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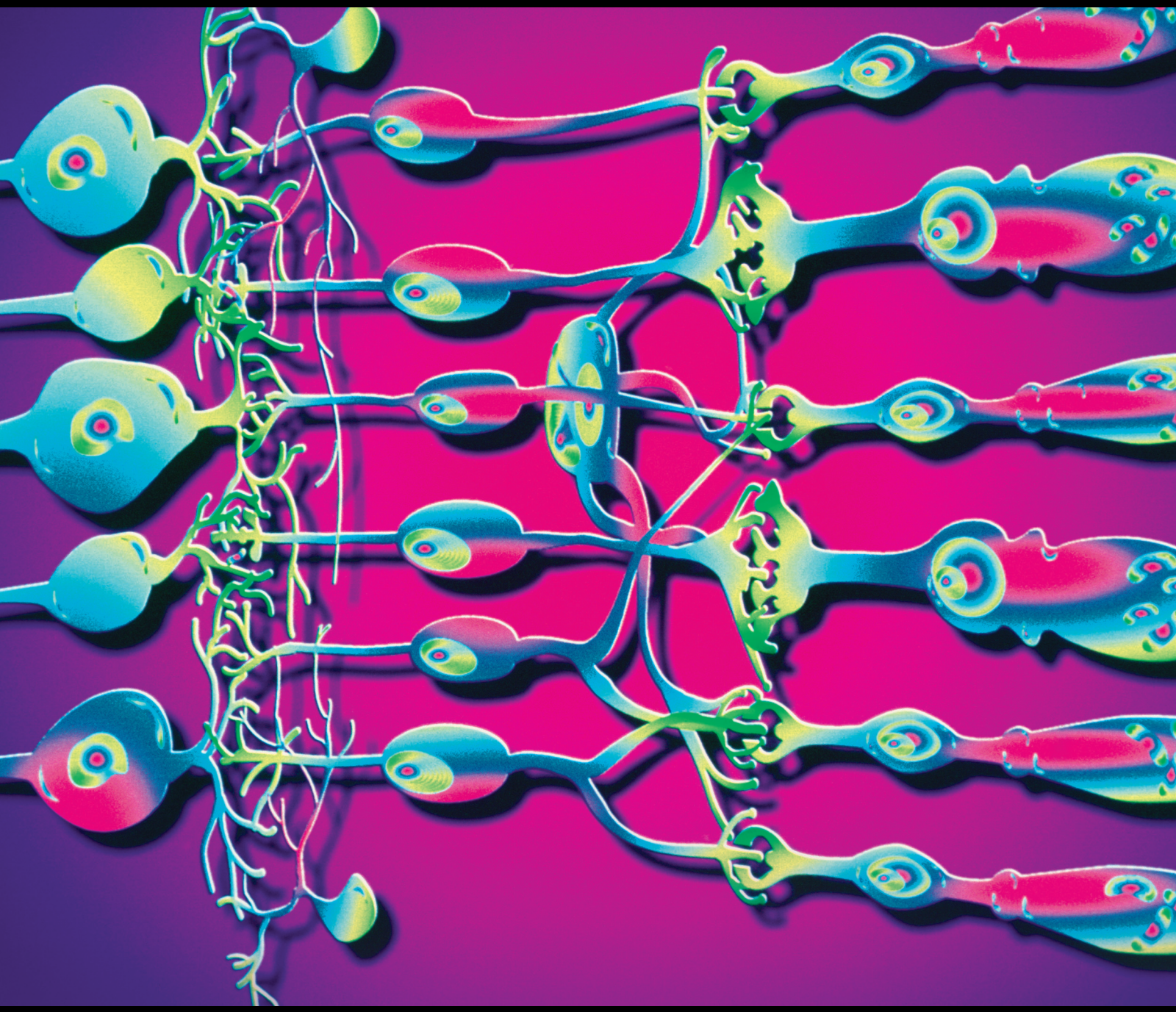
New Trends in Anterior Segment Diseases of the Eye

Guest Editors: Francisco Javier Romero, Bjorn Nicolaissen, and Cristina Peris-Martinez



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Editorial Board

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Editorial

New Trends in Anterior Segment Diseases of the Eye

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Disorders of the anterior segment of the eye are leading causes of ocular morbidity. Such conditions include dry eye conditions, infections, traumas of various types, inflammatory reactions, hereditary disorders, and cataract. For a number of these patients, the rule is a continuous progression and aggravation of symptoms. The end stage is varying degrees of visual loss with or without pain.

Despite continuous advances in ophthalmology, a number of these patients represent a challenge even in highly specialized clinics in western countries. On a worldwide basis, such conditions represent a significant public health problem. Cataract and loss of corneal transparency are still two of the most common causes of blindness worldwide [1]. While cataract is a disorder of the adult and aged population, blindness due to corneal opacities is observed in all age groups. In children, loss of corneal transparency represents the third most common cause of blindness.

During the past two decades, translational research has increased our ability to understand the pathogenesis of, and also to treat, selected disorders of the ocular surface and cornea. Although still in their shaping and improved by continuous translational and clinical research, procedures for ex vivo production of corneal and conjunctival epithelial tissue allow treatment of patients with previously untreatable corneal disorders [2, 3]. Refinement of corneal transplant procedures permits targeted intervention and replacement of opaque and nonfunctioning tissues with lamellar donor tissue [4, 5]. By such techniques, the volume of foreign tissue with a potential for stimulation of immunoreactions is reduced as is the trauma induced by the surgical intervention. However, there is a pronounced lack of donor corneas. In western countries, one main indication for corneal transplantation is loss of endothelial function. Ongoing research within the field of tissue engineering will provide procedures for production of transplantable layers of corneal endothelium and thereby add a new and significant tool to our treatment options [6]. Procedures for cataract surgery are continuously being advanced, accompanied by a decline in the rate of complications such as astigmatism and corneal endothelial loss with subsequent corneal hydration [7, 8]. Due to the complexity of challenges within these areas, further progress relies to a significant extent on interaction between clinical and basic research environments. In translational research projects, extraction of information is facilitated by cooperation between clinical and basic research environments [9, 10]. The intent is to warrant that advances in basic and clinical knowledge may serve a purpose: a better understanding of the disease pathophysiology to ensure a better disease prevention, new diagnostic procedures, and novel types of treatment including drugs, whose final end point may be preclinical or clinical testing.

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Research Article

Vision Related Quality of Life in Patients with Keratoconus

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Purpose. The purpose of this study is to evaluate the vision related quality of life in patients with keratoconus by using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25). *Methods.* Thirty patients presented with keratoconus (keratoconus group) and 30 healthy patients (control group) were included in this study. Twenty patients were using rigid gas permeable and 10 patients were not using contact lenses in keratoconus group. High and low contrast visual acuity and mean K values of the patients were recorded. Each subject completed the 25-item NEI-VFQ-25. *Results.* All subscales of NEI-VFQ-25 were lower in the keratoconus patients. The difference was more evident in the subscales of general vision, ocular pain, near vision, vision-specific mental health, vision-specific role difficulties, and peripheral vision ($P < 0.05$). Overall composite score was 75.2 ± 17.2 in the keratoconus group and 93.2 ± 5.6 in the control group ($P = 0.00$). Contact lens wearers had higher best corrected visual acuity in comparison with noncontact lens wearers ($P = 0.028$). Patients with low visual acuity (logMAR > 0.4) in the better eye had lower distance vision, social functioning, mental health, and role difficulties. Meanwhile, patients with low visual acuity (logMAR > 0.4) in the worse eye had lower general health scores ($P < 0.05$). *Conclusions.* Vision related quality of life was worse in keratoconus patients. Success in the contact lens usage and maintaining higher visual acuity may improve vision related quality of life.

1. Introduction

Keratoconus is a progressive, bilateral asymmetric, noninflammatory corneal ectasia with an incidence of 1 per 2,000 in the general population [1]. While keratoconus mainly affects young adults, other eye diseases that affect vision such as glaucoma and macular degeneration have a much later onset. The corneal thinning induces irregular astigmatism, myopia, and protrusion, leading to mild to marked impairment in the quality of vision. Keratoconus patients report ocular discomfort and poor vision typically treated with contact lenses or spectacles [1, 2].

Health related quality of life (HR-QoL) measures functioning and well-being in physical, mental, and social health realms of life and reflects the influence of a broad range of health conditions simultaneously. The National Eye Institute (NEI) sponsored the development of the National Eye Institute-Vision Function Questionnaire (NEI-VFQ) with the goal of creating a survey that would measure the dimensions of self-reported vision targeted health status that are most important for persons who have chronic eye diseases. VFQ-25 is the product of an item reduction analysis of the longer field test version of the survey called the 51-item NEI-VFQ [3].

NEI-VFQ-25 assesses vision related quality of life multidimensionally by several subscales such as general, near, distance and color vision, role limitations, dependency, mental health, and social function. They have been validated by a variety of studies showing they are useful tools in assessing vision-specific quality of life [4–8]. NEI VFQ-25 is demonstrated to be sensitive to the influence of age related macular degeneration (AMD) [9, 10], glaucomatous field loss [11], cataract [12], Behcet uveitis [13], after penetrating keratoplasty for keratoconus [14], after retinal detachment surgery [15], vitrectomy [16], diabetic retinopathy [17], strabismus [18], multiple sclerosis [19], osteoporotic fractures, and low vision from any cause [20]. The correlations with clinical markers of disease severity provide evidence of clinical validity for the measure. Significant impairment in vision related

quality of life (VR-QoL) with average scores comparable to age related macular degeneration has been shown by the collaborative longitudinal evaluation of keratoconus study group [21].

NEI-VFQ-25 evaluates not only visual function and limitations in daily activities related to impaired visual function but also the impact of ocular disease on patients' lives from various standpoints. Apart from clinical evaluation, anatomical success, and visual acuity, other aspects of visual outcome should also be considered in the keratoconus patients. For this reason, to understand the effect of the keratoconus disease on VR-QoL and to evaluate disease from the perspective of these younger-age patients in their active years should be an important concern. The purpose of this study was to evaluate the VR-QoL and visual function in the keratoconus patients by using the NEI-VFQ-25.

2. Methods

Consecutive patients with keratoconus attending to the cornea and contact lens department of Fatih Sultan Mehmet Education and Research Hospital were enrolled in this study. The patients with ophthalmic surgery and corneal pathologies other than keratoconus were excluded. All participants provided written informed consent in accordance with the Declaration of Helsinki after explanation of the nature and possible consequences of the study. Thirty patients presented with keratoconus (keratoconus group) and 30 healthy patients (control group) were included in this study. Twenty patients were using rigid gas permeable and 10 patients were not using contact lenses in the keratoconus group.

Keratoconus diagnosis was based on corneal topography and slit lamp observation. In all cases in the keratoconus group, clinical findings of keratoconus were evident: corneal topography revealing an asymmetric bowtie pattern, with or without skewed axes and at least one keratoconus sign on slit lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar.

We performed complete ophthalmological examination and corneal topography to all patients and determined their high and low contrast visual acuity and simulated K (sim K) values. Visual acuity testing was performed with Snellen and logMAR for each eye separately. Low contrast visual acuity was measured with Bailey-Lovie low contrast sensitivity chart as the maximum number of letters that patients can read. Corneal topography was performed with Nidek Magellan Mapper and corneal curvature was calculated as the average of right and left eyes steep sim K keratometry. The patients in the keratoconus group were graded according to the Amsler-Krumeich keratoconus classification system as grades 1 to 4.

The eyes of the patients in the keratoconus group were designated as better or worse on the basis of his or her logMAR visual acuity scores. For those with bilateral involvement, worse eyes were defined as those with a 0.1 logMAR unit or worse logMAR visual acuity score than the other eye. If both eyes of a patient had identical logMAR visual acuities, then both eyes were designated as better eyes for purposes of analyses. In patients with unilateral involvement, the visual acuity of the eye with involvement was grouped under worse eyes [14].

A validated version of NEI-VFQ-25 in Turkish was administered to each subject [4, 5]. NEI-VFQ-25 consists of 25 core and 13 optional items. It is divided into 12 subscales as general health, general vision, ocular pain, near vision, distance vision, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision specific dependency, driving, color vision, and peripheral vision. Questionnaire subscales were graded between 0 and 100 with higher scores representing better function. Driving question was excluded because of a large proportion of nondrivers in the study.

2.1. Statistical Analysis. A mean for the overall NEI-VFQ-25 score and for each subscale score was computed. The mean values of the scores within the ordered categorical variables (keratoconus category, visual acuity ≥0.4 or <0.4 in the better or worse eye, and contact lens use) were calculated. Descriptive analyses were presented as mean ± standard deviation. Scale scores were compared with Mann-Whitney U test and Kruskal Wallis test. The degree of linear agreement between parameters was calculated using the Spearman correlation coefficient. All statistical analyses were performed with SPSS 16.0 program. P value < 0.05 was considered as statistically significant.

3. Results

Sixty patients were included in the study. Demographic characteristics of the patients (age, gender, education, and contact lens use) are presented in Table 1. We did not observe a significant difference for age, gender, and education level between the groups ($P > 0.05$).

Best corrected binocular mean visual acuity was worse in the keratoconus group both in the better eye and worse eye when compared to the control group ($P = 0.001$). Low contrast visual acuity was also worse in the keratoconus group when compared to the control group ($P = 0.001$).

Average of the steep K values of both eyes was 52.9 ± 5.7 D for keratoconus group and 43.1 ± 1.9 D for the control group ($P = 0.00$). Keratoconus group was graded according to the Amsler-Krumeich keratoconus classification as stage I: 4 eyes (13.3%); stage II: 14 eyes (46.6%); stage III: 6 eyes (20.0%); stage IV: 6 eyes (20.0%). Keratoconus was unilateral in 9 patients (30%) and bilateral in 21 patients (70%). In the keratoconus group, best corrected mean visual acuity of both eyes was significantly better in the patients using contact lenses than noncontact lens users ($P = 0.028$).

All subscales of NEI-VFQ-25 were lower in the keratoconus group compared to control (Table 2). The difference was more evident in the subscales of general vision, ocular pain, near vision, vision-specific mental health, vision-specific role difficulties, and peripheral vision ($P < 0.05$). Overall composite scores were 75.2 ± 17.2 in the keratoconus group and 93.2 ± 5.6 in the control group ($P = 0.00$).

Table 1: Demographic characteristics of the patients (age, gender, education, and contact lens use and high contrast (Snellen) and low contrast visual acuity (letters)) according to the groups ($^{*}P < 0.05$; $^{**}P < 0.001$).

