inhibitor of metalloproteinase 3 (TIMP-3) [74]; collagen types I [26], IV, and V [75]; laminin [76]; fibronectin [26, 77, 78]; heparan sulfate proteoglycan; and hyaluronic acid [79, 80].

The secreted ECM components (collagen and fibronectin) stimulate integrin signaling and consequent formation of focal adhesion complexes, which facilitate cell migration [72]. This fact has also been confirmed for RPE cells. Adult human RPE cells cultured *in vitro,* compared to native RPE, show an increased expression of integrins, which form receptors for laminin, fibronectin, and collagen, thereby making the attachment of cells to the substrate more effective and facilitating their migration [77]. The secretion of ECM proteins by RPE cells can also be stimulated by certain factors added to the culture medium. For example, protein S100β stimulates fibronectin secretion [41, 81], and TGF-β1 added to ARPE-19 cell culture enhances the expression of fibronectin, laminin, matrix metalloproteinase 2 (MMP-2), and collagen type I [10, 82].

Dedifferentiation of adult human (or animal) RPE cells *in vitro* is accompanied by the onset or intensification of expression of proteins associated with motor cell function. Thus, α-smooth muscle actin (α-SMA), a marker of myogenesis, appears in cells that acquire a spindle-shaped morphology [10, 82]. However, neither the α-actinin-1 isoform specific for skeletal muscle cells [55] nor markers of mesenchymal stem cells such as STRO-1 [25, 55], CD90, and CD105 [55] can be detected in human RPE cell culture.

The expression of desmoplakin and other desmosomal components decreases in the course of EMT, but the effect of this decrease on other events involved in EMT is as yet unclear. It has only been shown that changes take place in the expression pattern of cytoskeletal proteins, including a decline in the expression of specific intermediate filaments structurally associated with desmosomal proteins. RPE cells cultured *in vitro* cease to express cytokeratins 8 and 18, which are characteristic of native RPE [83, 84] but start to express cytokeratins 7 and 19 [67, 84]. There is evidence that cytokeratin 19 is synthesized in migrating RPE cells [84].

Thus, RPE cells cultured as an adhesive monolayer gradually lose epithelial characteristics, including polarity and specific markers (pigmentation and expression of E-cadherin, CRALBP, and cytokeratins 8 and 18) and acquire migratory properties and mesenchymal cell-like features (e.g., express collagen type I and fibronectin), which is similar to phenotypic changes of RPE cells *in vivo* under pathological conditions.

In addition to phenotypic manifestations of EMT, RPE cells *in vitro* begin to display some features characteristic of neural cells, which may reflect the neuroepithelial origin of the RPE itself. Thus, adult rat RPE cells in culture were shown to express both neuronal markers—nestin, β-tubulin 3 (TUBB3), cortin, NG2, MAP2, and 200 kDa neurofilament protein (neurofilament 200)—and glial cell marker (GFAP) [85]. Using immunohistochemical methods and Western blot analysis, Vinores et al. [86] found that TUBB3 (an early neuronal marker) was not initially expressed in a primary culture of adult human RPE but could be detected beginning from day 5, with its expression being maintained in subsequent monolayer subcultures. Experiments with human RPE cell lines H80HrPE and ARPE-19 confirmed that these cells were immunoreactive for TUBB3 and could be induced to express mature neuronal protein markers NSE, MAP5, and neurofilament 200 [7].

Our immunohistochemical and molecular genetic studies on primary cultures of adult human RPE cells have shown that they begin to express stem cell gene markers such as *Oct4 (POU5F1), Nanog, Prox1, Musashi 1,* and *Pax6*, which is evidence for dedifferentiation of RPE cells in the course of culturing [87]. Moreover, these cells are capable of subsequent transdifferentiation into neural cells, as indicated by the expression of *Musashi 1, Pax6,* and *TUBB3* (Figure 1(a)) and positive staining with antibodies against protein markers of neuronal differentiation—nestin, TUBB3 (Figure 1(b)), tyrosine hydroxylase, neurofilaments 68 and 200 (Figure 1(c)), and nNOS—and glial differentiation (CNPase, GFAP) [25, 26, 87, 88]. RPE cells *in vitro* also show positive staining for vimentin, a marker of intermediate filaments [26, 73]. Simultaneous expression of vimentin and intermediate filament proteins of other classes, nestin and GFAP, observed in RPE cell culture [26] is also characteristic of human neural stem cells [89]. This fact indicates that RPE cells *in vitro* are apparently multipotent.

Evidence for multipotency of adult human RPE cells has also been obtained by other authors. Thus, Salero et al. [55] have shown that a subpopulation of these cells *in vitro* can be activated into self-renewing retinal pigment epithelial stem cells (RPESCs) that lose RPE markers, proliferate, and, depending on culture conditions, can either redifferentiate into stable RPE monolayers or transdifferentiate into neural or mesenchymal cells (adipocytes, chondrocytes, or osteogenic cells). In other words, RPESCs are multipotent stem cells that, under certain conditions, can generate both neural and mesenchymal progeny.

Experimental evidence that adult human RPE cells *in vitro* can acquire some features of neural cells suggests the existence of factors preventing RPE transdifferentiation into neural retinal cells *in situ*. Therefore, the search for means to

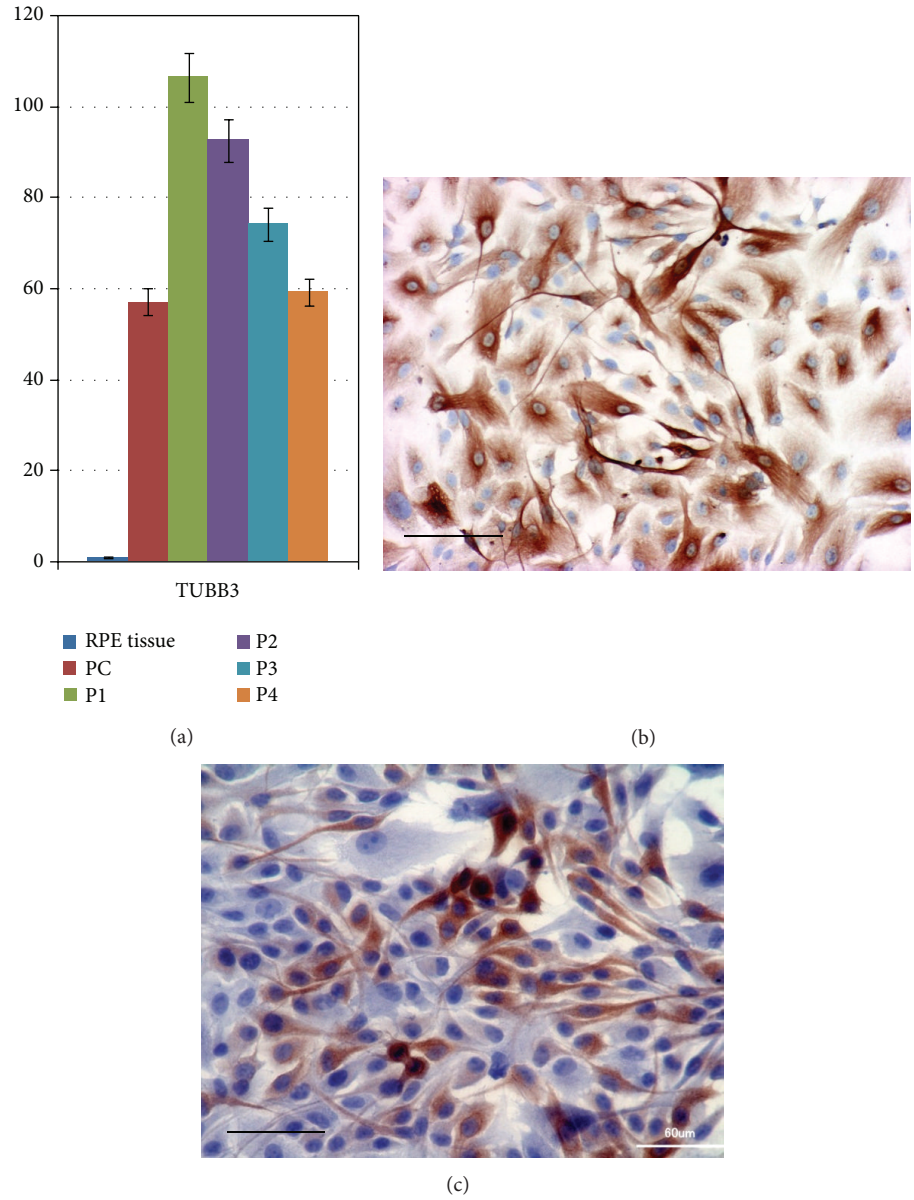

Figure 1: Some characteristics of adult human RPE cells *in vitro*. (a) The results of real-time PCR analysis of *TUBB3* expression in primary culture (PC) and subsequent passages (P1–P4) of RPE cells in adhesive monolayers, compared to freshly isolated RPE (RPE Tissue). (b) Immunoperoxidase staining for TUBB3 (brown) in passage 2 RPE cells. (c) Immunoperoxidase staining (brown) for neurofilaments 68 and 200 in passage 4 RPE cells. Cell nuclei are stained with hematoxylin. Scale bar, 60 μm.

induce RPE cell differentiation into neuronal direction, suppressing their mesenchymal differentiation, is of obvious fundamental and practical importance and may offer new possibilities for restoring the retina after injury or pathology.

