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Double-Pass Retina Point Imaging for the Evaluation of Optical Light Scatter, Retinal Image Quality, and Staging of Keratoconus

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Abstract

PURPOSE—To measure retinal image quality using point spread function (PSF) analysis by double-pass retina point imaging (DPRPI) in patients with keratoconus and to correlate visual quality with disease severity.

METHODS—Patients diagnosed with keratoconus by clinical exam, topography, and tomography and normal eyes were included in this study. Exclusion criteria were age under 18, aphakia, pseudophakia, lens opacity, or previous ocular surgery. A commercially available DPRPI instrument (OQAS 108 II AcuTarget HD, Visiometrics S.L., Spain) was used to collect objective scatter index (OSI) values in 21 keratoconic and 22 normal eyes. Eyes were also subjected to corneal topography, tomography, and staged using the Keratoconus Severity Score (KSS) and Amsler-Krumeich (AK) scale.

RESULTS—OSI was increased in keratoconic eyes (5.85 ± 0.98) versus control (0.83 ± 0.12 ; mean $\pm$ SEM), in AK stages 1–4, and KSS stages 3–4. Receiver-operator characteristic analysis obtained an area under the curve (AUC) of 0.859 when evaluating OSI as a unimodal diagnostic indicator for any KSS stage and 0.993 for KSS stages 3 and higher. An AUC of 0.949 was obtained in comparing eyes with lower severity topographic aberrations (KSS 1 & 2) versus mild-moderate keratoconus (KSS 3 & 4). Increasing corneal steepening patterns on tomography and topography were associated with PSF broadening and increased OSI.

CONCLUSION—DPRPI is useful in correlating retinal image quality with keratoconus severity. Objective scatter index may represent a clinically significant parameter for staging keratoconus with a unique ability to directly evaluate quality of vision in this population.

Precis

This study is the first to use double-pass retina point imaging (DPRPI) to reconstruct visual distortion and correlate ocular light scatter with keratoconus severity, which may assist in the diagnosis, staging and evaluation of visual quality in patients with keratoconus.

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Introduction

Keratoconus is a progressive, noninflammatory, bilateral and asymmetric corneal disease resulting in protrusion of the cornea, high myopia and irregular astigmatism.¹ As the most common primary ectasia, keratoconus affects all genders and ethnicities.^{2, 3} Although variable, keratoconus tends to present during puberty.⁴ Keratoconus can be asymptomatic in its earliest stages, making detection difficult.² As it progresses, keratoconus causes a large decrease in visual acuity which becomes difficult to correct due to irregular astigmatism.⁵ The diagnosis of keratoconus is an important risk factor in the development of ectasia status post laser assisted in situ keratomileusis.^{6, 7} Early detection and staging of keratoconus is thus key to aid in clinical decision making and preventing the development of severe disease.²

Multiple imaging technologies have been proposed and used to evaluate the cornea to more accurately detect the onset of keratoconus. Corneal topography and tomography have been used to diagnose keratoconus by measuring the curvature, anterior and posterior elevation of the cornea, the minimal corneal thickness, anterior chamber angle, corneal volume, and anterior chamber depth.^{8, 9} Anterior segment optical coherence tomography (OCT) has detected corneal thinning in keratoconus patients with similar sensitivity and specificity to corneal topography, with significant changes observed in epithelial thickness profile.^{10–12} Interestingly, OCT of the retina has been shown to reveal small increases (~10 µm) in macular thickness in keratoconic eyes.¹³ Studies have shown posterior corneal measurement by the Scheimpflug camera to dispute the theoretical properties of the posterior cornea, cautioning its use alone in diagnosing a keratoconic eye.^{14, 15} The biomechanical parameters of corneal hysteresis and the corneal resistance factor have been shown to significantly decrease following LASIK surgery or with the diagnosis of keratoconus.^{16–18}

The purpose of this study is to explore the role of double-pass retina point imaging (DPRPI) in keratoconus and to determine if qualitative and quantitative measurements from this technique can be used to aid in its diagnosis and staging of severity. By measuring the point-spread function (PSF) of the entire optical system (cornea, aqueous humor, lens and vitreous), this method enables mathematical reconstruction of the way a point of light is scattered by aberrant structures it passes in the subject-fixated coaxially sighted corneal light reflex axis (Chang-Waring Axis) before reaching the retina.^{19–21} Thus, this method allows the clinician to “see” images as they are cast on the patient’s retina. Objective Scatter Index (OSI) is a single number quantification of DPRPI measured by examining the ratio of extra-axial (scattered) to central (unscattered) light. DPRPI has been successfully used to objectively classify the maturity of cataracts.^{20, 22} A significant correlation between OSI and logarithm of the minimum angle of resolution (logMAR) but not between the size of higher order corneal aberrations and logMAR in patients status post corneal transplant has also been observed²³, indicating DPRPI may be superior to Hartmann-Shack aberrometry in these cases. Encouragingly, OSI has been shown to detect corneal surface abnormalities; elevated OSI was observed over a 20 second course of no blinking in dry eye patients compared to no changes in controls.²⁴