	Keratoconus group	Control group	P
Age	29.36 ± 10.60	30.23 ± 8.80	0.573
Gender			
Female/male	16/14 (53/47%)	18/12 (600/40%)	0.916
Education level			
Primary school	3 (10%)	6 (20%)	
High school	20 (67%)	12 (40%)	0.562
University	7 (23%)	12 (40%)	
Contact lens wear			
None	10 (33%)	30	
One eye only	5 (17%)		0.00**
Both eyes	15 (50%)		
Visual acuity			
Better eye	0.73 ± 0.23 (0.21 ± 0.23 LogMAR)	1.0 (0.0 logMAR)	0.00**
Worse eye	0.47 ± 0.27 (0.4 ± 0.33 LogMAR)	1.0 (0.0 logMAR)	0.001**
Low contrast visual acuity	23.27 ± 11.28 (0.54 ± 0.22 LogMAR)	45.00 ± 3.20 (0.10 ± 0.08 LogMAR)	0.001**

Table 2: NEI-VFQ-25 subscale scores according to the groups ($^{*}P < 0.05$; $^{**}P < 0.001$).

NEI-VFQ-25 scales	Keratoconus group	Control group	P
General health	65.0 ± 20.6	79.7 ± 15.8	0.030*
General vision	60.2 ± 24.4	89.7 ± 10.3	0.001**
Ocular pain	54.0 ± 23.8	78.8 ± 17.9	0.002*
Near vision	76.0 ± 23.0	93.5 ± 13.6	0.014**
Distance vision	84.0 ± 18.0	94.7 ± 8.7	0.80
Social functioning	85.0 ± 24.0	98.8 ± 4.8	0.069
Mental health	67.0 ± 27.8	98.8 ± 4.8	0.00**
Role difficulties	77.2 ± 26.4	96.4 ± 7.8	0.014*
Dependency	84.7 ± 26.4	96.4 ± 7.8	0.379
Color vision	91.0 ± 17.0	97.6 ± 6.6	0.424
Peripheral vision	80.7 ± 17.4	94.1 ± 9.3	0.020*
Overall composite score	75.2 ± 17.2	93.2 ± 5.6	0.00**

When we compared NEI-VFQ-25 subscale item scores between subgroups of the keratoconus group, NEI-VFQ-25 subscale scores were lower in the grade 4 patients compared to grade 1 keratoconus patients but the difference between the keratoconus grades was not statistically significant ($P > 0.05$). Overall composite scores were 82.6 ± 12.7, 77 ± 15.9, 72.7 ± 17.6, and 67.8 ± 25.1 for keratoconus grades I, II, III, and IV, respectively. Overall composite scores decreased with advancing keratoconus grades although the decrease was not statistically significant ($P > 0.05$).

The NEI-VFQ-25 subscale item scores showed statistically significant differences according to the visual acuity in the better eye. Patients with low visual acuity (logMAR visual acuity of 0,4 or worse) in the better eye had significantly lower distance vision, social functioning, mental health, role difficulties, and overall composite score ($P < 0.05$). Meanwhile, patients with low visual acuity (logMAR visual acuity of 0.4 or worse) in the worse eye had significantly lower general health scores compared to patients with high visual acuity.

Contact lens wearers had better best corrected visual acuity in comparison with non-contact lens wearers ($P = 0.028$). Although not significantly different ($P > 0.05$), the NEI-VFQ-25 subscale scores of distance vision, vision-specific mental health, role difficulties, social functioning, and dependency, color vision subscale scores of the patients using contact lenses were better than the patients who were not using contact lenses. Meanwhile general vision, ocular pain, near vision, and peripheral vision scores were worse in the patients using contact lenses compared to the patients who were not using contact lenses ($P > 0.05$) (Table 3).

During the correlation analysis, keratoconus grades negatively correlated with vision in the best eye and keratometry value. No significant correlation was observed between keratoconus grades and NEI-VFQ-25 subscales ($P > 0.05$). Visual acuity in the better eye correlated with near vision ($P = 0.002$; $r = 0.547$), distance vision ($P = 0.0$; $r = 0.615$), social functioning ($P = 0.0$; $r = 0.653$), vision-specific mental health ($P = 0.0$; $r = 0.663$), role difficulties ($P = 0.001$; $r = 0.598$), dependency ($P = 0.001$; $r = 0.584$), color vision

Table 3: Comparison of NEI-VFQ-25 subscale item scores in the keratoconus group according to the subgroups of the keratoconus grade; visual acuity in the better and worse eye and contact lens use are presented ($^{*}P < 0.05$; $^{**}P < 0.001$).

NEI-VFQ-25 scores	Keratoconus grade					Visual acuity, better eye			Visual acuity, worse eye			Contact lens use		
	I *n*: 6	II *n*: 9	III *n*: 7	IV *n*: 6	*P*	≥0.4 *n*: 5	<0.4 *n*: 25	*P*	≥0.4 *n*: 13	<0.4 *n*: 17	*P*	Yes *n*: 20	No *n*: 10	*P*
General health ±SD	66.6 15.2	67.7 21.0	53.7 26.8	70 20	0.771	52.5 12.5	69.6 21.5	0.102	54.4 12.3	77.2 21.9	0.013*	65 27.8	65 18.7	0.849
General vision ±SD	60.0 17.3	70 21.6	35 12.2	65 35	0.112	68.7 33.7	59.2 22.5	0.487	60.5 26.1	62.2 24.5	0.859	49 20.1	64.2 25.1	0.284
Ocular pain ±SD	60.0 20	51.1 27.01	48.7 23.2	61.2 25.9	0.774	59 23	53.2 25.3	0.604	59 25.4	50 23.3	0.454	46 31.1	56.6 21.5	0.351
Near vision ±SD	83.3 28.8	82.2 16.2	62.5 25	71.2 32.2	0.503	68 27.9	81 20.7	0.340	79 24.8	76.1 21.7	0.644	70 18.7	78.3 24.5	0.346
Distance vision ±SD	93.3 11.5	83.3 19.2	82.5 20.6	80 21.6	0.772	71 15.9	90.3 15.7	0.024*	83 18.1	87.7 17.8	0.517	87 13.9	83 19.6	0.891
Social functioning ±SD	100 0	81.6 26.6	93.7 12.5	72.5 32	0.371	64 25	91.4 20.42	0.030*	80 24.03	88.8 25.3	0.203	93 10.9	82.3 26.7	0.730
Mental health ±SD	66.6 11.5	72.7 32.8	65 30	56.2 28.09	0.730	38 24.6	79.2 20.1	0.008*	65 34.9	72.2 18.5	0.834	76 21.9	64 29.6	0.475
Role difficulties ±SD	83.3 15.2	75.5 27.5	81.2 37.5	72.5 27.5	0.818	53 24.3	84.2 22.8	0.022*	71 26.1	81.6 27.6	0.240	78 31.3	77 25.8	0.928
Dependency ±SD	93.3 11.5	83.8 27.8	87.5 25	75 43.3	0.975	63.7 33	89.6 23.2	0.057	83.8 27.8	83.8 27.8	1.0	90 22.3	82.8 28.3	0.536
Color vision ±SD	100 0	88.3 20.6	93.7 12.5	87.5 25	0.750	86 21.9	92.1 17.5	0.51	90.5 17	90.5 20.6	0.83	95 11.1	89.6 19.8	0.731
Peripheral vision ±SD	86.6 23	83.8 16.9	77.5 20.6	72.5 25	0.660	74 19.4	83.2 17.4	0.358	82.5 17.8	78.8 19	0.73	74 13.4	83 18.4	0.315
Overall composite score ±SD	82.6 12.7	77 15.9	72.7 17.6	67.8 25.1	0.682	61.9 17.7	80.2 15.4	0.042*	74 17.6	77 18.5	0.462	75.4 15.9	75.1 18.1	0.760

($P = 0.007$; $r = 0.490$) and peripheral vision ($P = 0.003$; $r = 0.531$), and total score ($P = 0.0$; $r = 0.699$). While, visual acuity in the worse eye correlated with general health ($P = 0.024$; $r = 0.425$), general vision ($P = 0.01$; $r = 0.472$), social function ($P = 0.038$; $r = 0.387$), mental health ($P = 0.007$; $r = 0.490$), role difficulties ($P = 0.025$; $r = 0.416$), and total score ($P = 0.007$; $r = 0.493$). No correlation was observed between the low contrast visual acuity and the parameters tested ($P > 0.05$).

Education level showed a negative correlation with social function ($P = 0.02$; $r = 0.496$), dependency ($P = 0.02$; $r = -0.516$), color vision ($P = 0.006$; $r = -0.594$), and peripheral vision ($P = 0.02$; $r = 0.498$).

4. Discussion

Keratoconus is an ectatic corneal disorder characterized by progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and decreased vision. Despite intensive clinical and laboratory investigation, the etiology of keratoconus remains unclear. Classic histopathologic features include stromal thinning, iron deposition in the epithelial basement membrane, and breaks in Bowman's layer. Contact lenses are the most common treatment modality. When contact lenses fail, corneal transplant is the best and most successful surgical option [1].

NEI-VFQ-25 is a vision-targeted questionnaire; meanwhile it includes items that capture concerns about the future, fear, and anxiety [10, 22]. The multidimensional nature of the NEI-VFQ-25 subscales is designed to capture the impact of visual problems on physical functioning, emotional well-being, and social functioning.

VR-QoL scores may be expected to be different in the keratoconus patients from the normal people. There are a few previous reports about the impact of keratoconus on NEI-VFQ-25 scales. Collaborative longitudinal evaluation of keratoconus (CLEK) study [21] examined the VR-QoL of keratoconus patients. Their results showed that binocular entrance visual acuity worse than 20/40 was associated with lower VR-QoL scores on all scales except general health and ocular pain. A steep keratometric reading (average of both eyes) >52 D was associated with lower scores on the mental health, role difficulty, driving, dependency, and ocular pain scales. Scores for CLEK patients on all scales were between patients with category 3 and category 4 except general health, which was better than AMD patients, and ocular pain, which was worse than AMD patients. Keratoconus is associated with significantly impaired VR-QoL that continues to decline over time. CLEK patients were followed up for seven years and estimated modest decline in all scales except ocular pain and mental health. A 10-letter decline in high-contrast binocular visual acuity or a 3.00 D increase in corneal curvature was associated with significantly larger declines [23].

Tatematsu-Ogawa et al. [24] evaluated VR-QoL in 45 Japanese keratoconus patients by using the Japanese version of the NEI-VFQ-25. In patients with keratoconus including those with normal visual acuity, all NEI-VFQ-25 subscale scores were significantly lower ($P < 0.05$) than the control subjects. Subscales evaluating general health, ocular pain, and vision-specific mental health showed particularly low values. Among patients with keratoconus, every subscale score other than color vision correlated with corrected visual acuity.

In our study, all subscales of NEI-VFQ-25 were lower in the keratoconus group similar to previous studies. The difference was more evident in the subscales of general vision, ocular pain, near vision, vision-specific mental health, vision-specific role difficulties, and peripheral vision ($P < 0.05$). Overall composite score was 75.2 ± 17.2 in the keratoconus group and 93.2 ± 5.6 in the control group ($P = 0.00$).

The NEI-VFQ-25 subscale item scores did not show significant differences according to keratoconus grades, contact lens use, and gender, while the visual acuity showed significant differences. Patients with low visual acuity (logMAR visual acuity of 0.4 or worse) in the better eye had significantly lower distance vision, social functioning, mental health, role difficulties, and overall composite score ($P < 0.05$). Meanwhile, patients with low visual acuity (logMAR visual acuity of 0.4 or worse) in the worse eye had significantly lower general health scores compared to patients with high visual acuity (logMAR visual acuity of 0.3 or better).

In our study, when the sample was divided into mild (grade I), moderate (grade II), and severe (grades III and IV) keratoconus cases, overall composite scores were 82.6 ± 12.7, 77.0 ± 15.9, 72.7 ± 17.6, and 67.8 ± 25.1 for keratoconus grades I, II, III, and IV, respectively. Overall composite scores seem to be decreased with advancing keratoconus grades, although our study contain only a small number of patients in each in each keratoconus group to obtain significative conclusions.

The general health question is treated as a stand-alone-list-item, because it is a robust marker of overall health status in many population-based studies and provides a comparative benchmark for groups of persons who complete the NEI-VFQ-25. In our study, general health score was 65.0 ± 20.6 in keratoconus group and 79.7 ± 15.8 in control group ($P = 0.030$). Interestingly, vision in the worse eye ≥ 0.4 logMAR had a significantly decreased general health score compared to patients with <0.4 logMAR vision.

NEI-VFQ results revealed differences in gender in self-reported difficulty with distance activities and driving in CLEK study. Women were more likely than men to report ocular symptoms of dryness and complaints based upon a composite score of ocular symptoms. Gender differences may exist in patient history, vision, and ocular symptoms in keratoconus patients [25].

In keratoconus patients who have undergone penetrating keratoplasty in one or both eyes VR-QoL remains impaired despite satisfactory results on visual outcome measures obtained [26]. Significantly lower NEI-VFQ scores are reported in postkeratoplasty keratoconus patients compared to CLEK historical control group for the subscales of role difficulties, dependency, driving, and peripheral vision. In general, scores of that study were between scores of patients with AMD categories 3 and 4. Patients with visual acuity better than 20/40 (in the better eye) showed significantly higher scores in all subscales except color vision [15].

It has been shown that keratoconus exerts a significant impact on keratoconus patients' VR-QoL, even in its early stages (grade I) with normal best-spectacle-corrected visual acuity compared to contact lens users without keratoconus. Corneal collagen crosslinking (CXL) and CXL combined with topography-guided photorefractive keratectomy (tCXL) have been shown to exert a beneficial impact on self-reported VR-QoL. Significant differences were detected in "mental health" and "dependency" VFQ-25 domains for both the CXL and tCXL groups ($P = 0.05$). Furthermore, the tCXL group demonstrated significant differences in the "near activities" ($P = 0.04$), "role limitations" ($P = 0.02$), and "driving" ($P < 0.01$) subscale scores in a study by Labiris et al. [27].

Contact lenses are one of the better solutions to correct refractive errors induced by keratoconus. Contact lens fitting on a conical cornea smooths out the highly irregular optical surface of the cornea and improves visual acuity considerably. The quality and quantity of vision is far better than with spectacle lens correction [28]. Success in the contact lens usage in the keratoconus patients may increase the visual acuity and vision related quality of life. In a study evaluating keratoconus patients using rigid gas permeable lenses, the NEI-VFQ-25 overall score was 79.2 and keratoconus was associated with lower scores in dependency, mental health, and ocular pain categories [29]. In our study, NEI-VFQ-25 overall score was 75.4 in the keratoconus group of contact lens users. Although not significantly different ($P > 0.05$), the NEI-VFQ-25 subscale scores of distance vision, vision-specific mental health, role difficulties, social functioning and dependency, and color vision subscale scores of the patients using contact lenses were better than the patients who do not use contact lenses. Meanwhile general vision, ocular pain, near vision, and peripheral vision scores were worse in the patients using contact lenses ($P > 0.05$).

Lee et al. [30] has demonstrated previously the importance of eye symptoms to general HR-QoL using the short form-36 version. Trouble seeing and blurred vision both had statistically unique associations with worse scores on the HR-QoL, while the presence of eye diseases, such as glaucoma, cataract, and macular degeneration, did not have an association after adjusting for other variables in the model. Similarly, vision in the better eye was the most significant parameter affecting VR-QoL in the keratoconus group of patients in our study.