7. Role of Signaling Pathways in Phenotypic Changes of RPE Cells *In Vitro*

Morphological and functional changes in RPE cells cultured as adhesive monolayers are similar to those observed in the RPE of patients with various degenerative or proliferative vitreoretinal diseases. For this reason, such cultures are used as *in vitro* model systems to study factors responsible for changes in RPE cells (with regard to their proliferation, migration, and differentiation) and signaling pathways coordinating the mechanisms of cell-to-cell interactions in the course of these processes.

Cells need to sense cues from their extracellular environment and integrate this information into appropriate developmental or physiological responses. Although there are a number of mechanisms that relay information from the exterior to the interior of the cell, a relatively small set of highly evolutionarily conserved signaling pathways stand out

as playing particularly important roles in this transmission of information [90]. In particular, they include Shh, Wnt, Notch, TGF-β/BMP, EGFR, PI3K/AKT/mTOR, JAK/STAT, and nuclear hormone receptor (NHR) pathways [90, 91]. Each of the pathways converts information about the concentration of extracellular ligands into specific transcriptional responses in the cell nucleus.

7.1. TGF-β/BMP Signaling Pathway. The TGF-β superfamily of ligands in mammals comprises not only three isoforms of this factor (TGF-β1, TGF-β2, and TGF-β3) but also other signaling proteins of similar structure, such as bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), activins, and inhibins [92].

A TGF-β ligand binds to a specific type II receptor dimer, which recruits a type I receptor dimer, both of them forming a complex with the ligand. The respective receptors for TGF-β ligands are named TGFβR2 and TGFβR1; for BMPs BMPR2 and BMPR1; and so forth. These are serine/threonine protein kinase receptors, and the type II receptor in the complex catalyzes phosphorylation of the type I receptor, thereby activating the latter. The type I receptor, in turn, phosphorylates receptor-regulated Smad proteins involved in different intracellular pathways: Smad2 and Smad3 in the TGF-β pathway or Smad1, Smad5, and Smad8 in the BMP pathway [93, 94]. These phosphorylated proteins form heteromeric complexes with Smad4 (a co-Smad) that enter the nucleus and interact with DNA-bound transcription factors of the Snail, ZEB, and bHLH families, which activate or suppress the transcription of genes involved in EMT (Figure 2).

TGF-β induces the expression of connective tissue growth factor (CTGF), and both these factors as strong activators of the synthesis and accumulation of ECM proteins play a key role in the development of PVR and transformation of RPE into fibroblast-like cells *in vitro* [10, 14]. Thus, experiments with ARPE-19 cells have shown that TGF-β and CTGF enhance the expression of ECM components such as fibronectin, laminin, MMP-2, and collagen type I; as a result, the cells undergo rearrangements in the cytoskeleton, start to express α-SMA, and acquire a mesenchymal phenotype [10, 82]. In the D407 cell line, TGF-β and activin A proved to stimulate not only reorganization of the cytoskeleton but also cell migration, acting through the TGF-β/Smad signaling pathway [93].

As shown by Li et al. [95], TGF-β1 induced EMT in ARPE -19 cells, as followed from the expected decline of E-cadherin and ZO-1 expression and enhancement of fibronectin and α-SMA expression, with the associated increase in the expression of Snail transcription factor at both mRNA and protein levels. Snail silencing significantly attenuated TGF-β1-induced EMT, reducing the expression of mesenchymal markers (fibronectin and α-SMA) and enhancing that of the epithelial marker E-cadherin and ZO-1. Snail knockdown could effectively suppress ARPE-19 cell migration. Finally, Snail was activated in epiretinal membranes from PVR patients. Thus, Snail plays an important role in TGF-β-1-induced EMT in human RPE cells and may contribute to the development of PVR, while its specific inhibition may provide a new approach to the prevention and treatment of PVR [95].

The results of numerous experiments with knockout animals show that BMPs (in particular, BMP-4 and BMP-7) play a major role in eye morphogenesis [96–98] and RPE specialization [99, 100], but information on the functions of BMPs and their receptors in the adult RPE under normal or pathological conditions is scarce. Mathura et al. [101] were the first to evaluate the expression of BMP-4 and BMPR2 mRNAs in fresh isolates of adult human RPE cells, their primary cultures, and the ARPE-19 cell line. BMP-4 has been shown to inhibit RPE cell proliferation [101]. As shown in subsequent studies, BMP-4 is differentially expressed in the macular RPE of patients with dry or wet AMD [102, 103], depending on microenvironment [104]. Thus, BMP-4 expression in the dry form is enhanced, but in the wet form it is reduced so that the protein cannot be detected by immunochemical methods in surgically excised choroidal neovascular (CNV) membranes [102] consisting of vascular endothelial cells, macrophages, and transdifferentiated RPE cells [8]. In dry AMD, BMP-4 mediates oxidative stress-induced RPE senescence and is responsible for increased p53 protein contents in RPE cells [103]. Therefore BMP-4 appears to be a new potential therapeutic target for suppressing the effects of oxidative stress and RPE senescence in dry AMD [103]. The data obtained by Xu et al. [104] appear to explain the mechanism of BMP-4 downregulation in CNV. These authors have found that the level of tumor necrosis factor alpha (TNFα), a major pleiotropic inflammatory cytokine, inversely correlates with the level of BMP-4 in laser-induced CNV lesions in mice, indicating that TNFα inhibits BMP-4 expression in the RPE cells during active CNV development. They have also shown that TNFα significantly downregulates BMP-4 expression in cultured human fetal RPE cells, ARPE-19 cells, and RPE cells in murine posterior eye cup explants [104].

Signaling proteins of the TGF-β family have a regulatory effect on EMT and can reverse this process during embryonic development and normal wound healing. Moustakas et al. [92] have shown that TGF-β acting on polarized epithelial cells stimulates their transformation into mesenchymal cells, while treatment of mesenchymal cells with BMPs stimulates mesenchymal-to-epithelial transition. However, the balance between EMT and reverse transition is thought to become deregulated under pathological conditions such as chronic inflammation, resulting in development of fibrotic disorders. Therefore, agents capable of inhibiting the EMT of RPE cells may be of great therapeutic value in the prevention of PVR after retinal detachment or active CNV development. For this reason, the mechanism of BMP4 downregulation revealed by Xu et al. [104] may be useful for defining novel targets for AMD therapy.

In addition to the canonical TGF-β/Smad pathway, there are also non-Smad-signaling cascades. Recent studies on changes in the RPE cytoskeleton under the effect of TGF-β1 confirm that this factor plays a major role in such cascades, in particular, the *Rho*A/*ROCK signaling cascade* (Figure 3(a))