Materials and Methods

All research was approved by the Medical University of South Carolina Institutional Review Board and informed consent was obtained from participants. A series of keratoconus patients evaluated prior to any ocular surgery and normal eyes underwent DPRPI analysis in addition to standard clinical exam. Inclusion criteria were patients with diagnosis of keratoconus by clinical exam, topography, and tomography or normal controls without signs of corneal ectasia including clinical evaluation, corneal topography and tomography prior to having LASIK. Exclusion criteria were age under 18, aphakic or pseudophakic lens status, lens opacity, or previous ocular surgery. For each patient, a complete eye exam was performed including uncorrected distance visual acuity (UDVA), best distance visual acuity (BDVA), manifest refraction, slit lamp and fundus examination. Power analysis was done for the primary outcome using the method of Lenth.²⁵ Patients were analyzed by a double-pass retina point imaging device (OQAS II/AcuTarget HD, Visiometrics S.L., Terrassa, Spain). OSI measurements were performed after defocus (low order aberration) correction. During the same visit, these same patients also underwent Placido corneal topography (Atlas Corneal Topography System Model 995, Zeiss, Oberkochen, Germany), and Scheimpflug camera tomography (Pentacam HR 70900, Oculus Optikgeräte GmbH, Wetzlar, Germany). The Amsler-Krumeich (AK) and Keratoconus Severity Score (KSS), and Collaborative Longitudinal Evaluation of Keratoconus (CLEK) scale for corneal scarring were used to categorize severity.^{26–28} These clinical scales use refractive power of the cornea, topography, thickness, as well as clinical evidence of scarring and axial patterns observed on tomography (Supplementary Tables 1–3). GraphPad Prism 6.07 was used for graphing and statistical analysis (GraphPad Software, Inc.). Student's t test with Welch's correction for unequal variance was used for comparisons involving only two groups. Comparisons across multiple groups were done via one-way ANOVA and multiple pairwise comparisons made using Holm-Sidak's correction. Pearson's correlation coefficient was calculated to examine the trend between continuous variables. An alpha of 0.05 was used to determine statistical significance in the reported results.

Results

Analysis determined 91% power could be achieved via one-way ANOVA with Dunnett's post-test amongst 5 groups with 3 patients in each group given a desired interest to observe a doubling in ocular light scattering as measured by objective scatter index (OSI) over control values (0.76 ± 0.52 ; mean $\pm$ SD). Patient demographics are displayed in Table 1. 21 control eyes (12 patients) and 22 keratoconic eyes (15 patients) were included. No statistically significant differences were noted between groups with respect to age or gender. Correlation analysis revealed a weak but significant positive correlation between OSI and age in keratoconic eyes (Pearson's $r=0.4719$ with $p=0.027$) but not in control eyes (Pearson's $r=0.264$ with $p=0.246$, respectively). KSS grade 5 patients were excluded from this study as the amount of non-scattered light was undetectable by the double-pass wavefront device.

Figure 1 demonstrates the changes observed in OSI stratified by AK and KSS criteria. Statistically significant increases in OSI compared to controls are observed overall, in all

AK grades 1–4, and in KSS grades 3 & 4 (mild and moderate keratoconus). In comparison to controls, keratoconus patients had an observed OSI of 5.85 ± 0.98 v. 0.83 ± 0.12 (mean $\pm$ SEM). Furthermore, a significant linear trend was observed from KSS grade 1 to KSS grade 4 ($p=0.0007$) and from AK grade 1 to AK grade 4 ($p<0.0001$).

The authors next sought to evaluate OSI's performance as an adjunctive diagnostic indicator using receiver-operator characteristic (ROC) analysis (Figure 2). Comparing OSI in control eyes to both those with lower severity topographic abnormalities (KSS 1 & 2) and keratoconic (KSS 3 & 4) eyes, an area under the curve (AUC) of 0.859 ± 0.059 ($p<0.0001$) is observed (Figure 2A). Comparing OSI in control versus eyes with lower severity topographic abnormalities yields a non-significant AUC of 0.667 ± 0.115 ($p=0.154$) (Figure 2B). As expected, OSI displayed a significant ability to discern control from keratoconic eyes (Figure 2C) with an AUC of 0.993 ± 0.010 ($p<0.0001$). Importantly, OSI also demonstrated a significant ability to discern lower from higher severity keratoconic eyes with an AUC of 0.949 ± 0.044 ($p=0.0003$) (Figure 2D). Supplementary Tables 4–7 display the sensitivity and specificity obtained at each OSI cut-off value used to generate each point in panels 2A–2D, respectively, as well as likelihood ratios associated with each value of OSI for a patient considered in the reference (first) category: controls in Figure 2A, 2B, and 2C, and KSS 1 & 2 in panel 2D.