Main limitation of our study is small sample size. Large sized prospective studies comparing treatment options of keratoconus including different types of contact lenses may be helpful in the future. As a conclusion, keratoconus patients have a decreased vision related quality of life as demonstrated by the NEI-VFQ-25 when compared to the controls. As the patients with keratoconus are generally young adults in their active years, to understand their concerns about their future is an important public health aspect that can be used to modify their treatments.

Our results suggest that vision in the best eye is the most important parameter affecting VR-QoL of the patients with

keratoconus. Keratoconus patients should maintain their best vision that they can have. Success in the contact lens usage and maintaining higher visual acuity in the keratoconus patients may improve VR-QoL.

Conflict of Interests

The authors report no conflicts of interests and have no proprietary interest in any of the materials mentioned in this paper.

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Clinical Study

Treatment of Corneal Neovascularization Using Anti-VEGF Bevacizumab

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Purpose. To evaluate antiangiogenic effect of local use of bevacizumab (anti-VEGF antibody) in patients with corneal neovascularization. *Methods*. Patients were divided into two groups. All patients suffered from some form of corneal neovascularization (NV). Patients in group A received 0.2–0.5 mL of bevacizumab solution subconjunctivally (concentration 25 mg/mL) in a single dose. Group A included 28 eyes from 27. Patients in group B applied bevacizumab eye drops twice daily (concentration 2.5 mg/mL) for two weeks. Group B included 38 eyes from 35 patients. We evaluated the number of corneal segments affected by NV, CDVA, and the incidence of complications and subjective complaints related to the treatment. The minimum follow-up period was six months. *Results*. By the 6-month follow-up, in group A the percentage reduction of the affected peripheral segments was 21.6% and of the central segments was 9.6%; in group B the percentage reduction of the central segments was 22.7% and of the central segments was 38.04%. In both groups we noticed a statistically significant reduction in the extent of NV. *Conclusion*. The use of bevacizumab seems to be an effective and safe method in the treatment of corneal neovascularization, either in the subconjunctival or topical application form.

1. Introduction

Corneal transparency is determined by many factors including avascularity. Since the year 1872, when Arnold demonstrated that the process of angiogenesis utilizes the striae of intracellular cement for neovascularization (NV) formation in the cornea [1], the results of new research examining the process of new vessel formation in the cornea have been published [2, 3]. Recent research has focused on understanding the mechanisms that keep the cornea avascular under homeostatic conditions and that provide an avascular healing process. These studies agree that corneal angiogenic privilege includes several active cascades and therefore is not a passive process [4–7].

Corneal NV is the pathological ingrowth of vessels to the cornea from the limbal vascular plexus. This process is the result of the chronic reduction of oxygen in the cornea. Physiologically oxygen is absorbed from the air. Other reasons for the formation of pathological vessels in cornea are corneal infections, trauma, and immunological processes. Corneal NV can be asymptomatic, but more often it results in severe visual disorders, and in some cases in practical blindness because of unfavorable corneal opacification. Common available therapy is limited to removing the primary cause of new vessel formation in the cornea, local application of corticosteroids, laser photocoagulation of bigger vessel strains, and corneal transplantation in extreme cases [3].

Many stimulators and inhibitors regulating the hemangiogenesis were isolated in vitro. Factors from the Vascular Endothelial Growth Factor (VEGF) family were shown to be the primary mediators of this process [8]. VEGF was originally identified as a stimulator of vascular permeability (called VPF (Vascular Permeability Factor)) but subsequently has been shown to be a mitogen and angiogenic factor, especially for endothelial cells. After VEGF isolation, further isolated factors from the VEGF family were named VEGF-B, VEGF-C, and VEGF-D. The original form is currently called VEGF-A. VEGF factors are a part of the VEGF/PDGF (platelet-derived growth factor) supergene family [6, 9, 10]. VEGF-A binds to the VEGFR-1 and VEGFR-2 receptors and

its expression is strictly regulated [11]. Increased production of VEGF-A was observed in cases of hypoxia and during inflammation. Overproduction of VEGF-A was observed in tumor cell proliferation, similarly to corneal neovascularization formation. VEGF-A sustains several steps of angiogenesis including proteolytic activity, vascular endothelial cell proliferation, and migration and capillary lumen formation [10, 12]. The importance of VEGF-A in corneal angiogenesis was demonstrated experimentally on animal models by inhibiting NV after stromal application of an anti-VEGF-A antibody [13].

Bevacizumab (Avastin, Roche) is an antibody that acts against all isoforms of VEGF. This molecule inhibits the interactions between VEGF and its receptors, blocking any VEGF activity [14]. Bevacizumab is currently approved for the treatment of colorectal carcinoma, mamma carcinoma, non-small-cell lung carcinoma, and renal carcinoma. It is widely used "off label" for the treatment of choroidal neovascularization secondary to age related macular degeneration [15].

2. Materials and Methods

The case series was performed at the Ophthalmology Department of the 3rd Medical Faculty and University Hospital Kralovske Vinohrady, from December 2007 to June 2011. "Off label" use of bevacizumab for the treatment of corneal NV in both application forms was approved by the local Ethics Committee of University Hospital Kralovske Vinohrady. The tenets of the Declaration of Helsinki were followed and all patients gave their informed consent before enrolling.

The study was designed as a prospective, nonrandomized, and noncomparative case series. The patient groups included 66 eyes from 62 patients, 35 women and 27 men, aged from 19 to 84 years. All patients had a certain form of corneal NV. The aim of this study was to evaluate the antiangiogenic effect of the subconjunctival and topical application of anti-VEGF antibody bevacizumab on several diseases related to corneal neovascularization.

Patients were divided into groups A and B according to the means of application of bevacizumab. Patients in group A received a single-dose injection of 0.2–0.5 mL of bevacizumab subconjunctivally using an insulin syringe after applying topical anesthetic eye drops (oxybuprocaine 0.4%, tetracaine 0.1%) for 15 minutes. The concentration of the bevacizumab solution used for group A was 25 mg/mL. Group A included 28 eyes from 27 patients, 17 women and 10 men, with a mean age of 60 years (27–84). Patients in group B applied bevacizumab eye drops twice daily for two weeks. The concentration of the bevacizumab solution used for group B was 2.5 mg/mL. Group B included 38 eyes from 35 patients, 18 women and 17 men, with a mean age of 63.5 years (19–79). The minimum follow-up time was six months. The reason for dividing patients into 2 groups was the fact that we started using bevacizumab subconjunctivally the first year but continued to use eye drops topically in order to improve patient's comfort, while maintaining the same efficiency.

The patients were further divided into 4 subgroups according to the primary cause of corneal NV. Subgroup 1 included patients with pterygium; subgroup 2 included patients with NV on a donor disc after penetrating keratoplasty; subgroup 3 included patients with other ocular pathology (corneal leucoma after alkali burns, vascularized scars after corneal ulcers, NV after herpetic keratitis, and Stevens-Johnson syndrome or corneal NV of another etiology); and subgroup 4 included patients under preparation for high-risk penetrating keratoplasty (Table 1). Patients in subgroup 4 had a shorter follow-up time because of following surgery maximum 3 months after treatment. These patients were excluded from overall statistics.

Table 1: Distribution of patients into groups A and B and subgroups 1, 2, 3, and 4.

		Group A	Group B
1	Pterygium	6	12
2	NV after penetrating keratoplasty	8	6
3	Alkali burn	3	1
	Vascularized scar after corneal ulcer	3	2
	NV after herpetic keratitis	1	2
	Stevens-Johnson syndrome	2	1
	Other etiology	4	9
4	Preparation for penetrating keratoplasty	1	5

Before initiation of the treatment, all patients underwent a standard slit lamp ophthalmologic examination of the anterior and posterior segments of the eye. Corrected distance visual acuity (CDVA) and intraocular pressure were measured. The follow-up examinations were performed in both groups the first, third, and sixth months after the treatments were started. Changes in corneal neovascularization were documented on digital photographs during each visit (SONY DXC-950P, 3CCD color video camera, Japan).

We used a special pattern to evaluate the extent of and change in corneal NV. These details were attached to the digital photograph of the cornea of each patient (Figure 1). The total diameter of the pattern was 12 mm with a central 6 mm zone. It consisted of 96 triangular segments of identical size, 72 peripheral segments (PS), and 24 central segments (CS). The extent of corneal NV was expressed in the number of segments containing blood-filled vessels. We evaluated the number of corneal segments affected by NV, CDVA, and the incidence of complications and subjective complaints related to the treatment. The evaluation of the masked photographs was done by a single doctor.

Each patient was treated with at least one application of the substance. Repeated treatment was not indicated before the first month following the first application of bevacizumab. We decided to repeat the treatment in the case of either a positive response to the first application, in order to achieve further regression of the NV, or a recurrence of corneal NV.

Using the SPSS Statistics program (version 19.0; SPSS, Inc., Chicago, IL, USA), a one-way ANOVA was performed for the purpose of statistical analysis. A P value below 0.05 was considered statistically significant.

Table 2: Results of separate subgroups of group A before and 6 months after initiation of treatment; mean number of affected peripheral (PS) and central segments (CS) of neovascularization; corrected distance visual acuity (CDVA).

		Before treatment			6 months after treatment (1 month in group 4)			
		CDVA	PS	CS	CDVA	PS	CS	*P*
1	Pterygium ($n = 6$)	**0.85** (±0.21)	**8.5** (±5.12)	**0**	**0.9** (±0.18)	**6.66** (±4.49)	**0**	PS: 0.03 CS: 0.2
2	NV after penetrating keratoplasty ($n = 8$)	**0.02** (±0.04)	**41.25** (±17.42)	**1.75** (±1.78)	**0.05** (±0.08)	**30.5** (±11.37)	**1.25** (±1.45)	PS: 0.001 CS: 0.02
3	Other etiologies ($n = 13$)	**0.14** (±0.17)	**33.77** (±25.16)	**7.76** (±6.76)	**0.16** (±0.21)	**27.61** (±19.78)	**7.23** (±6.99)	PS: 0.000 CS: 0.002
4	Preparation for penetrating keratoplasty ($n = 1$)	**0.0001**	**14**	**0**	**0.001**	**7**	**0**	

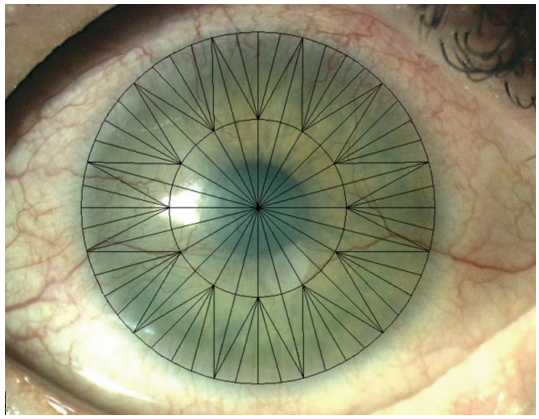

Figure 1: Pattern for the evaluation of the corneal neovascularization.

3. Results

3.1. Subconjunctival Injection of Bevacizumab: Group A. The mean number of affected peripheral segments and of central segments before the treatment that was initiated in group A was 30.37 (±23.40)—42.18% and 4.26 (±5.92)—17.75%, respectively. The mean corrected distance visual acuity (CDVA) before the treatment was 0.26 (±0.35). One month after the first bevacizumab subconjunctival injection, the mean number of affected peripheral segments and of central segments was reduced to 25.65 (±20.4)—35.63% ($P = 0.003$) and 3.42 (±5.44)—14.25% ($P = 0.001$), respectively. The mean number of repeated bevacizumab injections in group A was 2.07 (1–4). At six months after initiation of the treatment, the mean count of the peripheral segments and of the central segments was 23.81 (±17.80)—33.07% ($P = 0.000$) and 3.85 (±5.92)—16.04% ($P = 0.000$), respectively. The resulting mean CDVA was 0.28 (±0.36). The results of the separate subgroups are summarized in Table 2 and Figure 4.

The number of segments affected by corneal neovascularization at the one-month and six-month follow-ups compared with the number of segments before the treatment was statistically significantly lower.

Almost all of the patients tolerated the injection without any complaints, with the exception of patients who had experienced a chemical burn. Chemical-burn patients reported that the subconjunctival injection was very painful, even after the repeated application of anesthetic eye drops (oxybuprocaine 0.4%, tetracaine 0.1%).

We did not notice the progression of NV immediately after the injection in any of the patients in group A. We observed progression of NV in three eyes after initial regression. After further injections of bevacizumab, the NV reduced again in all three eyes. Picture 2 shows corneal NV in a patient treated with subconjunctival bevacizumab.

3.2. Topical Application of Bevacizumab: Group B. The mean number of affected peripheral segments and of central segments before the initiation of the treatment in group B was 27.94 (±20.29)—38.81% and 2.97 (±4.88)—12.38%, respectively. The mean corrected distance visual acuity (CDVA) before treatment was 0.55 (±0.42). One month after the topical application of the bevacizumab solution, the mean number of affected peripheral segments and of central segments reduced to 24.5 (±19.3)—34.07% ($P = 0.000$) and 1.97 (±3.59)—8.2% ($P = 0.000$), respectively. The mean number of repeated topical bevacizumab treatments in group B was 1.16 (1-2). At six months after initiation of the treatment, the mean count of peripheral segments and of central segments was 21.60 (±18.21)—30% ($P = 0.000$) and 1.84 (±3.79)—7.67% ($P = 0.000$), respectively. The resulting mean CDVA was 0.57 (±0.41). The results of the separate subgroups are summarized in Table 3 and Figure 5. Statistical analysis shows significant differences between the results at one-month and six-month follow-ups, compared with the number of affected segments before initiation of the treatment.

We noticed progression of NV immediately after the topical treatment in one patient with NV after a herpetic corneal ulcer. One month after discontinuing topical treatment, the NV regressed dramatically compared with the pretreatment

Table 3: Results of separate subgroups of group B before and six months after initiation of treatment; mean number of affected peripheral (PS) and central segments (CS) of neovascularization; corrected distance visual acuity (CDVA).

					6 months after treatment (1 month in group 4)			
		CDVA	PS	CS	CDVA	PS	CS	P
1	Pterygium ($n = 12$)	**1.0** (±0.02)	**12.75** (±9.91)	**0.25** (±0.82)	**1.0** (±0.02)	**9.0** (±4.08)	**0**	PS: 0.003 CS: 0.000
2	NV after penetrating keratoplasty ($n = 6$)	**0.06** (±0.04)	**35.5** (±20.13)	**0.83** (±1.21)	**0.12** (±0.13)	**28.0** (±23.12)	**0.33** (±0.74)	PS: 0.002 CS: 0.000
3	Other etiologies ($n = 15$)	**0.58** (±0.32)	**37.0** (±21.49)	**3.4** (±4.01)	**0.59** (±0.32)	**29.53** (±18.73)	**2.53** (±3.98)	PS: 0.000 CS: 0.000
4	Preparation for penetrating keratoplasty ($n = 5$)	**0.05** (±0.07)	**28.2** (±12.37)	**10.8** (±6.65)	**0.05** (±0.08)	**20.40** (±14.25)	**6.0** (±5.62)	PS: 0.02 CS: 0.001

level. In six eyes, we repeated the treatment three months after initiation because of repeated progression of corneal NV. All patients in subgroup B1 (pterygium) showed significant improvement in subjective complaints, that is, itching, a sense of the presence of a foreign body, cosmetically annoying redness of the eye.