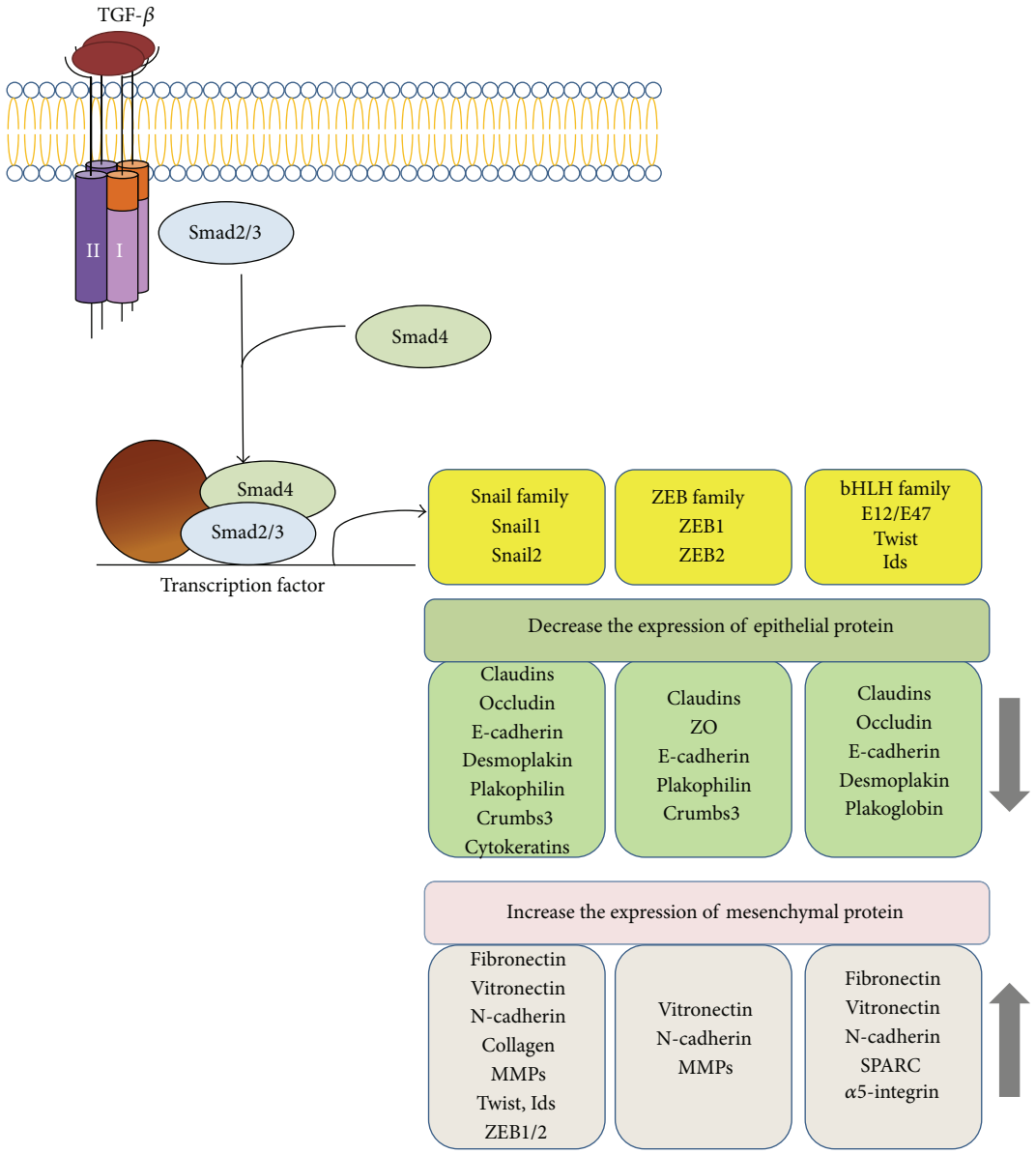

Figure 2: Transcriptional regulation of EMT induced by TGF-β (according to Xu et al. [94]). In response to TGF-β, Smad2 and Smad3 are activated to form complexes with Smad4, which then regulate the transcription of target genes through interactions with other DNA binding transcription factors. In the induction of EMT, the activated Smads mediate transcriptional regulation through three families of transcription factors, which results in repression of epithelial marker gene expression and activation of mesenchymal gene expression.

[9, 10, 82]. The RhoA protein, which is important for the formation and maintenance of cell-to-cell contacts [105], is a small GTPase of the Rho family. These GTPases activate Rho-associated protein kinase (ROCK) belonging to the superfamily of serine/threonine protein kinases. About 20 substrates phosphorylated by ROCK are known. They include cytoskeletal proteins, myosin light chains, myosin phosphatase, and LIM kinase, which plays an important role in actin polymerization by phosphorylating cofilin [106]. ROCK is involved in various functions and activities of cells, including organization of the cytoskeleton, formation of stress fibers and focal contacts, proliferation, migration, and apoptosis [107]. Thus, TGF-β1 treatment of primary isolates of adult human RPE cells and ARPE-19 cell line resulted not only in the increased phosphorylation of Smad2/3 but also in the RhoA and Rac1 activation [9, 82]. Fibroblast-like changes in the cytoskeleton of ARPE-19 cells could be prevented by cell pretreatment with hydroxyfasudil, a specific inhibitor of Rho [82]. Moreover, the expression of fibronectin, MMP-2, and collagen type I in these cells was blocked when the culture medium was supplemented with Y27632, a specific small-molecule inhibitor of ROCK. This is evidence that the expression of mesenchymal ECM components is enhanced due to activation of the RhoA/ROCK signaling

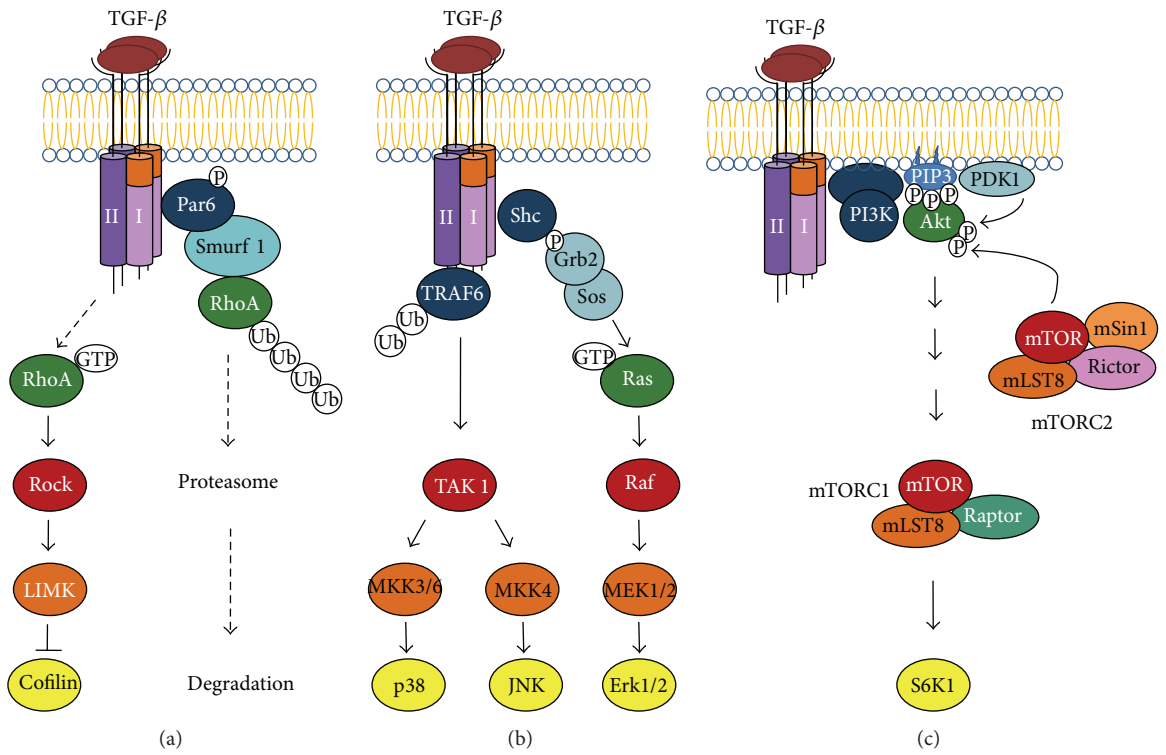

FIGURE 3: Non-Smad signaling in response to TGF-β (according to Xu et al. [94]). (a) Activation of RhoA in response to TGF-β and induction of ubiquitin-mediated RhoA degradation at tight junctions. (b) TGF-β activates p38 MAP kinase and JNK MAP kinase signaling through the activation of TAK1 (TGF-β-activated kinase) by receptor-associated TRAF6, and ERK MAP kinase signaling through recruitment and phosphorylation of Shc by the TβR1 receptor. (c) TGF-β induces PI3-kinase signaling, leading to the activation of AKT-mTOR signaling and consequently to increased translation.

cascade, while suppression of this cascade reduces manifestation of mesenchymal properties in transformed RPE cells.

In the normal eye, TGF-β has been revealed in photoreceptors, aqueous humor, hyalocytes of the vitreous body, and choroid [108], and its expression has proved to increase in PVR [82, 109]. Huang et al. [9] cultured early passages of adult human RPE cells (from healthy donors) in the presence of 25% vitreous humor and revealed rearrangements in their cytoskeleton that were similar to those observed by Lee et al. [82] in ARPE-19 cells treated with TGF-β1. These rearrangements, however, could be prevented by treating RPE cells with NSC23766, a specific small-molecule inhibitor of Rac1 activation. It is known that the Rac protein plays a key role in the regulation of actin polymerization and contributes to the formation of lamellipodia at the leading edge of migrating cells [9]. Zhu et al. [10] consider that an effective way to prevent RPE cell transformation (EMT) under the effect of TGF-β is to inhibit the RhoA/ROCK signaling cascade in these cells. This appears to be a promising therapeutic approach to PVR treatment, which is being developed on the model of RPE cell cultures.

Chung et al. [12] in experiments of mouse RPE cell culture have shown that TGF-β activates Ras proteins (Figure 3(b)) involved in different signal transduction cascades, including the well-studied *MAPK/ERK signaling cascade*. Mitogen-activated protein kinases (MAPK) are involved in signal transduction from membrane receptors to transcription factors in the nucleus. They comprise three small protein kinase families: p38 mitogen-activated protein kinases (p38 MAPK), c-Jun N-terminal/stress-activated protein kinases (JNK/SAPK), and extracellular signal-regulated kinases (ERK). Activation of ERK kinases is almost always connected with cell survival, stimulation of proliferation, and activation of p38 and JNK kinases, with induction of apoptosis [110]. The data by Chen et al. [111] provide evidence that ERK1/2 signaling pathway can cross-interact with the canonical TGF-β/Smad and the Jagged/Notch pathways in RPE cells during EMT. In particular, these authors have shown that the activation of ERK1/2 signaling by TGF-β2 is independent of the canonical TGF-β2/Smad pathway in ARPE-19 cells. On the other hand, inactivation of ERK1/2 signaling by U0126, a small-molecule phosphorylation inhibitor of MEK-1/2 (a type of MAPK/ERK kinase), prevents TGF-β2-induced downregulation of P-cadherin and upregulation of α-SMA, collagen type IV, N-cadherin, and fibronectin in the RPE cells through inhibiting both canonical TGF-β2/Smad and Jagged/Notch pathways. Finally, Notch pathway blockade with specific inhibitor DAPT can suppress TGF-β2-induced activation of ERK1/2 pathway [111].

According to Chung et al. [12], the Ras-ERK signaling pathway is involved in the regulation of neuronal cell differentiation. Thus, TGF-β added to the culture medium

of mouse RPE cells proved to enhance the expression of neuron-associated genes, *TUBB3* in particular; on the other hand, cell pretreatment with U0126 effectively blocked TGF-β-induced ERK phosphorylation and markedly suppressed *TUBB3* expression. These results show that TGF-β stimulates *TUBB3* expression by activating the MAPK/ERK signaling pathway and agree with published data on the involvement of the MAPK/ERK pathways in RPE transdifferentiation into the neural retina. In particular, it has been shown that the ectopic expression of a constitutively activated allele of MEK-1 (MEK^{DD}), the immediate upstream activator of MAPK/ERK, in chicken embryonic retina *in ovo* induces transdifferentiation of the RPE into a neural-like epithelium, which is correlated with downregulation of *MITF* expression in the presumptive RPE [112]. Therefore, TGF-β activates RPE cell differentiation in both mesenchymal and neuronal directions.

Saika et al. [113] have reported that p38 MAPK is involved in EMT of RPE cells: inhibition of p38 MAPK by the specific inhibitor, SB202190, interferes with stimulatory effects of exogenous TGF-β2 on migration of ARPE-19 cells and on production of ECM components, such as collagen type I and fibronectin.

Further evidence that TGF-β activates non-Smad MAPK/ERK and PI3K signaling pathways (Figures 3(b) and 3(c)) comes from the studies by Lee et al. [82] and Huang et al. [9]. They show that the level of ERK1/2 and AKT phosphorylation in human RPE cells increases after treatment with TGF-β1, compared to that in control cells. Activation of the *PI3K/AKT/mTOR pathway* by TGF-β is of special interest in view of the data by Zhao et al. [114] on its role in RPE dedifferentiation and hypertrophy. These authors experimented on transgenic mice with an RPE-selective postnatal loss of mtDNA transcription and replication in which early activation of this pathway accounted for dedifferentiation of the RPE, with morphological changes in it being similar to those observed in human retinal diseases. They found that RPE dedifferentiation and consequent degeneration of photoreceptors could be prevented by blocking mammalian target of rapamycin (mTOR) activation with rapamycin, an inhibitor of mTORC1 (the intracellular mTOR form sensitive to this inhibitor). Thus, specific inhibition of this pathway, mTOR in particular, appears to be a valid strategy for the treatment of degenerative retinal diseases caused by RPE damage.

Thus, the above data on the involvement of TGF-β in the activation of RhoA/ROCK and MAPK/ERK signaling pathways in the RPE suggest that postnatal RPE cells cultured *in vitro* not only undergo EMT but, in parallel, also transdifferentiate into neural cells, but this transdifferentiation in higher vertebrates, including humans, is not completed. To reveal factors restraining neural transdifferentiation of human RPE cells and understand the mechanisms of signaling responsible for EMT, it is necessary to take into account the crosstalk between the TGF-β/BMP and other signaling pathways, including the Wnt and Notch cascades (Figure 4).

Although TGF-β appears to play a key role in stimulating RPE cells to form a PVR membrane, many other factors may be involved in pathogenesis of vitreoretinal disorders and other EMT-related retinochoroidal diseases. They include platelet derived growth factor (PDGF) [115, 116], heparin-binding epidermal growth factor (HB-EGF) [117, 118], hepatocyte growth factor (HGF) [118], epidermal growth factor (EGF) [118], and TNFα [119–121]. It has been shown that the contents of various growth factors and cytokines, which are inflammatory products of cell activation, are increased in vitreous aspirates from the eyes with PVR [118, 119].

According to Liu et al. [120], TNFα activates AKT, mTORC1, and mTORC2 signaling in cultured ARPE-19 cells; however, it is AKT/mTORC1, but not mTORC2, signaling that is required for TNFα-mediated RPE cell migration *in vitro*. As shown in their subsequent study, mTORC1 (but not mTORC2) signaling is important for matrix metalloproteinase 9 (MMP-9) expression in RPE cells [121].

Takahashi et al. [119] have shown that TNFα induces the formation of fibrotic foci by cultured ARPE19 cells through activation of TGF-β signaling in a manner dependent on hyaluronic acid-CD44-moesin interaction. TNFα promotes the expression of CD44, the principal transmembrane adhesion receptor for hyaluronic acid, and moesin phosphorylation by protein kinase C (PKC), which leads to the pericellular interaction of hyaluronic acid and CD44. The formation of the hyaluronic acid-CD44-moesin complex results in cell-cell dissociation and increased cellular motility through actin remodeling. Furthermore, this complex has proved to associate with TGFβR2 and clathrin at actin microdomains, with consequent activation of TGF-β signaling and induction of the mesenchymal phenotype in RPE cells. Furthermore, the authors have demonstrated that the development of fibrosis induced by injection of TNFα into the mouse retina is markedly suppressed in CD44 knock-out mice. These findings indicate that the hyaluronic acid-CD44 interaction plays a key role in EMT-associated fibrotic disorders.

Chen et al. [118] have reported that HGF coupled with EGF or HB-EGF induces migration of both primary RPE cells and ARPE-19 cells in a synergistic manner, via enhancement of PKCδ and ERK.

7.2. EGFR Signaling Pathway. The actions of EGF, including those related to cell survival, begin with the binding of this factor to its receptor (EGFR), which belongs to the ErbB family of receptor tyrosine kinases. The interaction of EGF or any other specific ligand (e.g., TNFα, HB-EGF, and betacellulin) with EGFR (ErbB1) induces receptor dimerization, which activates an intrinsic tyrosine-specific kinase [122]. It has been shown that EGF enhances the survival of RPE D407 cells in serum-free suspension culture via signaling through both PI3K and ERK/MAPK pathways, with this effect of EGF being substantially reduced by either the PI3K inhibitor LY294002 or the MEK1/2 inhibitor U0126 [122].

As follows from the above data, different growth factors exert their effects on the cell via different signaling pathways, and this should be taken into account when developing drug therapy against EMT of RPE cells in fibrotic disorders. Consideration should also be given to crosstalk between different signaling pathways. For example, if phosphorylation

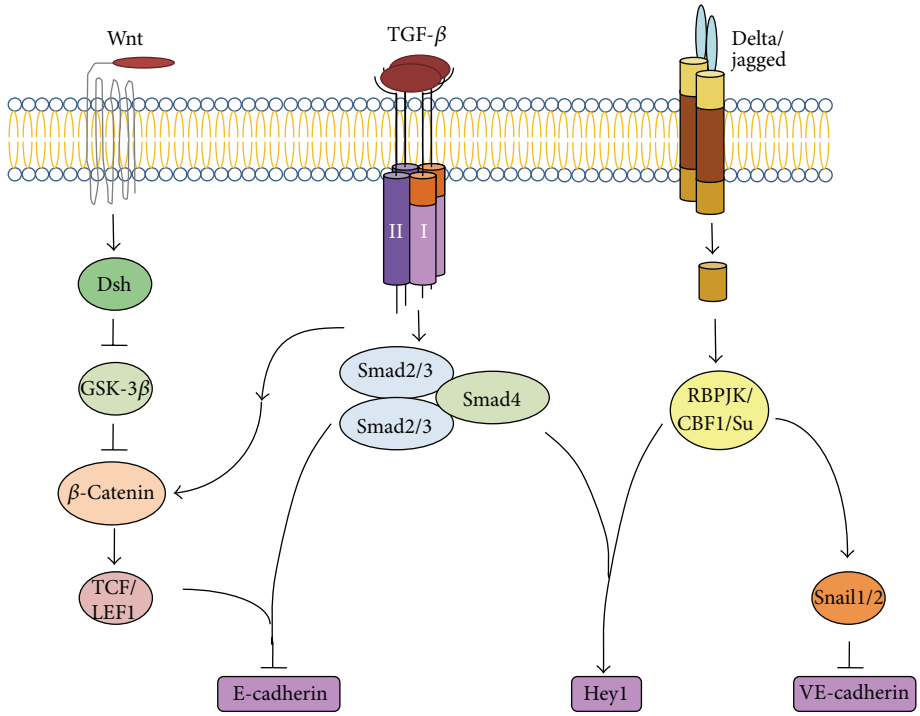

Figure 4: Signaling crosstalk between the TGF-β-activated pathway and other pathways during EMT (according to Xu et al. [94]).

of AKT and ERK1/2 in RPE cells is blocked in order to inhibit EMT, then the protective effect of EGF or other such factors on cell survival will also be blocked.