4. Complications

We detected a systemic complication in only one patient from group A. It manifested itself 12 hours after the subconjunctival injection in overall weakness, headaches, and upper extremity paresthesia. These symptoms corrected themselves without any intervention, and we attributed them to a panic attack on behalf of the patient as a reaction to the treatment. Due to the patient's excellent local response to the treatment, we decided to continue the treatment of subconjuntival bevacizumab injections. The subsequent applications passed without complication. As for local complications, we observed tiny epithelial corneal defects in three patients in both groups A and B. The defects were completely healed after intensification of lubrication therapy. We detected hypersensitivity reactions in two patients from group B. In both cases, this reaction appeared on the third day after the initiation of the treatment. It manifested itself in eyelid edema and conjunctival hyperemia with a papillary reaction. Within two days, this condition was resolved in both cases by discontinuing the bevacizumab eye drops and replacing them with a treatment of fluorometholone acetate. We did not indicate any further treatment of bevacizumab eye drops in these two cases.

5. Discussion

The most current knowledge with regard to understanding the mechanism of ocular NV has led to the identification of new pharmacological goals. As VEGF plays a crucial role in the creation of corneal NV, its treatment with anti-VEGF antibodies seems to be the right method [7, 16, 17]. Several publications with this topic have already been published. Both subconjunctival injections [18, 19] and the topical use of bevacizumab [20–23] were experimentally used with promising results in treatment of herpetic keratitis [24, 25], recurrent pterygium [23, 26], corneal transplant rejection [19], and Stevens-Johnson syndrome [27]. The publications referred mostly to a small series of patients who had not undergone a uniform treatment scheme. Some authors reported the excellent effects of the anti-VEGF bevacizumab antibody in inhibiting and regressing corneal NV [18, 22, 24, 27]. No regression of corneal vascularization was observed in 2 studies involving cases of recurrent pterygium and corneal transplant rejection, after penetrating keratoplasty [28, 29]. Other studies proved some degree of regression of vessels from the affected cornea [19, 23, 30]. Complications were described in only a few studies, and always as superficial epithelopathy, tiny epithelial defects, or progressions of corneal thinning [22]. The reason for these adverse effects may be the fact that VEGF supports the growth of neural fibers and its blocking reduces the reparation of corneal nerves [31].

In our series we observed improvements immediately following the initiation of the treatment in the majority of patients and a stabilization of findings in all patients for a minimum of three months (Figures 2 and 3). Treatments using the anti-VEGF antibody bevacizumab provided statistically significant results. In all patients, we observed either an improvement in or stabilization of the corneal neovascularization. In both groups, mean visual acuity at the final follow-up had improved compared with the initial one. If there was any recurrence, we indicated another application of the bevacizumab treatment. With this regimen, we have been successful in keeping all monitored patients free of complaints for a long time. According to the particular cases with a longer follow-up (up to 15 months) and to the average number of retreatments in both study groups, the effect of the topical treatment seems to be more stable, without the need to repeat the treatment. Since the study was noncomparative, it is necessary to prove the hypothesis by means of a comparative study and on a larger group of patients.

We are convinced, based on the results of our study that the use of bevacizumab in the treatment of active corneal neovascularization could be beneficial. It may also be useful in high-risk keratoplasty, with regard to preoperative preparation and postoperative care. Thanks to the anti-VEGF antibodies, the blood vessels which can lead to corneal graft rejection are held beyond the corneal graft border. Our experience has shown that the use of bevacizumab seems

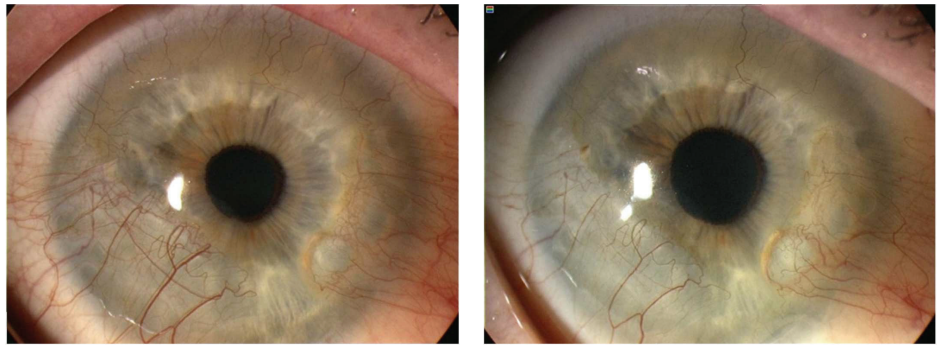

Figure 2: Representative case of corneal neovascularization treated with subconjunctival injection of bevacizumab. Patient was a 63-year-old female with chronic keratoconjunctivitis and rheumatoid arthritis. The baseline photograph shows circumferential (360 degrees) neovascularization (NV) of cornea (left). Six months after subconjunctival bevacizumab treatment, NV decreased significantly (right).

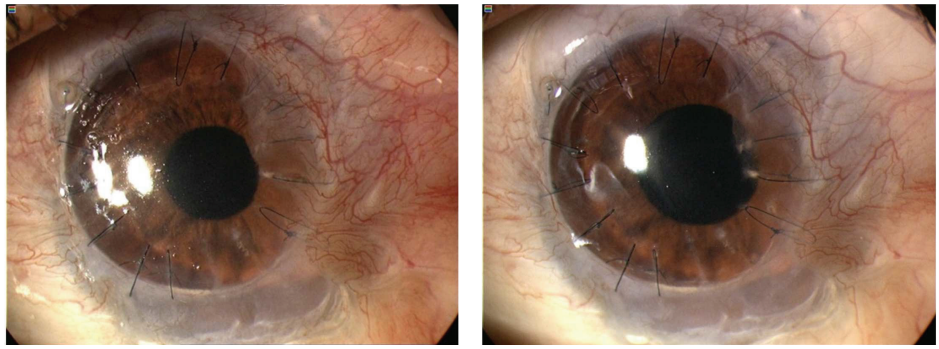

Figure 3: Representative case of corneal neovascularization treated with topical bevacizumab. Patient was a 19-year-old male who underwent penetrating keratoplasty combined with autologous limbal stem cell grafting for corneal leucoma after alkali burn. The baseline photograph shows active neovascularization (NV) reaching donor graft (left). Three months after topical bevacizumab treatment, NV decreased and is held on corneal graft border (right).

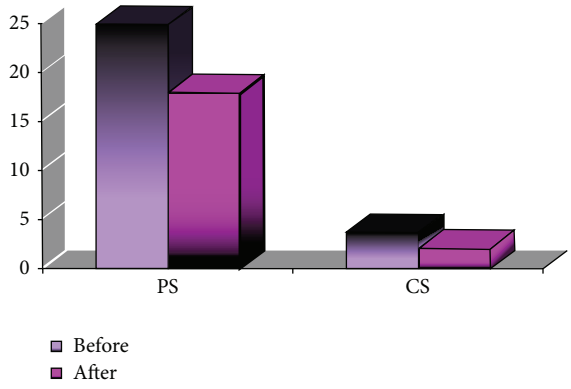

Figure 4: Comparison of affected peripheral (PS) and central (CS) segments before and after treatment in group A.

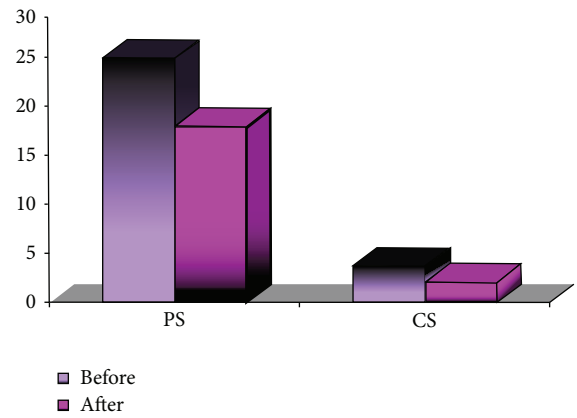

Figure 5: Comparison of affected peripheral (PS) and central (CS) segments before and after treatment in group B.

to benefit the complex treatment of pterygium by reducing subjective complaints and delaying surgical intervention. While in some cases retreatment was necessary due to the temporary worsening of local findings, retreatment led to improvement.

However, treating corneal NV with the anti-VEGF antibody bevacizumab does have some limits. It is only a symptomatic treatment of corneal NV that does not cure the cause of the disorder and in some cases it is necessary to repeat the treatment to maintain its positive effect over a period of time. In addition, its effect on deep vascularization is lower in contrast to superficial and active vascularization, in which clear regression is observed.

Another possible limiting factor is the fact that anti-VEGF antibodies affect only one group of angiogenic agents. It is clear that the maintenance of the avascular cornea is an active process that requires an accurate balance between angiogenic and antiangiogenic mechanisms [7]. The use of other antiangiogenic factors or angiogenic inhibitors has been investigated using in vitro and experimental animal research. For example, the use of anti-PDGF antibodies seems to be an excellent supplementary therapy for anti-VEGF antibodies or the strong antiangiogenic factor PEDF [32].

6. Conclusion

The use of bevacizumab seems to be an effective and safe method in the treatment of corneal neovascularization, either in a subconjunctival or topical application form. The minimal incidence of complications and negative side effects promise the future evolution of the treatment as well as its adoption into broader clinical practice. Other clinical studies are necessary in order to evaluate the drug's efficacy, dosage, and safety in every case of corneal neovascularisation.

Conflict of Interests

The authors declare that there is no financial or proprietary conflict of interests regarding any material or method mentioned in this paper.

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Clinical Study

Medium-Term Visual Outcomes of Apodized Diffractive Multifocal Intraocular Lens with +3.00 D Addition Power

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Purpose. To evaluate 2-year visual acuities and questionnaire after bilateral implantation of SN6AD1 multifocal intraocular lens (MIOL) or SN60WF IOL. *Methods*. Patients randomly scheduled for bilateral implantation of SN6AD1 MIOL and SN60WF IOL with 2-year follow-up were enrolled. Uncorrected/corrected distance and near visual acuity, uncorrected intermediate visual acuity at 63 cm under high and low contrast, reading activity, the defocus curve, and a quality-of-life questionnaire were evaluated. *Results*. Each group comprised 20 patients. Uncorrected intermediate visual acuities and uncorrected near visual acuity were better in SN6AD1 group than in SN60WF group ($P = 0.005$, $P = 0.011$, and $P < 0.001$). In SN6AD1 group, the uncorrected intermediate and near visual acuities 1 year and 2 years postoperatively were reduced than postoperative 3-month outcomes, respectively. SN6AD1 group reported superior overall spectacle independence and inferior satisfaction. SN6AD1 group had a longer reading newspaper duration than SN60WF group ($P = 0.036$). When using mobile phone, SN6AD1 group had a more comfortable distance than SN60WF group ($P < 0.001$) and higher speed of reading fixed text message ($P < 0.001$). *Conclusion*. SN6AD1 MIOL provided a satisfactory full range of visual acuities and questionnaire performance 2 years postoperatively. One-year and 2-year uncorrected near and intermediate visual acuities of SN6AD1 MIOL were lower than those 3 months postoperatively.

1. Introduction

Multifocal intraocular lens (MIOL) is considered a prevailing alternative to restore the functional vision from far to near independent of glasses. Many clinical studies on diffractive MIOLs [1–3], refractive MIOLs [4–6], or hybrid MIOLs [7–11] in enhancing quality of vision showed promising outcomes. AcrySof ReSTOR SN6AD1 MIOL was developed in 2008. So far, studies have confirmed the satisfactory visual outcomes of SN6AD1 MIOL over a short period [12–15]. In our previous study, we found SN6AD1 MIOL provided a full range of functional visual acuity, reading ability, and high patient satisfaction in spite of a relatively more undesired visual disturbance [16–18]. However, to the best of our knowledge, no medium-term or long-term studies of this type of MIOL are available.

The purpose of this study was to assess the visual performance 2 years after cataract surgery with bilateral implantation of SN6AD1 MIOL. SN60WF IOL, being of the same material and aspherical optic design, was used as the control.

2. Material and Methods

The prospective, random study was approved by the ethics committee of our hospitals and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients after the nature and possible consequences of the study were explained. Forty consecutive patients (80 eyes) who had sequential bilateral cataract extraction and IOL implantation from January 2011 to May 2011 were included in this study. SN6AD1 group and SN60WF group were divided

according to the types of IOL implanted. Patient selection was continued until 20 patients scheduled for multifocal SN6AD1 IOL implantation and 20 patients scheduled for SN60WF IOL implantation were enrolled.

The inclusion criteria were age between 50 and 78 years, corneal preoperative astigmatism less than 1.0 D, and availability for postoperative examinations. Exclusion criteria included diseases other than cataract (severe systemic diseases, amblyopia, corneal diseases, uveitis, retinopathy, or glaucoma), history of ocular surgery, and astigmatism greater than 1.0 D. The intraoperative exclusion criteria were significant vitreous loss with inability of in-the-bag IOL implantation and anterior chamber hyphema.

The target refraction was −0.25 D to +0.25 D for both IOL groups. The SRK-T or Haigis formula was used for IOL power calculations according to the axis length.

2.1. Surgical Technique. All surgeries were performed by only one experienced surgeon using phacoemulsification with the Infiniti Vision System (Alcon). After topical anaesthesia with Alcaine 0.05% and a temporal 3.0 mm clear corneal incision, a central continuous curvilinear capsulorhexis approximately 5.5 mm in diameter was created. Phacoemulsification with torsional ultrasound was followed by irrigation and aspiration of the cortex and IOL implantation in the capsular bag using a Monarch II injector (Alcon, Inc.). The position of IOL postoperatively was detected by slit-limp microscopy imaging system with maximum pupil dilation. Anterior Segment Optical Coherence Tomography will be needed if necessary.

2.2. Main Outcome Measures. All patients had examinations over a 2-year follow-up period after surgery. Postoperative evaluations were performed at 1 day, 1, 3, and 6 months, and 1 and 2 years. Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), uncorrected near visual acuity (UNVA), corrected near visual acuity (CNVA), uncorrected intermediate visual acuity (UIVA) with high and low contrast at 63 cm, binocular defocus curve, and reading performance were measured. A patient satisfaction and visual phenomenon questionnaire was administered.

ETDRS chart was used to measure UDVA and CDVA at 4 m and UNVA and CNVA at 35 cm. UIVA under high contrast (100% contrast) and low contrast (10% contrast) at 63 cm was tested using Colenbrander Mixed Contrast Card Set (Precision vision, USA) in all eyes. A cord on each card ensured that the viewing distance was maintained accurately. The intermediate visual acuity at 63 cm was recorded when at least 4 high-contrast or low-contrast targets in each card were identified correctly.