7.3. Wnt/β-Catenin Signaling Pathway. The canonical Wnt/β-catenin signaling pathway plays a key role in the regulation of tissue differentiation not only in the course of embryonic development but also in the postnatal period, having an effect on cell proliferation, senescence, and tumor growth [123]. β-Catenin is the central mediator of this pathway. For example, it accounts for activation of *MITF* и *TYR* genes in the committed $Otx2^+$ precursor cells of the developing retina, which leads to their differentiation into RPE cells [124].

When the Wnt pathway in the RPE is inactive, β-catenin is contained in the cytoplasm and cell membranes, where it is phosphorylated and associated with E-cadherin. The association between these proteins is indicative of stable cell-to-cell adhesion. This pathway is activated by extracellular Wnt ligands, which interact with Frizzled receptors and their Lrp5/6 coreceptors on the cell membrane and thereby inhibit β-catenin phosphorylation. As a result, its binding to E-cadherin is hindered, with consequent impairment of cell adhesion, and β-catenin is translocated to the nucleus [125]. In the RPE cell nuclei, β-catenin interacts with T-cell-specific transcription factor (TCF) to form the β-catenin-TCF complex which induces gene transcription, including that of *cyclin D1* and *c-Myc* [123, 126, 127]. This leads to activation of cyclin-dependent kinases responsible for cell cycle progression through G1 to S phase.

In the postnatal period, Wnt/β-catenin signaling in RPE cells regulates the expression of genes pertaining to the antioxidant protection system [42, 128]. A protective effect of the Wnt3a ligand was demonstrated in experiments on ARPE-19 cells treated with Wnt3a in the presence or absence of cytotoxic agents, hydrogen peroxide, and paraquat. The results showed that such treatment improved cell viability, with its effect being mediated by STAT3 activation [42].

Rak et al. [129] in calcium switch experiments on adult human RPE cell cultures revealed a relationship between calcium-dependent cell adhesion, morphology, and pigmentation. The observed changes in cell morphology (gradual transformation of pigmented cells with an epithelial phenotype into spindle-shaped depigmented cells) proved to be reversible, depending on calcium concentration in the medium. The RPE cells were plated at high density in a low-calcium medium and cultured through at least six serial passages to minimize their differentiated properties. Thereafter, they were transferred to a high-calcium medium and maintained at confluence for up to 4 months, being examined for phenotype, pigmentation, and the expression of epithelial cell markers by Western blot analysis. The calcium switch resulted in a rapid restriction of N-cadherin to lateral cell borders and expression of tyrosinase by day 4. The pigment was again detected in the cells after 8 weeks; CRALBP expression, after 12 weeks; and myocilin, after 4 months. Myocilin is known to have a role in actin cytoskeletal reorganization, cell-to-cell interactions, and cell migration. This protein is a modulator of the Wnt cascade: it competes with Wnt for binding with certain Frizzled receptors and interacts with β-catenin [130].

Mechanisms of Wnt/β-catenin signaling can provide explanation for many pathological processes associated

with changes in the structure and function of RPE cells. Studies in this field are developing rapidly, since disclosure of these mechanisms and approaches to their regulation will help in understanding the essence of EMT not only of RPE cells *in vivo* but also of pathological processes in the senescent RPE.

7.4. JAK/STAT Signaling Pathway. Signal transducers and activators of transcription (STATs) comprise a well-characterized family of proteins that transmit a signal from the cell surface to the nucleus and directly participate in gene regulation and cell responses to cytokines and growth factors. In particular, the STAT3 protein induces the expression of antiapoptotic genes in various tissues and activates receptors for IL-6, leukemia inducing factor (LIF), ciliary neurotrophic factor (CNTF), and tyrosine kinase. STAT3 is expressed in the developing and adult RPE and neural retina [131]. Its expression in the RPE of patients with AMD increases upon formation of CNV membranes [132]. In the ARPE-19 cell line, STAT3 activation has proved to result in enhancement of proliferation. JAK/STAT signaling can initiate angiogenesis by activating the production of angiogenic factors, including VEGF and MMPs. Analyzing cytokine-induced changes in the JAK/STAT pathway on the model of ARPE-19 cells, Fasler-Kan et al. [132] have shown that different cytokines (interferon-α, interferon-γ, IL-4, and IL-6) are involved in stimulation of different signaling molecules (STAT1, STAT2, STAT3, or STAT6). As STAT3 plays a central regulatory role in the pathogenesis of AMD, specialists regard it as a potential therapeutic target for the treatment of this disease.

Fragoso et al. [42] in experiments with ARPE-19 cells were the first to reveal the relationship between Wnt3a-mediated STAT3 activation and cell survival, showing that there is a crosstalk between the corresponding two signaling pathways. The role of STAT3 in the Wnt pathways is so significant that STAT3 knockdown by siRNA impairs Wnt3a-dependent cell protection from oxidative stress.

7.5. Notch Signaling Pathway. In canonical Notch signaling, a Notch transmembrane receptor undergoes proteolysis in a presenilin/γ-secretase-dependent manner when exposed to ligand-expressing cells (Delta or Serrate/Jagged). Proteolysis of the Notch receptor releases the Notch intracellular domain (NICD), which translocates to the nucleus, where it binds to the transcription factor RBP-Jk/CBF1/Su(H) and converts it from a repressor into an activator of target genes, including the Hes and Hey family genes [90, 94]. In epithelial cells, for example, *Hey1* was found to be required for TGF-β-induced EMT and migration [94].

Studies on the role of Notch signaling pathway in pigment cells began relatively recently. It has been shown that Notch signaling, mediated in rodents by the RBP-Jk transcription factor (homologous to human CBF1), is necessary for self-maintenance of melanoblasts and melanocyte stem cells [133]. Available data on its role in the regulation of RPE differentiation have been obtained only in experiments with animal models. During normal development, RPE cell differentiation is regulated via the canonical Notch signaling pathway [134], with its target gene *Hes1* being implicated in the formation of the lens, optic cup, and RPE in early embryos [135]. Optic cup and lens defects, plus precocious neurons, were found in E10.5 Hes1$^{-/-}$ eyes [136]. Loss- and gain-of-function studies in the late embryonic and postnatal mouse retina demonstrate that *Hes1* represses the formation of retinal ganglion cells, rods, and horizontal and amacrine neurons [136, 137]. Lee et al. [135] propose that *Hes1* is a temporal brake that integrates the timing of neurogenesis with morphogenesis. According to recent data, constitutive activation of RBP-Jk-dependent Notch signaling during mouse embryonic development leads to hyperproliferation and tumor formation in the adult RPE [138].

Experiments of Saad et al. [139] with kidney tubule epithelial cells have shown that Notch signaling combined with Snail expression plays an important role in EMT and fibrosis formation. Notch inhibition by DAPT in the course of EMT has proved to retard decrease in E-cadherin expression and increase in α-SMA, MMP-2, and MMP-9 expression, with the level of Snail expression being also reduced. The authors consider that inhibition not only of Snail but also of Notch can provide a means of control over EMT.

As noted previously, Notch signaling can cross-interact with both canonical Smad-dependent and noncanonical TGF-β signaling pathways in RPE cells during EMT [111]. Moreover, it has also been shown that elements of the Notch signaling pathway—including Jagged-1, Notch-3, Hes-1, and Hey-1—are upregulated in TGF-β2-stimulated EMT in human RPE cells, while blockade of this pathway with DAPT completely reverses TGF-β2-induced EMT [140].

Not only does the Notch signaling pathway interact with Wnt and TGF-β/BMP but there is also evidence for its interactions with other pathways, such as Shh and NF-κB [141], but their role in phenotypic changes of human RPE cells *in vitro* has not yet been studied.

8. Prospective Therapeutic Agents

Several strategies aimed at the inhibition of signaling pathways involved in RPE pathologies have been elaborated to date [142, 143]. Modulation of signal transduction molecules—for example, RhoA/Rho-kinase, Smad, or MAPK—by small molecules, gene transfer, or some other technology appears promising as a means of prevention and treatment of such pathologies [143]. Systemic administration of ALK5 inhibitors effectively suppresses fibrogenic reaction and development of tissue fibrosis in animals [144–146]. Increasing attention has been recently devoted to the inhibitory role of different microRNAs [147], specific small molecules [148–151], antibiotics, immunosuppressants [114], steroids [152], and histone deacetylase inhibitor [153]. Another group of interest comprises antiangiogenic agents capable of blocking different steps in the pathway of angiogenesis under pathological conditions: antibodies to the VEGF, novel steroids, triamcinolone acetonide, siRNAs, high-affinity VEGF antagonists (angiostatin, endostatin), PEDF, and so forth, [154]. Future studies are needed

to identify other key modulators involved in the process of RPE damage, which is necessary for gaining a deeper insight into the causative mechanisms of RPE pathologies and finding effective ways of their prevention and treatment.

9. Conclusions

Human RPE cell cultures provide wide possibilities for research on the mechanisms of pathological processes taking place *in vivo* and the methods of their regulation at the cell and molecular levels. Depending on culture conditions, RPE cells can change their differentiation status, losing cell type-specific features and redifferentiating into epithelial cells. In directed experiments, adult RPE cells undergo EMT and acquire certain properties of mesenchymal and proneural cells. Pioneering studies on signaling pathways involved in pathological processes in the RPE have revealed novel molecular targets for suppressing mesenchymal differentiation. The TGF-β/BMP signaling pathway plays a crucial role in the mesenchymal transformation of RPE cells. The inhibition of Snail and RhoA/ROCK in the canonical and noncanonical TGF-β cascades reduces manifestations of mesenchymal properties in the transformed RPE cells, which offers a new approach to the prevention and treatment of PVR. Another promising therapeutic strategy consists in inhibiting mTOR, a component of the PI3K/AKT/mTOR signaling pathway. Moreover, BMP-4 signaling is regarded as a target for suppressing the effects of oxidative stress and RPE senescence in AMD. The same is true of STAT3, a component of the JAK/STAT pathway, since it plays a regulatory role in the pathogenesis of this disease. The inhibition of Notch signaling impedes EMT, retarding mesenchymal differentiation. Thus, a series of promising research approaches to control over mesenchymal differentiation of RPE cells have already taken shape. On the other hand, no less important is to find ways to stimulate and maintain neuronal differentiation of RPE with a view to restore the retina after injury or pathology. Factors operating *in vivo* restrain RPE transdifferentiation into the neural retina, but RPE cells manifest their proneural properties *in vitro*. This is of major interest for further research aimed at developing methods for retinal repair in ocular pathologies. The search for factors regulating RPE differentiation is obviously of both fundamental and practical interest. Experiments with *in vitro* cultures of human RPE allow extensive screening for changes at the cell and molecular levels that occur under pathological conditions, and profound analysis and interpretation of the results will help to find adequate approaches to correction of RPE abnormalities *in vivo*.

Abbreviations

AMD: Age-related macular degeneration
BMPs: Bone morphogenetic proteins
CNV: Choroidal neovascularization
CRALBP: Cellular retinaldehyde-binding protein
ECM: Extracellular matrix
EMT: Epithelial-mesenchymal transition
ERK: Extracellular signal-regulated kinase
hTERT: Human telomerase reverse transcriptase subunit
MAPK: Mitogen-activated protein kinases
PEDF: Pigment epithelium-derived factor
PVR: Proliferative vitreoretinopathy
ROCK: Rho-associated protein kinase
RPE: Retinal pigment epithelium
RPE65: Retinal pigment epithelium-specific 65 kDa protein
TNFα: Tumor necrosis factor alpha
STAT: Signal transducer and activator of transcription
TER: Transepithelial electrical resistance
VEGF: Vascular endothelial growth factor.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Prevalence of Corneal Astigmatism in Patients before Cataract Surgery in Northern China

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Purpose. To analyze the prevalence and presentation patterns of corneal astigmatism in cataract surgery candidates in a teaching hospital in northern China. *Methods*. From May 1, 2012, to April 30, 2013, partial coherence interferometry (IOLMaster) measurements of all qualified cataract surgery candidates were retrospectively collected and analyzed. *Results*. The study evaluated 12,449 eyes from 6,908 patients with a mean age of 69.80 ± 11.15 (SD) years. The corneal astigmatism was 0.5 diopters (D) or less in 20.76% of eyes, 1.0 D or more in 47.27% of eyes, 2.0 D or more in 13.16% of eyes, and 3.0 D or more in 3.75% of eyes. With-the-rule astigmatism was found in 30.36% of eyes, while against-the-rule was found in 52.41% of eyes. The percentage of against-the-rule astigmatism increased with age. *Conclusion*. Our study showed that almost one-half of preoperative eyes (47.27%) in northern China have a corneal astigmatism of 1.0 D or more, indicating that more surgical techniques or toric IOLs are needed to achieve better visual rehabilitation.

1. Introduction

Phacoemulsification is one of the most successfully and commonly performed cataract surgeries worldwide. With the development of modern surgical techniques and intraocular lenses (IOLs), patients expect and demand refractive error correction after cataract surgery. Advances in the calculation of IOL power have significantly reduced the incidence of spherical refractive errors, while residual astigmatism after surgery is a concern for both ophthalmologists and patients and can leave patients with symptomatic decreased visual function [1–5].

Partial coherence interferometry (IOLMaster, Carl Zeiss Meditec, Berlin, Germany) is widely used due to its superior performance in the measurement of ocular axial length. The IOLMaster analyzes six light reflections projected onto the anterior corneal surface within a 2.3 mm radius and can also be used as an automated keratometer (AK). Recent reports have shown that IOLMaster can precisely measure preoperative corneal astigmatism and can predict the residual corneal astigmatism after cataract surgery [6].

The distribution and prevalence of corneal astigmatism in cataract patients of different countries have been previously reported [5, 7–10]. An estimated 13,780,000 cases of blindness have been caused by cataracts in China [11] and two groups from Guangzhou [8] and Shanghai [12] have reported the distribution of corneal astigmatism before cataract surgery in southern and central China. However, there are no similar reports for cataract patients in northern China. This study reviewed all of the cataract cases in one year in one of the largest eye hospitals in China to investigate the prevalence of corneal astigmatism in a large sample in northern China. The findings may aid hospitals and manufacturing companies in evaluating the requirement for the use of toric IOLs or other reported surgical methods.

Table 1: Patient demographics compared with 5 other published studies.

	Present	Guan et al. [12]	Chen et al. [8]	Ferrer-Blasco et al. [7]	Khan and Muhtaseb [5]	De Bernardo et al. [14]
Eyes/patients	12449/6908	1430/827	4831/2849	4540/2415	1230/746	757/380
Age (y)						
Mean ± SD	69.80 ± 11.15	72.27 ± 11.59	70.56 ± 9.55	60.59 ± 9.87	75.54 ± 0.71	71.89 ± 10.19
Range	30, 97	16, 98	49, 95	32, 87	30, 104	33, 96
Male/female	3199/3709	359/468	1090/1759	768/1647	343/403	176/204
Corneal astigmatism (D)						
Mean ± SD	1.15 ± 0.84	1.07 ± 0.73	1.01 ± 0.69	0.90 ± 0.93	1.03 ± 0.73	1.02 ± 0.69
Range	0.0, 6.63	0.06, 5.52	0.05, 6.59	0.25, 6.75	0.0, 6.2	0.06, 4.57
K1 mean ± SD	43.93 ± 1.67	43.57 ± 1.56	43.76 ± 1.53	43.48 ± 1.61	43.43 ± 1.49	43.54 ± 1.43
K2 mean ± SD	45.08 ± 1.73	44.64 ± 1.65	44.76 ± 1.56	44.08 ± 1.59	44.46 ± 1.56	44.56 ± 1.52
Corneal astigmatism (%)						
≤0.5 D	20.76	21.2*	23.14	58.8	24.47	23.38
≥1.0 D	47.27	45.37	41.3	34.8	40.4	41.74
≥2.0 D	13.16	10.33	8.22	9.26**	9.67	8.32
≥3.0 D	3.75	2.22	3.52	5.61***	4.61	2.64

*Not including 0.5 D, **not including 2.0 D, and ***not including 3.0 D.
D = diopter, K1 = flat keratometry, and K2 = steep keratometry.

2. Patients and Methods

Retrospective biometry data were collected for all patients who had routine cataract surgery at the Tianjin Eye Hospital between May 1, 2012, and April 30, 2013. Cataract patients with a history of ocular surgery, corneal disease, and inflammation and with an age younger than 30 years old and a dense cataract that did not allow IOLMaster measurement were excluded. Routine eye examinations were performed before operation, including visual acuity, refraction, tonometry, slit lamp evaluation, and dilated fundus examination. The study was approved by the Human Research Ethics Committee at the Tianjin Eye Hospital and all procedures adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent. Three experienced technicians collected the keratometric data for consecutive patients using IOLMaster version 5.3 and the mean of five measurements was used for the parameters.