Binocular defocus testing was performed using a 100% contrast ETDRS chart at 4 m under photopic conditions. Manifest refraction was used to designate the zero baselines. A defocus of −5.00 D spherical correction from the corrected distance visual acuity (manifest refraction) was set; the decimal equivalent acuity at this refraction was recorded. Negative spherical power was decreased in 0.50 D increments, with decimal equivalent acuity recorded at each change in correction until only manifest refraction remained. Then, a defocus of +2.00 D spherical correction from the manifest refraction was set and the decimal equivalent acuity was recorded. Positive spherical power was decreased in 0.50 D increments, with decimal equivalent acuity recorded at each change in correction until only manifest refraction remained. The depth of focus was calculated as half the values of visual acuity better than 0.3 LogMAR at different defocus values.

Reading speed was tested at the preferred reading distance using the same text with a 12-point print size and 1.5 line spacing, in accordance with the Radner Reading Charts. Patients were asked to read the same text binocularly as quickly and accurately as possible. The reading time and reading distance were recorded.

A patient satisfaction and visual phenomena questionnaire [11] was administered 2 years postoperatively. Patients rated satisfaction with their vision on a scale from 1 to 10 (1 = incapacitating; 10 = excellent). Patients also rated the incidence of visual phenomena (e.g., glare, halos) on the following scale: 0 = none; 1 = minimal; 2, 3, and 4 = moderate; 5 = severe. Patients' education was assessed from 1 to 5 (1 = primary; 2 = junior; 3 = senior; 4 = college; 5 = university). In addition, patients' reading habit was questioned, including daily reading duration and the percentage of just reading newspaper title.

3. Statistical Analysis

All visual acuity values were converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. Results were expressed as means ± standard deviation. Statistical analysis was performed using SPSS advanced statistical 13.0 software (SPSS Inc.). The Shapiro-Wilk test was used to check normality. The t-test or Mann-Whitney U test was used to compare the 2 groups. Differences were considered statistically significant when the P value was less than 0.05.

4. Results

Forty patients had all scheduled examinations. The patients' demographics were shown in Table 1. After cataract extraction and in-the-bag IOL implantation, the pupils of all patients were round and showed good responsiveness to light; there was no case of iris trauma. All IOLs were well centered with no obvious tilt or decentration. Two years postoperatively, spherical diopter was (−0.09 ± 0.40) D versus (−0.02 ± 0.42) D, respectively (range (−0.75~0.75) D versus (−0.50~0.75) D, resp.) (P = 0.636). Cylinder diopter was (−0.17 ± 0.49) D versus (−0.22 ± 0.51), respectively (range (−1~0.50) D versus (−1~0.75) D, resp.) (P = 0.561).

4.1. Visual Acuities. Table 2 shows the mean distance, intermediate, and near visual acuities 2 years after surgery. The UDVA was 20/25 or better in 72.5% of eyes in SN6AD1 group and in 92.5% of eyes in SN60WF group. But the percentage of CDVA 20/25 or better increased to 90% in SN6AD1 group and

Table 1: Patients' characteristics preoperatively.

Characteristics	SN6AD1 group	SN60WF group	P value
Number of eyes	40	40	—
Male/female (n)	11/9	10/10	—
Age (y)			
Mean ± SD	69.1 ± 9.7	73.3 ± 4.9	0.090
Range	45–81	61–81	
IOL power (D)			
Mean ± SD	19.5 ± 1.0	19.2 ± 1.5	0.339
Range	18–21	17–21	
Axial length (mm)			
Mean ± SD	23.6 ± 0.6	23.7 ± 0.8	0.787
Range	22.5–24.8	22.4–25.3	
Keratometry (D)			
Mean ± SD	44.3 ± 1.9	43.9 ± 1.3	0.474
Range	39.2–47.9	40.5–45.8	

IOL: intraocular lens; D: diopter.

Table 2: The distance, intermediate, and near visual acuity (LogMAR) tested at 2 years postoperatively.

	SN6AD1 group	SN60WF group	Z	P
UDVA	0.041 ± 0.563	0.026 ± 0.850	−0.722	0.474
CDVA	−0.014 ± 0.682	−0.020 ± 0.965	−0.256	0.802
UIVA (100%)	0.163 ± 0.667	0.260 ± 0.702	−2.805	0.005
UIVA (10%)	0.396 ± 0.890	0.491 ± 0.964	−2.536	0.011
UNVA	0.111 ± 0.897	0.361 ± 0.798	−7.032	<0.001
CNVA	0.081 ± 0.959	0.088 ± 0.857	−0.618	0.554

UDVA: uncorrected distance visual acuity; CDVA: corrected distance visual acuity; UIVA: uncorrected intermediate visual acuity; UNVA: corrected near visual acuity.

100% in SN60WF group. However, there was no statistically significant difference between the 2 groups in mean UDVA ($P = 0.474$) or CDVA ($P = 0.802$).

All eyes in SN6AD1 group and 50% of eyes in SN60WF group achieved a UNVA of 20/40 or better, with 57.5% of eyes in SN6AD1 group and 0 in SN60WF group obtaining the UNVA of 20/25 or better. 85% in SN6AD1 group and 70% of eyes in SN60WF group gained CNVA 20/25 or better. SN6AD1 group acquired significantly better UNVA 0.111 ± 0.897 LogMAR than SN60WF group 0.361 ± 0.798 LogMAR ($P < 0.001$). But statistically significant difference was not found in mean CNVA between the 2 groups ($P = 0.554$).

The SN6AD1 group had statistically significant better UIVA at 63 cm under high and low contrast than SN60WF group ($P = 0.005$ and $P = 0.011$). In SN6AD1 group, 42.5% of eyes and 32.5% of eyes had a 20/25 or better high contrast UIVA and 20/40 or better low contrast UIVA, respectively. In SN60WF group, the percentages were 17.5% and 15%, respectively.

In terms of SN6AD1 MIOL, 1-year UDVA 0.039 Log MAR and 2-year UDVA 0.041 Log MAR were reduced significantly than postoperative 3-month UDVA −0.051 Log MAR ($P = 0.000$ and $P = 0.000$). Similarly, UNVA, UIVA (100%), and UIVA (10%) were statistically significantly lower than those

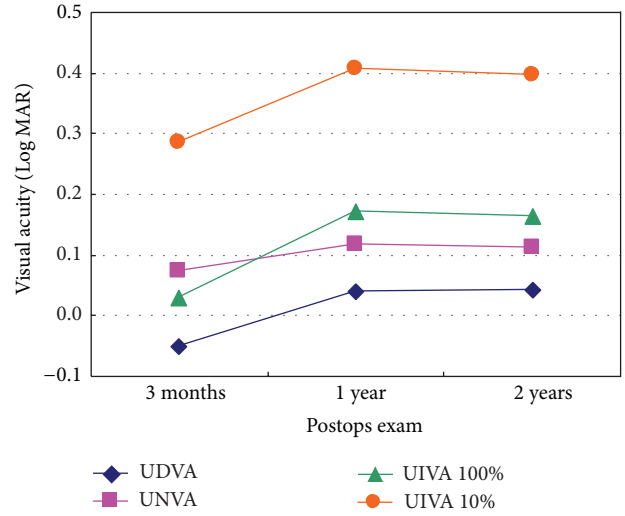

Figure 1: The change of UDVA, UNVA, UIVA (100%), and UIVA (10%) of SN6AD1 MIOL postoperatively.

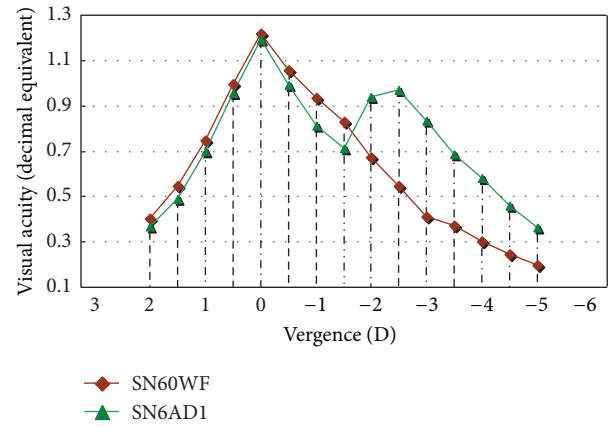

Figure 2: Mean defocus curve for SN6AD1 MOL and SN60WF IOL two years postoperatively. D = diopter.

of postoperative 3-month outcomes respectively ($P < 0.05$), while statistical significance was not found in UDVA, UNVA, UIVA (100%), and UIVA (10%) between 1-year and 2-year postoperatively in SN6AD1 group ($P > 0.05$) (Figure 1).

5. Defocus Curves

The mean binocular defocus curves in Figure 2 indicated that SN6AD1 MIOL provided an extended range of visual acuity from near to far. It was shown from the curves that both IOLs achieved approximately the same level of visual acuity at the distance peak (−0.076 LogMar). However, unlike a single distance point at 0 D in SN60WF group, a plateau of visual acuity from the vergence of −2.0 D to −2.5 D was found in SN6AD1 group, the equivalent of 40 cm to 50 cm from the eye. The depth of focus was 5.5 D in SN6AD1 group and 4 D in SN60WF group.

5.1. Preferred Reading Distance, Reading Speed, and Reading Habit. The preferred reading distance in both groups was

Table 3: Patients' reading habits.

	SN6AD1 group	SN60WF group	Z	P
Percentage of reading	20/20	16/20		
Daily reading newspaper duration (min)	99.00 ± 45.76	66.25 ± 45.88	−2.096	0.036
Just reading newspaper title (%)	5% (1/20)	31% (5/16)		
Percentage of using mobile phone	20/20	19/20		
Spectacle independence when using phone	20/20	19/19		
Difficulty in reading message	No (n = 20)	No (n = 19)		
Reading pint size	16.00 ± 1.45	16.21 ± 1.47	−0.457	0.670

Table 4: Results of patient satisfaction and visual phenomena questionnaire administered 2 years postoperatively.

Questions	Mean score* ± SD		P value
	SN6AD1	SN60WF	
How satisfied are you with your vision?	7.23 ± 1.33	7.95 ± 1.04	0.032
glare/halos	0.75 ± 0.85	0.15 ± 0.49	0.011
How much difficulty do you have with...			
watching TV?	0.05 ± 0.22	0.00 ± 0.00	1.000
reading and near work/activities?	0.00 ± 0.00	0.13 ± 0.34	0.190
cooking?	0.00 ± 0.00	0.00 ± 0.00	1.000
using a cell phone?	0.00 ± 0.00	0.00 ± 0.00	1.000
doing sports?	0.00 ± 0.00	0.00 ± 0.00	1.000
shopping?	0.00 ± 0.00	0.00 ± 0.00	1.000

*Scale for satisfaction with vision ranged from 1 to 10 (1 = incapacitating; 10 = excellent).
Scale for all other questions was 0 = none; 1 = minimal; 2, 3, and 4 = moderate; 5 = severe.

37.6 cm and 52.8 cm, respectively. SN6AD1 group had a higher speed of reading the fixed text message, (21.40 ± 1.70) s, than SN60WF group, (25.95 ± 2.59) s ($P < 0.001$). Patients' reading habits were shown in Table 3.

5.2. Patient Satisfaction and Visual Phenomena Questionnaire. The quality-of-life questionnaire showed a higher overall vision satisfaction in SN60WF group ($P = 0.032$) (Table 4). But both groups reported no difficulty in all distance activities such as reading, cooking, and shopping ($P > 0.05$) (Table 3). Both groups could perform distance jobs independent of glasses completely ($P = 1.000$), while the near ($P < 0.001$) and intermediate ($P < 0.05$) spectacle independence were higher in SN6AD1 group (Figure 3). Although glare and halo were more severe in SN6AD1 group 0.75 ± 0.85 than SN60WF group 0.15 ± 0.49 ($P = 0.011$), no patient required MIOL removal. Three eyes (7.5%) in SN6AD1 group had moderate glare as a result of posterior capsule opacification (PCO). The symptom glare/halo diminished to a mild level after Nd:YAG laser capsulotomy. SN6AD1 group had a more advanced education level ($P = 0.038$) and higher salary ($P = 0.022$) than SN60WF group (Table 5). SN6AD1 group had higher requirement for reading than that of SN60WF group.

Table 5: Patients' education level and job status.

	SN6AD1 group	SN60WF group	P
Education level*	3.65 ± 1.27	2.70 ± 1.42	0.038
High school or advanced	80% (16/20)	50% (10/20)	0.047
Working	30% (6/20)	10% (2/20)	0.235
Monthly salary over RMB 5000	80% (16/20)	45% (9/20)	0.022

*Education level: 1 = primary; 2 = junior; 3 = senior; 4 = college; 5 = university.

6. Discussion

To the best of our knowledge, study of the medium-term or long-term visual performance of SN6AD1 MIOL was not available. In the present study, SN6AD1 MIOL provided better uncorrected/corrected near and distance visual acuity, and uncorrected intermediate visual acuity 2 years postoperatively. SN6AD1 patients had a more comfortable reading distance, faster reading speed, and higher spectacle independence. Although SN6AD1 patients reported a higher incidence of glare and halo, the symptoms improved after Nd:YAG laser capsulotomy.

No comparison with previous studies can be made due to the lack of available long-term data on this type of IOL. However, the outcomes of SN6AD1 group can be compared with the information in our 3-month study for the same participants [16]. UDVA 0.041 LogMar 2 years postoperatively was lower than UDVA −0.051 LogMar 3 months postoperatively. Similarly, UNVA 0.111 LogMar, UIVA (100%) 0.163 LogMar, and UIVA (10%) 0.396 LogMar were inferior to those of 3 months postoperatively. These findings may indicate visual acuities of SN6AD1 MIOL have a decreasing trend over

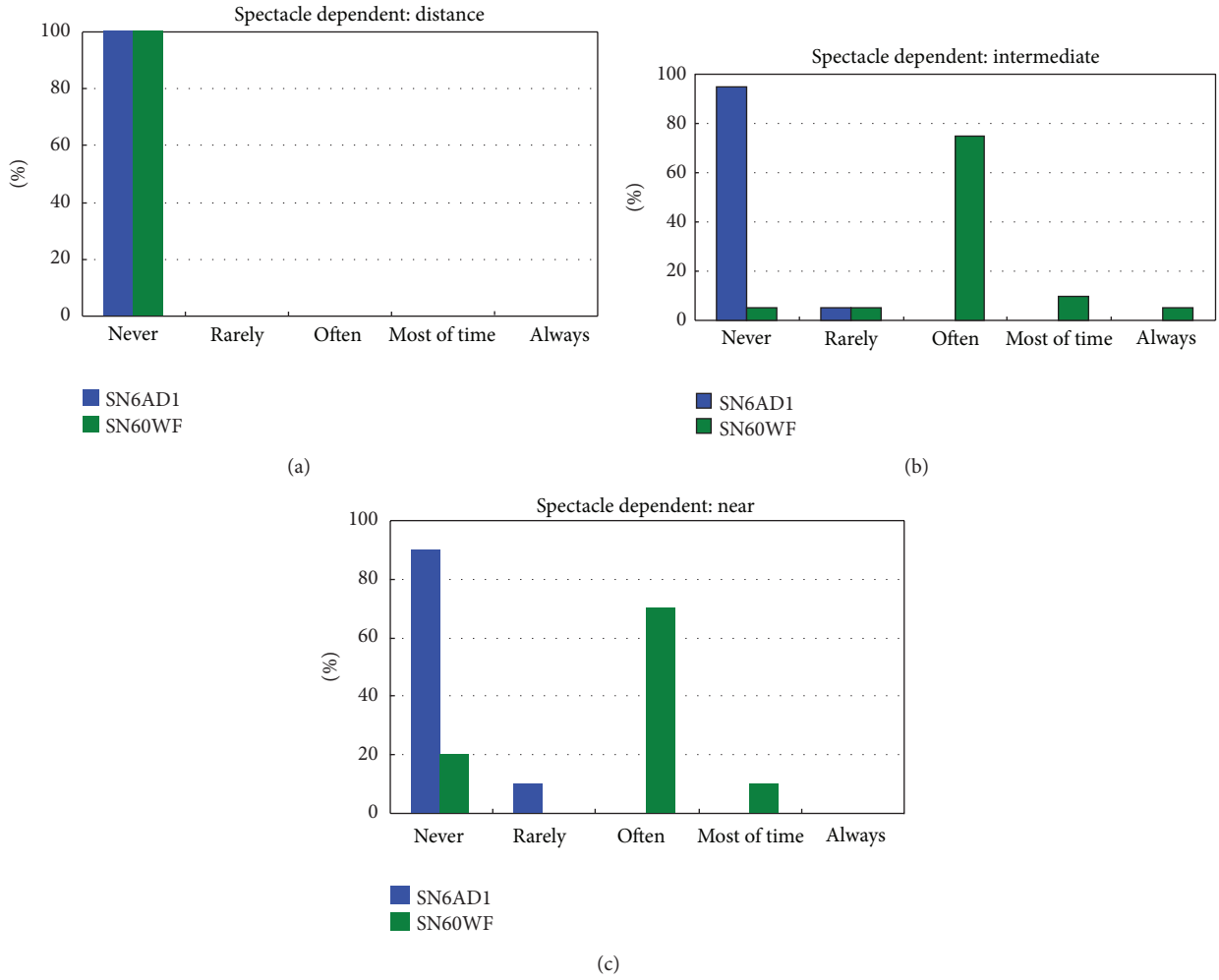

Figure 3: Results of spectacle wearing for distance (a), intermediate (b), and near activities (c).

a long-term follow-up. Nevertheless, in the current study, the 2-year UNVA 0.111 LogMar, UIVA (100%) 0.163 LogMar, and UIVA (10%) 0.396 LogMar in SN6AD1 group were statistically significantly better than SN60WF group 0.361 LogMar, 0.260 LogMar, and 0.491 LogMar, respectively, despite that UDVA, CDVA, and CNVA were not statistically different between both groups. In addition, the defocus curves demonstrated SN6AD1 MIOL provided a full range of vision from near to far, with the depth of focus 5.5 D in SN6AD1 group while being 4 D in SN60WF group. This means SN6AD1 MIOL can still provide good visual acuities over a long time after surgery. Regarding SN6AD1 MIOL, 1-year and 2-year UDVA, UNVA, UIVA (100%), and UIVA (10%) were lower than those of 3-month but still much better than SN60WF IOL. It might be a clue that visual acuities of SN6AD1 MIOL would be stable after 1 year postoperatively, which should be verified by long-term study with follow-up for more than 2 years.

One factor in maintaining good full range of vision is the long-term stability of SN6AD1 MIOL and accurate IOL power calculation. Distance visual acuity is affected when decentration of the refractive multifocal IOL exceeds 0.9 mm [19], which expresses the importance of in-the-bag MIOL implantation completely. In fact, it is easy to access the degree of decentration with SN6AD1 MIOL according to its ring structure. In the present study, all MIOLs were implanted in the capsular bag and there was no case of IOL decentration or tilt. It reflected the fact that the perfect surgery was one of the key steps assuring excellent visual function. Moreover, the postoperative refractive error will affect visual acuity [20]. In our study, spherical diopter in SN6AD1 group was (−0.75~0.75) D, and cylinder diopter was (−1~0.50) D. The slight refractive error will aid in obtaining the favorable vision. We believe IOL Master is a reliable instrument for the accurate IOL power calculation.

Although excellent visual acuity is essential to the success of SN6AD1 MIOL, the vision quality it produces is equally important. In the present study, the quality-of-life questionnaire illustrated a relatively lower overall vision satisfaction in SN6AD1 group. It was associated with PCO, patients' different reading habits, education level, and preoperative expectation.

PCO is the most common complication of modern cataract surgery, with an incidence up to 50% at 2 years postoperatively [21]. It has been considered that as MIOLs

distribute light to 2 foci, even minor PCO might create symptoms. In our study, 3 eyes (7.5%) complaining about moderate glare in SN6AD1 group required Nd:YAG capsulotomy during the 2-year follow-up, 1 at 9 months, 1 at 15 months, and 1 at 20 months. After Nd:YAG capsulotomy, the moderate glare reduced to mild level and the visual satisfaction scores increased to 7.88 ± 1.11. Considering our study, careful observation of PCO in eyes with SN6AD1 MIOL is important and use of Nd:YAG capsulotomy for the treatment of PCO is a safe method to alleviate undesired visual disturbances and improve visual satisfaction.

Patients' reading habit is another factor influencing visual satisfaction. In our study, all patients with SN6AD1 MIOL read newspapers or magazines daily for average 99 minutes, 95% of whom were reading the main text. By contrast, only 80% patients in SN60WF group had the habit of reading for average 66.25 minutes per one day, and 31% of patients just browsed the headlines. Moreover, the preferred reading distance 37.6 cm in SN6AD1 group was more comfortable for most people, while the distance 52.8 cm in SN60WF group was too far away from eyes. The higher reading speed 21.40 ± 1.70 s in SN6AD1 group partly reflected the better near visual function. However, SN6AD1 patients had to perform more near (including reading) activities, which was in line with their more advanced education level. Although SN60WF patients had no difficulty in performing some near activities revealed in the questionnaire, the simple near tasks likely contributed to the higher satisfaction for SN60WF patients while the stricter requirements and demand for reading in SN6AD1 group would bring down satisfaction.

It is believed that spectacle independence has been positively correlated with overall satisfaction with presbyopia-correcting IOLs [22]. In our study, in accordance with the superior UIVA and UNVA, spectacle independence for intermediate and near vision in SN6AD1 group was higher than SN60WF group.

90% of SN6AD1 patients and 20% of SN60WF patients reported complete spectacle independence for near vision; this changed to 95% and 5% for intermediate vision, respectively. Spectacle freedom and a better vision in daily life will undoubtedly be exciting and are an impetus to high satisfaction. But patients had to pay a lot for the SN6AD1 MIOL and surgery because only part of the cost was refunded by the medical insurance in China. Therefore, they would wish to acquire the best possible visual outcome after operation. The satisfaction would be rated low once the preoperative unrealistic expectation was not achieved. So it is necessary and important for surgeons to try their best efforts to keep patients' preoperative expectation appropriate.

In conclusion, our study showed that SN6AD1 MIOL provided a satisfactory full range of visual acuity, comfortable reading distance, faster reading speed, and high overall spectacle independence 2 years after surgery. One-year and 2-year uncorrected near and intermediate visual acuities of SN6AD1 MIOL were reduced than those of 3-month but they are still much better than SN60WF IOL. SN6AD1 patients' lower vision satisfaction had something to do with PCO, patients' different reading habits, education level, and preoperative improper expectation.

Conflict of Interests

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

Authors' Contribution

Xiaohong Guo and Yi Sun contributed equally in the design, conducting and drafting of the work.

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Research Article

Assessment of Corneal Biomechanical Properties and Intraocular Pressure in Myopic Spanish Healthy Population

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Purpose. To examine biomechanical parameters of the cornea in myopic eyes and their relationship with the degree of myopia in a western healthy population. *Methods*. Corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann correlated intraocular pressure (IOP), and corneal compensated IOP (IOPcc) were measured using the ocular response analyzer (ORA) in 312 eyes of 177 Spanish subjects aged between 20 and 56 years. Refraction was expressed as spherical equivalent (SE), which ranged from 0 to −16.50 diopters (D) (mean: −3.88 ± 2.90 D). Subjects were divided into four groups according to their refractive status: group 1 or control group: emmetropia ($-0.50 \leq SE < 0.50$); group 2: low myopia ($-0.75 \leq SE < 3.00$ D); group 3: moderate myopia ($-3.00 \leq SE \leq -6.00$ D); and group 3: high myopia (SE greater than −6.00 D). We analyzed the relationship between corneal biomechanics measured with ORA and SE. *Results*. CH in the emmetropia, low myopia, moderate myopia, and high myopia groups was 11.13 ± 0.98, 11.49 ± 1.25, 10.52 ± 1.54, and 10.35 ± 1.33 mmHg, respectively. CH in the highly myopic group was significantly lower than that in the emmetropic group ($P = 0.07$) and low myopic group ($P = 0.035$); however, there were no differences with the moderate myopic group ($P = 0.872$). There were no statistically significant differences regarding IOP among the four groups ($P > 0.05$); nevertheless, IOPcc was significantly higher in the moderately myopic (15.47 ± 2.47 mmHg) and highly myopic (16.14 ± 2.59 mmHg) groups than in the emmetropia (15.15 ± 2.06 mmHg) and low myopia groups (14.53 ± 2.37 mmHg). No correlation between age and the measured parameters was found. CH and IOPcc were weakly but significantly correlated with SE ($r = 0.171$, $P = 0.002$ and $r = -0.131$, $P = 0.021$, resp.). *Conclusions*. Present study showed only a very weak, but significant, correlation between CH and refractive error, with CH being lower in both moderately and highly myopic eyes than that in the emmetropic and low myopic eyes. These changes in biomechanical properties of the cornea may have an impact on IOP measurement, increasing the risk of glaucoma.

1. Introduction

Myopia is the most common ocular disorder. Its worldwide prevalence is about 30% and up to 80% in certain Asian populations [1–4]. Corneal hysteresis (CH) is a parameter which measures the viscoelastic behaviour of the cornea, indicating its biomechanical integrity [5]. Some clinical conditions such as keratoconus, Fuchs corneal dystrophy, glaucoma, and corneal refractive surgery may induce changes in corneal biomechanical properties, leading to a decrease in CH [6–10]. Although several studies with the ocular response analyzer (ORA, Reichert Inc., NY, USA) have reported a relationship between the refractive error and corneal biomechanical properties, it is still under debate [4, 11]. Thus, whereas in several studies CH was found significantly lower in patients with high myopia [12–17], other authors did not find any correlation

[18–20]. Most of the studies were performed in myopic Singaporean and Chinese populations [12, 14, 18, 20] and others in Brazilian [21] or Turkish people [15], with only a few ones in Caucasian individuals [13, 16]. Moreover, since biomechanical properties of the cornea are known to change with age [22], some slightly mixed findings in children may not be applicable to adult populations [16]. The aim of present study was to measure with the ORA device several corneal biomechanical parameters in an adult western healthy population containing emmetropes, low myopes, moderate myopes and highly myopic individuals, and the relationship between these parameters and the values of intraocular pressure (IOP) determined with ORA, including Goldmann correlated IOP (IOP) and corneal compensated IOP (IOPcc).

2. Methods

In this observational comparative study, 312 eyes of 177 healthy subjects were analyzed (76 men and 101 women). They were recruited sequentially among patients and healthy volunteers in the Department of Ophthalmology at the Lozano Blesa University Clinic Hospital and Quirón University Hospital, Zaragoza, Spain. The average age of the patients was 33.27 ± 7.65 years (range, 20–56). All subjects received a complete ophthalmic examination including measurement of best-corrected visual acuity (BCVA) with ETDRS chart, slit-lamp anterior segment biomicroscopy, fundus examination, and corneal topography (Orbscan II) in order to discard the existence of subclinical corneal pathology. Automated and subjective refractions were performed to determine refractive error in order to use it for the statistical analyses. Their spherical equivalent (SE) of refractive error ranged continuously from 0 to −16.50 D (mean: −3.88±2.90 D). For the pur-pose of the study, subjects were divided into four groups according to their refractive status: group 1 or control group: emmetropia ($-0.50 \leq SE < 0.50$); group 2: low myopia ($-0.75 \leq SE < -3.00$ D); group 3: moderate myopia ($-3.00 \leq SE \leq -6.00$ D); and group 4: high myopia (SE greater than −6.00 D). All participants had monocular BCVA of 20/32 (0.20 logMar notation) or better. Subjects who had refractive errors such as hyperopia > 0.5 D or astigmatism > 1 D, IOP > 21 mmHg, signs of glaucomatous optic neuropathy, family history of glaucoma in a first-degree relatives, corneal dystrophy, and myopic macular degeneration, those who had undergone previous eye surgery or trauma, eye infection, diabetes mellitus, corticosteroid use or other acute or chronic diseases, or using any topical eye medication, or subjects that did not meet normal topographic criteria were excluded from the study.

Corneal biomechanical properties, such as CH and CRF, were measured by the same masked technician with the Ocular Response Analyzer (ORA software version 2.04; Reichert Ophthalmic Instruments, Buffalo, NY) using standard technique [5, 8, 23]. Briefly, a rapid air puff deformed the cornea, and the induced corneal deformation was detected with an electrooptical system. The air pulse induced inward, and then outward, corneal movement, which provided two applanation measurements. CH resulted from the damping of the cornea because of its biomechanical properties and was derived from the difference of the two measurements during the applanation process. CRF, also derived from corneal hysteresis, is calculated as a linear function of the pressures corresponding to the two applanations. CRF is an indicator of the overall resistance of the cornea, which, according to previous data, seems to be related to central corneal thickness (CCT) and GAT determined IOP, but not to IOPcc [5]. The ORA also determined the values of noncontact tonometer Goldmann correlated IOP and IOPcc. IOPcc is a pressure measurement that utilizes the new information provided by the CH measurement to provide an IOP measurement less affected by corneal properties. CCT was measured, following corneal biomechanical properties measurements, by ultrasound pachymetry (20 MHz) using an ORA-integrated handheld pachymeter. Three measurements of good quality were obtained for each patient; the signals with the highest Waveform Score (WS) were highlighted as the best score value (BSV) and were used for statistical evaluation. The study and data accumulation were performed with the approval of the local ethics committee, informed consent was obtained from each subject participating in the study, and the study protocol was consistent with the tenets of the Declaration of Helsinki.

3. Data Analysis

Values were presented as mean ± SD. Statistical analyses were conducted using a commercial software (SPSS software, version 13.0; SPSS, Inc., Chicago, IL). The distribution of the measured variables was estimated by the one-sample Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) and post hoc tests were used for determining whether the values of a particular variable differed between the three diagnostic groups. We combined data from both eyes using the mixed model method [24], which adjusts for the correlation between the two eyes in a unique person. Multivariate mixed-model analysis adjusted by age and sex was used to determine the relationship between two con-tinuous variables. Pearson's correlation coefficient (r) was used to assess the relationship between spherical equivalent power and the corneal biomechanical properties (CH and CRF) as well as IOP (IOPcc and IOP) and CCT. The level of statistical significance was set to $P < 0.05$.