Data were analyzed by the R software package version 2.15.2 R Core Team (R Foundation for Statistical Computing, Vienna, Austria, ISBN 3-900051-07-0, URL http://www.R-project.org/). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of variables. The results showed that the data were normally distributed, except for the data regarding astigmatisms. One-way analysis of variance and the Kruskal-Wallis test were applied for the comparison of variance for normally and nonnormally distributed data among different age groups, respectively. The t-test was used to compare keratometry between the two groups and a Wilcoxon signed rank test was used to compare corneal astigmatism data. Spearman's rank test was used to assess the relationship between age and astigmatism. A P value less than 0.05 was considered statistically significant.

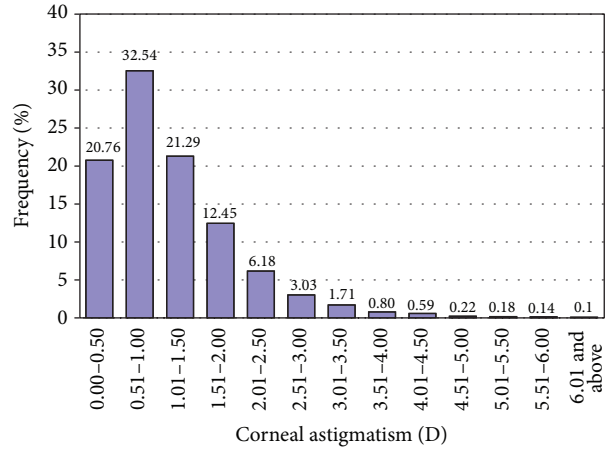

Figure 1: Distribution of corneal astigmatism in 0.5 D increments for all 12,449 eyes.

3. Results

This study was composed of 12,449 eyes from 6,908 patients. The patient demographics are shown in Table 1, which also shows a comparison of 5 other published papers. Figure 1 presents a histogram of the frequency distribution of corneal astigmatism. Among all of the patients, astigmatism of 0.51 to 1.00 D was the most common cylinder value (32.54%), followed by 1.01 to 1.50 D (21.29%) and 0.0 to 0.50 D (20.76%). In total, 3200 eyes (25.41%) exhibited a corneal astigmatism of 1.5 D or greater.

Table 2 presents the descriptive flat keratometry (K1) and steep keratometry (K2) in the 7 age groups. A gradually

Table 2: Descriptive statistics by age group.

Age group (y)	Astigmatism (D)	K1 (D) mean ± SD	K2 (D) mean ± SD	Eyes (%)
30–40	1.33 ± 0.85	42.77 ± 2.23	44.10 ± 2.38	164 (1.32)
41–50	1.10 ± 1.10	43.51 ± 1.83	44.61 ± 1.92	571 (4.59)
51–60	0.99 ± 0.71	43.91 ± 1.61	44.90 ± 1.70	1869 (15.01)
61–70	1.05 ± 0.80	44.04 ± 1.63	45.10 ± 1.70	3226 (25.91)
71–80	1.20 ± 0.83	43.95 ± 1.65	45.14 ± 1.69	4517 (36.28)
81–90	1.34 ± 0.90	43.95 ± 1.68	45.28 ± 1.70	1993 (16.01)
≥91	1.39 ± 0.82	43.73 ± 1.65	45.12 ± 1.76	109 (0.88)
P^*	<0.001	<0.001	<0.001	<0.001

D = diopter, K1 = flat keratometry, and K2 = steep keratometry.
*Kruskal-Wallis test.

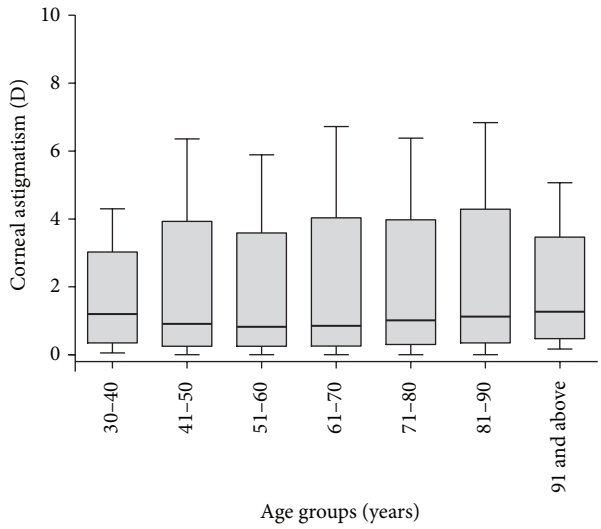

Figure 2: Corneal cylinder in all 7 age groups. The bold lines in the boxes represent the median (50% percentile), the upper and lower limits of the box represent the first quartile (25% percentile) and third quartile (75% percentile), and the bars represent the minimum and maximum values.

increasing keratometry value was observed with age, particularly in K2. Most eyes in this cohort were between 71 and 80 years old, which represented more than one-third (36.28%) of all cases. Patients between 61 and 70 years old represented one-fourth (25.91%) of all cases.

Figure 2 shows the corneal astigmatism values in each age group. Spearman's rank correlation between age and astigmatism was $r = 0.12$ with $P < 0.001$. Figure 3 depicts the distributions of corneal astigmatism in the different age groups.

With-the-rule (WTR, the steep meridian of the cornea being within 90 ± 30 degrees) corneal astigmatism was found in 3779 eyes (30.36%), against-the-rule (ATR, the steep meridian of the cornea being within 180 ± 30 degrees) corneal astigmatism was found in 6524 eyes (52.41%), and oblique (neither WTR nor ATR) corneal astigmatism was found in 2146 eyes (17.22%). The ATR astigmatism proportion increased with age and the WTR astigmatism proportion decreased with age, except in the 30–40-year-old age group, which showed a slightly higher percentage of ATR astigmatism (Figure 4).

No significant difference was found between the right and left eyes in K1 (43.91 ± 1.76 versus 43.94 ± 1.66, $t = 0.75$, $P = 0.45$) or K2 (45.08 ± 1.73 versus 45.06 ± 1.72, $t = 0.66$, $P = 0.51$). A statistically significant difference was found between right and left eye corneal astigmatisms with the Wilcoxon signed rank test (1.17 ± 0.85 D versus 1.13 ± 0.82 D, statistic = 19840457, $P = 0.02$).

The K1 and K2 values in females were higher than those in males (K1: 44.11 ± 1.67 versus 43.71 ± 1.74, $t = 13.20$, $P < 0.0001$; K2: 45.30 ± 1.72 versus 44.82 ± 1.80, $t = 15.34$, $P < 0.0001$). The corneal astigmatism in females was significantly greater than that in males according to the Wilcoxon signed rank test (1.19 ± 0.87 versus. 1.11 ± 0.80, statistic = 18500144, $P < 0.0001$).

4. Discussion

This study determined the distribution of corneal astigmatism in different age groups in northern China. Several studies have investigated the prevalence of corneal astigmatism using IOLMaster [5, 7, 9, 12–14], which not only affords the measurement of corneal status but also enables the easy and reliable calculation of IOLs as well as postoperative refraction data. The IOLMaster database was accessed for all cataract candidates in an entire year. The results showed that the mean age was slightly younger than previously reported data [8, 12] and that the 71–80-year-old age group occupied 36.28% of all cases, followed by the 61–70-year-old age group (25.91%) and the 81–90-year-old age group (16.01%); these results were similar to those of Chen et al. report from Guangzhou [8] but differed from those of Khan and Muhtaseb's report [5]. Khan et al. reported that the 71–80-year-old age group was the largest, followed by the 81–90- and 61–70-year-old age groups [5]. In terms of gender distribution, our study showed that the number of female patients was greater than that of males, which is consistent with other published studies [5, 7, 8, 12].