4. Results

A total of 177 patients (312 eyes) were enrolled in this study. The refraction among all included eyes ranged from 0 to −16.50 D (SE). 45 eyes corresponding to 25 patients (15 women and 10 men) were included as healthy controls (group 1). 71 eyes of 47 patients (20 women and 27 men) were included in group 2. One hundred forty-five eyes of 72 patients were included in group 3. And, finally, 51 eyes of 33 patients (23 women and 10 men) were included in group 4. Significant differences in refraction distribution were found between the four diagnostic groups ($P < 0.05$; Table 1). The one-sample Kolmogorov-Smirnov test showed that CH, CRF, IOP, IOPcc, and CCT were normally distributed ($P = 0.77$, 0.78, 0.92, 0.42, and 0.51, resp.) (Figure 1). Parameters such as age,

Table 1: Baseline data of the four diagnostic groups.

Parameters	Emmetropia (45 eyes/25 patients)	Low myopia (71 eyes/47 patients)	Moderate myopia (145 eyes/72 patients)	High myopia (51 eyes/33 patients)	P
SE (D)	0.25 ± 0.43	−2.15 ± 0.69	−4.23 ± 0.77	−8.69 ± 2.88	<0.001[a]
Sex (M/F)	10/15	27/20	29/43	10/23	0.057[b]
Age (years)	35.37 ± 7.73	33.60 ± 7.12	32.24 ± 6.68	33.88 ± 9.85	0.091[a]

D: diopters; F: female; M: male.
Data were presented as mean ± SD of the indicated variables.
[a]One-way analysis of variance.
[b]χ-test.
Significant differences in refraction were present among the four groups (*post hoc* test, $P < 0.05$).

BCVA, IOP, and CCT were not significantly different among groups ($P > 0.05$) (Table 2). CH in the emmetropia, low myopia, moderate myopia, and highly myopic groups were 11.08±0.98, 11.00±1.25, 10.52±1.54 mmHg, and 10.35±1.33, respectively (Table 2). CH in the moderately and highly myopic groups was significantly lower than in the emmetropic ($P = 0.02$ and $P = 0.01$, resp.; Games-Howell post hoc test) and low myopic group ($P = 0.07$ and $P = 0.04$, resp.; Games-Howell post hoc test). CRF of the emmetropic group was significantly higher than that in the moderately and highly myopic groups ($P < 0.001$ and $P = 0.04$, resp.; Games-Howell post hoc test). There was no significant difference in IOP ($P = 0.083$ ANOVA test; $P > 0.05$ least significant difference post hoc test); however, IOPcc was significantly higher in the moderate (15.47 ± 2.47) and highly myopic (16.14 ± 2.59) groups compared to the emmetropia group (15.15 ± 2.06) ($P = 0.046$ resp. to highly myopic group; least significant difference post hoc test) and low myopia group (14.53 ± 2.37) ($P = 0.008$ and $P < 0.001$, resp.; least significant difference post hoc test) (Table 2).

No correlations were found in the measured parameters with the age. CH and IOPcc were parameters significantly correlated with SE ($r = 0.171$, $P = 0.013$ and $r = -0.131$, $P = 0.021$, resp., Pearson's correlation coefficient) (Figure 2).

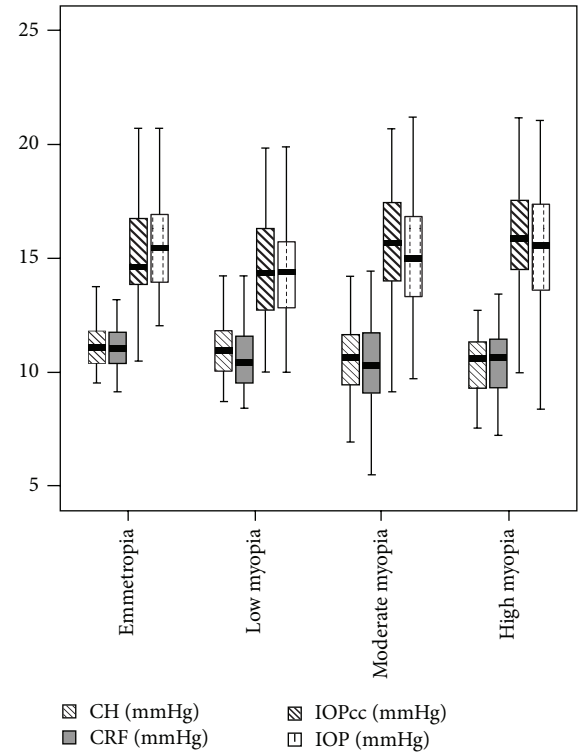

Figure 1: Box-and-whisker plot for corneal hysteresis (CH) and corneal resistance factor (CRF) and noncontact tonometer intraocular pressure (IOP) and corneal compensated intraocular pressure (IOPcc). Average and standard deviation values are presented in mmHg.

5. Discussion

Corneal hysteresis is the result of viscoelastic properties of the cornea, together with the combined effect of the corneal thickness and rigidity [5]. Low values of CH indicate a soft or floppy cornea. According to Reichert, CRF is dominated by the corneal elastic properties and appears to be an indicator of the overall resistance of the cornea [5, 23, 25]. There is strong evidence that corneal biomechanical properties are correlated to the degree of myopia. Thus, the abnormal elongation of the myopic eye is associated with corneal flattening and thinning [11], resulting in a decreased CH and CRF [12, 26]. Moreover, myopic eyes have a lower ocular rigidity than emmetropic and hyperopic eyes [27, 28]. Therefore, corneal rigidity, as part of the global rigidity, is likely to be low in myopic eyes as suggested by the decreased CH. Finally, corneal biomechanical properties reflect viscoelastic characteristics of the cornea and the mechanical strength of stromal collagen fibrils interacting with the extracellular proteoglycan matrix [22].

Several studies have used ORA to study the correlation between corneal biomechanics and the degree of myopia. Nevertheless, the results are contradictory. Thus, whereas some authors found a significantly lower CH in highly myopic patients compared with nonmyopic or low myopia subjects [12–17], other studies did not show a correlation between CH and myopia [18–20]. This could maybe be due to the narrow range of myopia selected for the individuals [20]. We found that CH in moderate and highly myopic groups was significantly lower than that in the emmetropic/low myopic group. However, our study differs in a few aspects. Most of the studies were performed in myopic Asian populations, whereas we measured corneal biomechanical characteristics

Table 2: Differences in corneal biomechanical parameters and CCT in the four diagnostic groups.

Parameters	Emmetropia (45 eyes/25 patients)	Low myopia (71 eyes/47 patients)	Moderate myopia (144 eyes/72 patients)	High myopia (51 eyes/33 patients)
CH (mmHg)	11.08 ± 0.98 (9.51 ± 13.70)	11 ± 1.25 (8.70–14.20)	10.52 ± 1.54 (5.02–14.20)	10.35 ± 1.33 (7.48–12.7)
CRF (mmHg)	11.07 ± 1.06 (9.15 ± 13.70)	10.63 ± 1.39 (8.40–14.20)	10.34 ± 1.64 (5.46–14.40)	10.36 ± 1.46 (7.23–13.40)
CCT (μm)	573.82 ± 38.03 (513–653)	557.29 ± 38.03 (500–658)	553.22 ± 34.21 (466–658)	552.79 ± 26.86 (463–595)
IOP (mmHg)	15.61 ± 2.23 (11.96–20.7)	14.55 ± 2.52 (10–20.2)	15.05 ± 2.53 (9.7–21.2)	15.54 ± 2.78 (8.36–21.06)
IOPcc (mmHg)	15.15 ± 2.06 (10–18.50)	14.53 ± 2.37 (10–19.80)	15.47 ± 2.47 (9.1–20.7)	16.14 ± 2.59 (10–23)

CH: corneal hysteresis; CRF: corneal resistance factor; CCT: central corneal thickness; IOP: noncontact tonometer intraocular pressure; IOPcc: corneal compensated IOP.
Data were presented as mean ± SD of the indicated variables.

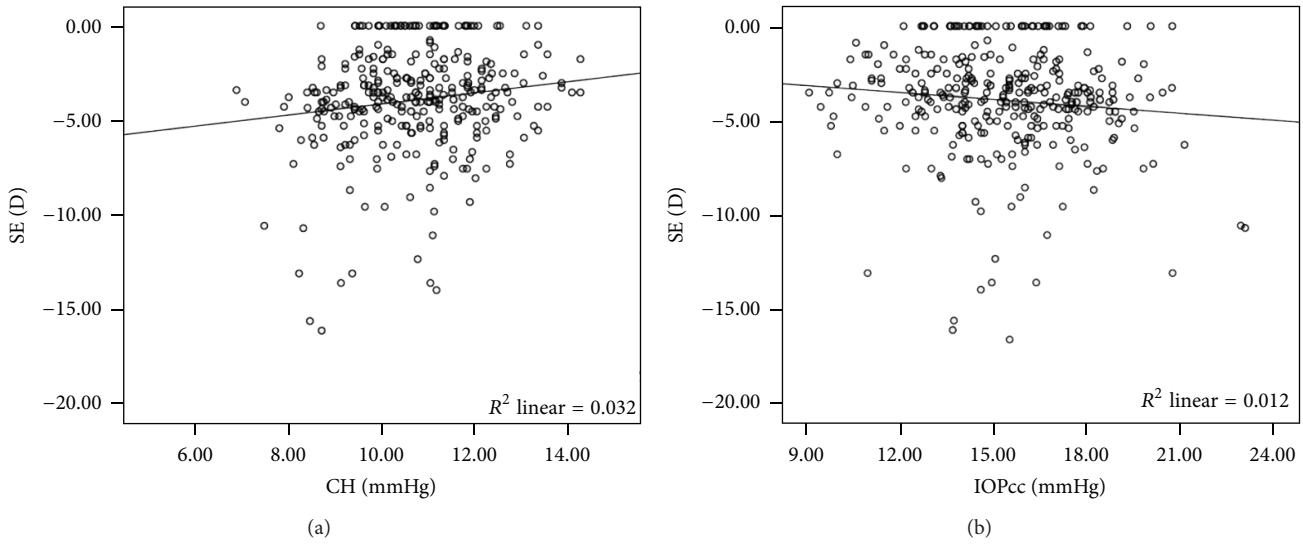

Figure 2: Correlation between spherical equivalent (SE) and (a) corneal hysteresis (CH) and (b) corneal compensated intraocular pressure (IOPcc).

in a western population. Furthermore, we analyzed these parameters in adults, avoiding the possible influence of age if children would have been included. We included not only highly myopic eyes but also moderate myopes and emmetropes/low myopes. Finally, an exhaustive selection of the subjects was carried out for the present study, excluding eyes with topographical patterns suspected or indicatives of keratoconus as well as signs of endothelial damage or glaucoma, since these disorders would cause a decrease in CH.

It has been suggested that the elastic properties of the cornea may influence the accuracy of IOP measurement [22]. In that case, the ORA may be useful for the diagnosis and management of glaucoma and ocular hypertension (OHT) [25]. Several studies have reported that myopic subjects, especially in the highly myopic group, showed higher IOP than controls [12, 29–32]. Altan et al. [15] found that IOPcc measured by ORA, but not IOP, was significantly higher in highly myopic eyes than in nonmyopia or low myopia group. Additionally, we observed that IOPcc was significantly higher in both the moderately and highly myopic groups compared to the emmetropia/low myopia group. Several studies [15, 20] have revealed a significant correlation between axial length and IOPcc. The positive correlations between CCT and CH have also been confirmed [5, 23, 33]. In accordance with Altan et al. [15], IOP and IOPcc were also significantly correlated with CCT. However, we found a significant relationship between IOP and IOPcc with CH, but not with CCT. The changes in CH with refraction are not related to the differences in CCT [16]. CCT in all our myopic patients was typically within normal limits and independent of the degree of myopia, in agreement with previous studies which found no significant differences between myopes and emmetropes in terms of corneal thickness [34, 35].

Unlike previous studies, the present study showed that not only high myopic eyes but also moderately myopic ones have a compromised corneal mechanical strength. These inconsistent results could be justified by differences related to other factors such as race, range of age, gender, refractive status, axial length, corneal curvature, and CCT. [14, 19, 20] Although there is a higher prevalence of glaucoma among myopic eyes than that in nonmyopic eyes [29, 32], it is still unclear why myopia increases IOP. Jiang et al. [14] attributed these differences of corneal biomechanical properties to the difference of age between groups. Nevertheless, in our study the variable age was not significantly different among the four groups.

The main limitations of this study would include that axial length and corneal curvature were not measured. Because of this, the importance of both factors in the refraction-related mechanical changes of the cornea is unknown.

Concluding, the present study shows a very weak but significant correlation between CH and refractive error, with CH being lower in both moderately and highly myopic groups than that in the emmetropic/low myopic ones, indicating that some aspects of corneal biomechanics may need to be interpreted in light of the refraction, especially in myopia. These changes in biomechanical properties of the cornea may have an impact on IOP measurement, increasing the risk of glaucoma. Further studies with larger sample size should be performed.

Conflict of Interests

The authors have neither conflict of interests nor commercial interest in the devices mentioned in the paper.

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Research Article

Association of eNOS Polymorphisms with Anterior Chamber Depth in Han Chinese: Jiangsu Eye Study

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Recently, a study reported that single nucleotide polymorphisms (SNP) in endothelial nitric oxide synthase (eNOS) were associated with primary angle closure glaucoma (PACG) in Australian cohort. In this study, we aimed to investigate whether those eNOS SNPs are associated with primary angle closure (PAC) or ocular biometric characteristics such as axial length (AL), anterior chamber depth (ACD), and diopter of spherical power (DS) in Han Chinese. The samples consisted of 232 PAC subjects and 306 controls collected from a population-based prevalence survey conducted in Funing County of Jiangsu, China. The rs3793342 and rs11771443 in eNOS were genotyped by TaqMan-MGB probe using the RT-PCR system. Our data did not identify any association of the eNOS SNPs with PAC. However, the analysis on the quantitative traits of ocular biometrics showed that the ACD of rs11771443 AA and GA carriers is significantly deeper than that of rs11771443 GG carriers ($P = 0.0025$), even though the AL and DS are not associated with rs11771443 genotypes. Rs3793342 was not associated with any biometric parameters including ACD, AL and DS. In summary, our data indicates that eNOS rs11771443 is associated with ACD and its role in the pathogenesis of PACG warranted further study.

1. Introduction

Glaucoma is the second leading cause of blindness worldwide. Clinically, primary glaucoma presents two major subtypes: primary open-angle glaucoma (POAG) and primary angle closure glaucoma (PACG). The classification relies mainly on the anterior segment anatomy, particularly that of the anterior chamber angle. PACG is characterized by obstruction of aqueous fluid drainage through the trabecular meshwork from the anterior chamber of the eye. The anterior chamber depth (ACD) is a main factor affecting the drainage of aqueous humor. It has been reported that Asian populations are at higher risk of developing PACG than other ethnic groups [1].

Eyes with PACG usually display characteristic anatomical features such as a shorter corneal diameter, a steeper corneal curvature, a shallower anterior chamber, a thicker and more anteriorly positioned lens, and a shortened eyeball, often accompanied by hyperopic refraction error [2]. The risk factors for developing PACG include age, family history, and being female [3]. First-degree relatives were found to have a 6- to 9-fold increased risk of developing PACG [4]. Siblings of Chinese patients with primary angle closure (PAC) or PACG have almost a 50% probability of having narrow angles and are more than 7 times more likely to have narrow angles than the general population [5]. Ethnic differences are also associated with PACG. There is also a higher prevalence among Inuits and Asians compared to Caucasians, suggesting a genetic predisposition for the disorder [6].

Because the ocular anatomic features are predisposing factors for PACG, genes involved in regulation of axial length and structural remodeling of connective tissues may contribute to development of PACG. Some genes related to eye development or tissue remodeling including membrane frizzled-related protein (MFRP) [7, 8], extracellular matrix metalloprotease-9 (MMP-9) [9–11], and methylenetetrahydrofolate reductase (MTHFR) [12] have been reported to be associated with PACG.

Endothelial nitric oxide synthase (eNOS) is a nitric oxide synthase that generates nitric oxide (NO) in blood vessels and is involved with regulating vascular tone by inhibiting smooth muscle contraction and platelet aggregation [13].

Studies also found that eNOS is a pressure-dependent regulator of intraocular pressure and a well-known predisposition gene for POAG [14, 15]. eNOS was recently reported to be associated with PACG assumed by regulating the expression of extracellular matrix metalloproteases [16, 17]. A sequence variation in the intron 4 of eNOS was associated with both POAG and PACG in the Pakistani population [16]. A C-T haplotype established by eNOSrs3793342 and eNOSrs11771443 may be a genetic marker for POAG but not for PACG in the Han Chinese population [18]. Recently, eNOSrs3793342 was reported to be associated with PACG in the Australian population but not in the Nepal population [17]. In short, the relationship of common variations in eNOS and PACG was inconsistent in different populations and the mechanism of eNOS in PACG pathogenesis is unclear. We hypothesized that eNOS might contribute to PACG by influencing ocular anatomical features. Considering that both PACG and POAG are characterized by apoptotic cell death of the retinal ganglion cells in the optic disc or retinal nerve fiber, we attempted to focus on PAC instead of PACG for its possible association with eNOS variants. PAC is the earlier stage of PACG and shares the same anatomical features. We also sought to investigate whether the SNPs of these loci are associated with ocular biometry.

Table 1: Demographics of study participants.

Demographic features	Control *n* (%)	PAC *n* (%)	*P*
Female	248 (81.05)	191 (82.33)	0.70
Male	58 (18.95)	41 (17.67)	
Mean age (year) ± SD	65.08 ± 7.53	64.84 ± 8.59	0.74
Age range	50–85	50–83	
Hypertension	66 (19.64)	46 (19.83)	0.69
Diabetes	24 (7.36)	20 (8.62)	0.76
Cardiovascular	10 (3.27)	4 (1.72)	0.41

Table 2: Clinical features of PAC subjects.

	Right eye (Mean ± SD)	Left eye (Mean ± SD)	Mean of both eyes (Mean ± SD)
Axial length (mm)	22.17 ± 0.83	22.17 ± 0.82	22.17 ± 0.83
ACD (mm)	2.49 ± 0.29	2.45 ± 0.30	2.47 ± 0.29
Refractive (diopter)	0.53 ± 1.85	0.68 ± 1.87	0.58 ± 1.84
Tonometry (mmHg)	15.18 ± 4.31	15.78 ± 4.46	15.52 ± 4.39

2. Methods

2.1. Subjects. The study was a part of the Jiangsu Eye Study and was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Nantong University. Each participant was fully informed of the purpose and procedures involved in the study and signed the informed consent form. The general demographic information of the participants is listed in Table 1. All participants were recruited from a population-based prevalence survey on eye diseases using a cluster random sampling strategy in Funing County of Jiangsu, China. Of the 6032 people screened, 232 people with PAC and 306 controls were enrolled in the study. PAC subjects and controls were matched in groups for sex and age and were ethnically homogenous. The participants were unrelated and self-identified Han Chinese. There was no difference between the control group and the PAC group in gender, age, or systemic disease distribution.

All study participants were residents of Funing County of Jiangsu, China, aged 50 years and above. Each participant received a thorough ophthalmic examination, included best-corrected visual acuity, anterior segment photography, Goldmann applanation tonometry, fundus examination, optic disc photography, visual field, objective refraction, and subjective refraction. The depth of the peripheral anterior chamber was determined using Van Herick technique [19]. The subjects with a peripheral chamber depth less than one-third of corneal thickness were invited for gonioscope, A-scan ultrasonography, and ultrasound biomicroscopy (UBM, SW-3200S, SUOER, China) examinations. UBM examinations were conducted in light and dark conditions in eight positions. The detailed protocol for gonioscopy and UBM was reported previously by Barkana et al. [20]. ACD and axial length (AL) were measured 3 times by A-scan to obtain mean values, and mean values of binoculus were used for statistical analyses.

PAC was defined according to the International Society of Geographical and Epidemiologic Ophthalmology (ISGEO) classification by Foster et al. [21]; it includes the following conditions: (1) either eye has the presence of an occluded angle (at least 180 degrees of closed angle in which the trabecular meshwork is not visible on gonioscopy or iris apposition to the trabecular meshwork is more than 180 degrees on UBM); (2) at least one of the following features was detected: peripheral anterior synechiae; intraocular pressure >21 mmHg; excessive pigment deposition on the superior trabecular meshwork; iris whorling; history of symptoms; or intraocular pressure elevated ≥8 mmHg after UBM examination in dark conditions; (3) no signs of secondary angle closure were present; (4) no signs of glaucomatous optic neuropathy and peripheral visual loss were present; (5) no previous ocular surgery or laser therapy was present. The clinical features of the PAC subjects are listed in Table 2.

The criteria for enrollment of the control group were (1) peripheral chamber depth more than one-third of corneal thickness; (2) intraocular pressure less than 21 mmHg; (3) normal optic nerve heads with cup-to-cup ratio less than 0.5; (4) normal visual field; (5) no family history of glaucoma; (6) no ophthalmic diseases except slight cataract; and (7) refractive error of less than three diopters.

2.2. SNP Genotyping. Genomic DNA was extracted from the peripheral blood of each individual using the Qiagen Blood DNA Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions and stored at −20°C.

Table 3: Allele frequency of SNPs in control and PAC subjects.

SNP	Allele distribution minor/major (minor %)		P	OR (95% CI)
	Control	PAC		
eNOS rs3793342 (G/A)	58/554 (9.48)	34/430 (7.33)	0.212	0.76 (0.49–1.17)
eNOS rs11771443 (G/A)	244/368 (39.87)	201/263 (43.32)	0.255	1.15 (0.90–1.47)

All HWE P values > 0.05.

The samples were genotyped for rs3793342 (in intron 4) and rs11771443 (in 5′-UTR region) by TaqMan genotyping assay (Applied Biosystems, Foster City, CA, USA) using the real-time PCR 7500 system (Applied Biosystems, Foster City, CA, USA). PCRs were performed in a total volume of 10 μL containing 1 μL (10 ng) DNA, 5 μL TaqMan Universal Master Mixture, and 0.20 μL TaqMan SNP Genotyping probes (40x). Amplification was carried out with an initial denaturation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 30 s, and annealing at 60°C for 30 s.

2.3. Statistical Analysis. Statistical analysis was performed with SPSS version 15.0 software. Differences in age and gender between PAC subjects and controls were assessed using t-test and Chi-Square test, respectively. Hardy-Weinberg equilibrium was tested using Chi-Square test. To analyze the association of these two SNPs with PAC and controls, the frequency of genotypes and alleles was evaluated using Chi-Square test. P values < 0.05 were considered statistically significant. Logistic regression analysis was performed to calculate the odds ratio (OR) value and the 95% confidence interval (95% CI) and to adjust the confounding effects of age and gender. Three genetic models were analyzed: the additive model defined as minor allele homozygotes versus heterozygotes versus common allele homozygotes, the dominant model as heterozygotes plus minor allele homozygotes versus common allele homozygotes, and the recessive model as minor allele homozygotes versus common allele homozygotes plus heterozygotes. The association of these two SNPs with AL, ACD, and spherical power (DS) was also assessed under the additive genetic model, dominant model using F-test, and t-test, respectively.

3. Results

The call rates of the SNPs genotyped were 100% and the call accuracy was 100% in randomly selected 10% of samples. Both SNPs conformed to Hardy-Weinberg equilibrium ($P > 0.05$) in the PAC group and in the control group.

The two SNPs did not show differences in the distribution of allele frequency (Table 3) and genotypes (Table 4) between the cases and controls.

The ACD of rs11771443 AA and GA carriers is significantly deeper than that of rs11771443 GG carriers ($P = 0.0025$ and $P = 0.0005$ for the additive model and dominant model, resp.). The AL and DS are not associated with rs11771443. Rs3793342 was not significantly associated with biometric parameters including ACD, AL, and DS (Table 5).

4. Discussion

This study, to the best of our knowledge, is the first population-based study to investigate the association of rs11771443 and rs3793342 with PAC and PAC relevant biometric parameters such as ACD, AL, and DS in a Han Chinese population. The design of a population-based study can minimize sample selection bias often present in hospital-based case-control study. Our results show that the variations of both SNPs were not associated with PAC. However, the variation of rs11771443 was associated with deeper ACD that is an anatomical feature against PACG. We are not aware of any publications describing the association between rs11771443 and ACD.

eNOS gene is a stress-regulating gene and its expression is triggered when organisms are exposed to stress, hypoxia, or injury. Under these unfavorable conditions, increased NO was produced in tissues to protect themselves against stress [22]. Normal NO level regulates blood flow to the tissues constantly. Low NO level may impair blood flow and related to neurodegenerative disorders, such as optic neuropathy [23]. Studies have found a decrease of nitric oxide in the plasma and aqueous humour of glaucoma patients, and a weak association of nonsynonymous SNP with glaucoma patient with a history of migraine [24]. Nevertheless, an abundance of NO has been found in the optic nerve head vessels of primary glaucoma patients, supporting that optic neuropathy in glaucoma may be related to eNOS overexpression [25]. Awadalla et al. demonstrated that eNOSrs3793342 was associated with PACG and suggested dysregulation of the NO system in this multifactorial optic neuropathy disease [17]. We excluded patients with optic nerve neuropathy from this study to verify the relationship between these SNPs and ocular anatomic features. Taking into account the result that the variation of rs11771443 was associated with deeper ACD, we appraise that the influence of eNOS on PACG may be owing to another mechanism.

The eNOS gene has been shown to play an important role in controlling the activity of matrix metalloproteinases [26]. Dysregulation of the NO system may downregulate MMP9 expression, which has been shown to be associated with PACG [11]. Awadalla et al. postulated that the downregulation in MMP9 activity causes deficiency in extracellular matrix remodeling during eye development and thus leads to hyperopic refractive error and shorter axial length [27]. However, although Awadalla et al. found that eNOSrs3793342 [28] and MMP9rs17576 [27] were associated with PACG, they did not investigate the relationship between these SNPs and AL or refractive status. Interestingly, MMP9rs17576 was also found to be associated with susceptibility to PACG in a Taiwanese population, but there were no differences in AL between the genotypes [11]. Similarly, Cong et al. found that MMP9rs2250889 was associated with PACG in Southern China, but the patients in their study have regular AL and no obvious microphthalmia [10]. In our present study, two SNPs

Table 4: Genotype frequency of SNPs in control and PAC subjects.

SNP		Genotype distribution n (%)		General P value	Dominant p/OR (95% CI)	Recessive p/OR (95% CI)
		Control	PAC			
eNOS rs3793342 (G/A)	GG	252 (82.4)	200 (86.2)	0.508	0.23/0.75 (0.46–1.20)	0.63/0.66 (0.12–3.62)
	GA	50 (16.3)	30 (12.9)			
	AA	4 (1.3)	2 (0.9)			
eNOS rs11771443 (G/A)	GG	110 (35.9)	75 (32.3)	0.513	0.38/1.17 (0.82–1.69)	0.32/1.26 (0.80–1.97)
	GA	148 (48.4)	113 (48.7)			
	AA	48 (15.7)	44 (19.0)			

Table 5: The relationship of biometric parameters with genotypes of rs3793342, rs11771443 in PAC group.

	Genotype	AL (mm) (mean ± SD)	ACD (mm) (mean ± SD)	Refractives (D) (mean ± SD)
eNOS rs3793342	GG	22.16 ± 0.73	2.46 ± 0.22	0.70 ± 1.47
	GA	22.10 ± 0.81	2.41 ± 0.26	0.76 ± 1.83
	AA	22.29 ± 0.33	2.55 ± 0.09	0.69 ± 1.50
	GA + AA	22.11 ± 0.14	2.42 ± 0.46	0.75 ± 1.79
p_a/p_d		0.891/0.741	0.444/0.33	0.980/0.848
eNOS rs11771443	GG	22.07 ± 0.77	2.38 ± 0.20	0.42 ± 1.17
	GA	22.22 ± 0.70	2.50 ± 0.25	0.54 ± 1.30
	AA	22.11 ± 0.78	2.49 ± 0.19	0.39 ± 1.25
	GA + AA	22.19 ± 0.72	2.49 ± 0.23	0.50 ± 1.29
p_a/p_d		0.355/0.245	0.0025/0.0005	0.471/0.475

p_a: additive model; p_d: dominant model.

in eNOS were not associated with either PAC or AL and DS. The possible mechanism in which MMP9 and eNOS might contribute to PACG needs to be further studied.

Nathanson and Mckee demonstrated an extensive NO-containing cells in the human ciliary muscle (CM) and outflow pathway [29]. Production of NO in CM could cause a relaxation of the muscle that would counteract the contractile effect of the neuronally released acetylcholine. Contraction of the CM, induced by cholinergic agonists such as pilocarpine, caused forward movement of lens that resulted in shallower ACD [30, 31]. In our present study, we found that the variation of rs11771443 was associated with deeper ACD but not associated with AL and DS. We speculate that the variation of rs11771443 might increase NO production in anterior segment endothelia, result in relaxation of ciliary muscle, and thus increase the depth of anterior chamber. A Singapore study reported that lens vault and posterior corneal arc length were responsible for approximately 75% of the variation of ACD, while axial length was a poor determinant of ACD [32].

In summary, our data indicates that eNOS rs11771443 is associated with ACD and its role in the pathogenesis of PACG warranted further study.

Disclosure

The authors alone are responsible for the content and writing of the paper.

Conflict of Interests

The authors declare no conflict of interests.

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