ATR astigmatism was the predominant group, comprising 52.41% of the cases, and the prevalence increased with

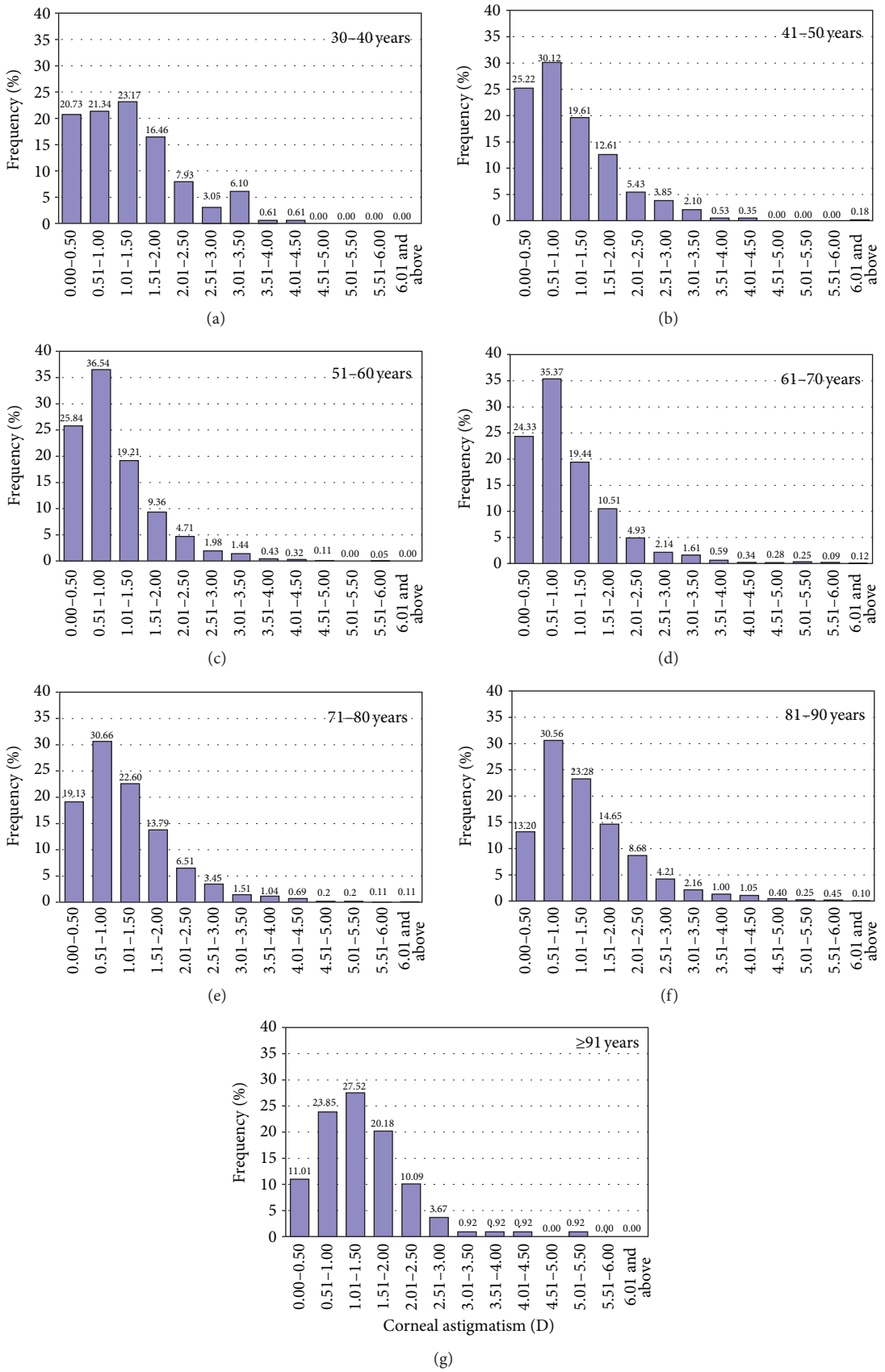

Figure 3: Frequency distribution of corneal astigmatism in 0.50 D steps for the 7 age groups.

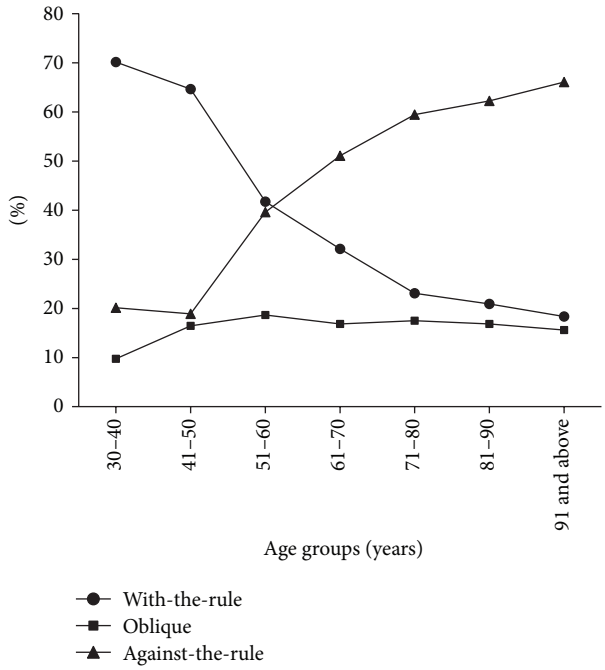

Figure 4: Percentages of WTR, ATR, and oblique corneal astigmatisms in the 7 groups.

age, except for the 30–40-year-old age group, which showed a slightly higher percentage than the 41–50-year-old age group. Selection bias may account for this finding because the 30–40-year-old age group represented only 1.32% of all cases. By contrast, the percentage of WTR astigmatism decreased with age. These findings are generally consistent with those of previous studies [7, 13, 15, 16].

The mean corneal astigmatism of this cohort was 1.15 ± 0.84 D (range from 0.0 to 6.84 D), which is slightly higher than that in other published studies [5, 7, 8, 12, 15]. The right (1.17 D) and left eyes (1.13 D) significantly differed, which is in contrast to the findings of Hoffmann and Hütz's study [15]. Interestingly, the corneal astigmatism in females (1.19 D) was significantly greater than that in males (1.11 D).

In our study, 20.76% of eyes had a corneal astigmatism of 0.5 D or less, which is lower than the results from other groups [5, 7, 8, 12]. A large proportion of eyes (47.27%) had a corneal astigmatism of 1.0 D or greater, which is higher than the results reported by the abovementioned groups. Additionally, 3.75% of eyes had 3.0 D of corneal astigmatism [8, 12], which is a greater prevalence than that reported by the other two Chinese studies (2.22%, 3.52%) but is lower than that reported by European studies (5.61%, 4.61%) [5, 7]. All age groups showed a similar distribution pattern of corneal astigmatism, except for the 30–40- and above 91-year-old age groups, which showed some variation in the astigmatism distribution. A previous study showed a similar distribution pattern [5, 7].

Several techniques exist to correct corneal astigmatism, including limbal relaxing incisions [17], opposite clear corneal incisions [18], excimer laser refractive procedures [19, 20], femtosecond laser-assisted astigmatic keratotomy [21, 22], and toric intraocular lens (IOL) implantation [23–25]. The procedure chosen primarily depends on the precise measurements of preoperative corneal astigmatism.

A clear corneal incision may result in a surgically induced corneal astigmatism in patients with 0.5 D [26]. In our study, 53.30% of eyes had a corneal astigmatism of 1.0 D or less and received sufficient correction through the performance of on-axis phacoemulsification combined with monofocal IOL implantation [5]. Meanwhile, 23.41% of eyes exhibited more than 1.50 D of corneal astigmatism in our study, which is similar to the findings of Khan et al. (20.5%) [5] and Ferrer-Blasco et al. (22%) [7], although their studies required more manipulations or techniques to correct for better visual rehabilitation. Other techniques, such as manual or femtosecond laser-assisted arcuate keratotomy, were used to correct much worse corneal astigmatisms [27, 28]. Recently, limbal femtosecond laser-assisted intrastromal arcuate keratotomy has been used for corneal astigmatisms of 1.50 ± 0.47 D [22]. However, the results of this procedure are unpredictable or are associated with complications [29, 30]. Considering the high cost of femtosecond laser surgery, the majority of the population in China cannot afford such procedures.

Toric IOLs have been used clinically since they were first described by Shimizu et al. [31], with encouraging results [32–35]. An analysis of the distribution of corneal astigmatism in a large cohort of cataract candidates will provide valuable information and benefits for manufacturers, ophthalmologists, and cataract patients. At present, toric IOLs can be used to correct corneal astigmatisms from 0.4 D to 8.4 D [7] during cataract surgery. In our case series, 1.51 D to 3.50 D represented 23.37% of all cases, most of which could be effectively corrected with toric IOLs. The higher cost of new IOLs may be another burden for patients and health insurance companies.

Corneal astigmatism changes significantly with age [15, 36–39]. Our study and the two previous Chinese investigations support this tendency [8, 12]. The mean values of K1, K2, corneal astigmatism, and other parameters in our study were slightly higher than those reported by some other studies [5, 7] but closely resemble those from reports from Shanghai [12] and Guangzhou [8], China. Possible reasons may be the inclusion of different racial and ethnic groups, different inclusion criteria, and different age distributions, among others. Our retrospective study was clinically based, which may lead to some selection bias. One advantage of our study is that we selected all of the cataract surgery candidates from an entire year, which presented more than one-half of cataract surgery cases in the same year in Tianjin, a city with 12,280,000 people http://en.wikipedia.org/wiki/Tianjin.

In conclusion, our study revealed the distribution of all cataract candidates in one year in a single hospital in northern China. A number of our cases (47.27%) exhibited a corneal astigmatism of 1.0 D or more. Corneal astigmatism increases with age. With an aging population and a higher demand for improved vision, the need for astigmatism correction with toric IOLs or other methods will increase accordingly.

Conflict of Interests

The authors report no conflict of interests. The authors alone are responsible for the content and writing of this paper.

Authors' Contribution

Xiaoyong Yuan and Hui Song contributed equally to this work and should be considered as co-first authors.

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