Figure 3 shows representative point-spread functions and corresponding OSI values as calculated by the double-pass retina point imaging device (Figure 3A–E) along with corneal topography determined by the Placido disc method (Atlas) (Figure 3F–J), tomography by Scheimpflug photography (Pentacam) (Figure 3K–O). Increasing quantity (OSI, cone width) and anisotropy of light scatter can be observed as KSS grades increase from the left to right column (Figure 3A–E). A visual trend for increasing levels of corneal steepening can be observed in the Placido disc topography with increasing KSS grades (Figure 3F–I) with significant data loss due to severe steepening in KSS grade 4 (Figure 3J). Scheimpflug tomography demonstrates the same trend of corneal steepening from control to mild keratoconus (Figure 3K–N) and succeeds in obtaining a complete image in the KSS4 cornea (Figure 3O).

Discussion

This study is the first to describe the use of double-pass retina point imaging (DPRPI) technology as an adjunctive diagnostic device to evaluate retinal image quality and ocular light scattering in patients with keratoconus. The results indicate that objective scatter index (OSI) may be adjunctively useful in the diagnosis and staging of keratoconus given the significant increases observed at mild and moderate keratoconus severity (KSS 3 & 4) and large areas under the ROC curves (Figures 1 and 2). This study was powered to detect a doubling in OSI over control yet did not show any significant difference between the OSI values of control subjects and those with mildly atypical topography (lower severity, or KSS 1 & 2), suggesting that the retinal image quality in these patients is relatively normal (Figure 1). Also, the point spread function patterns and magnitudes give important qualitative information, helping practitioners better understand the visual circumstances that patients with keratoconus suffer from, particularly with more advanced forms of the disease. Taken

together with the absence of any correlation between keratoconus stage and age, the significant upward trend in OSI values observed from lower to higher AK and KSS stages (Figure 1), and significant AUC in discriminating KSS grades 1 & 2 from KSS grades 3 & 4 by ROC analysis (Figure 2D) suggests OSI may aid in monitoring the progression of keratoconus.

An important limitation of this study is the lack of data in severe keratoconic eyes (KSS grade 5) secondary to an undetectable signal. Further developments in DPRPI technology – namely increased detector sensitivity – should provide higher precision for clinicians to screen for keratoconus and further measure the effect on retinal image quality in patients with visual impairment secondary to severe keratoconus (stage 5 KSS). Additionally, the authors recognize the limitations of clinical scales such as AK or KSS in keratoconus given their reliance on measures that do not necessarily correlate with visual quality. These scales do, however, allow the examiner to attempt to grade disease severity and contrast severity amongst patients. Although future studies are needed for validation, the current study objectively demonstrates that supports the concept that retinal image quality degrades with increasing severity, and that early stage disease can still maintain reasonable image quality, which correlates with our clinical experience.

The work of Ye et al. has demonstrated significant aberrations in forward light scatter in the topographically normal fellow eye of patients recently diagnosed with keratoconus (forme fruste keratoconus) in comparison to bilaterally normal controls using DPRPI.²⁹ Although related, the parameters describing scatter in their study are different from the parameter described in the present study (OSI). Furthermore, data from the eye diagnosed with keratoconus is not presented. While Ye et al. discovered significantly increased parameters in topographically normal eyes, the present study did not. This is not surprising as the calculation of OSI is different from their multiple frequency domain parameters including modulation transfer function (MTF) cutoff frequency and derivations thereof called OQAS values.

As DPRPI measures light scattering resulting from all aberrations anterior to the neural retina, it is important to interpret OSI in context with any pathologies observed on clinical exam combined with biomicroscopy, especially in older keratoconus patients. Correcting OSI for lens opacifications as determined by brightness acuity testing or Lens Opacities Classification System III (LOCS III) grading may be one strategy for extend the test's usefulness in older patients.³⁰ Patients were excluded if they displayed clinically detectable lens opacity. Furthermore, as no eyes in the study belonged to patients over the age of 55 (Figure 1), clinically silent variations in lens opacity are unlikely to confound these data.

OSI may be useful for objectively analyzing retinal image quality in keratoconic patients undergoing procedural interventions. OSI and qualitative analysis of point spread function may also play a role in decision making in therapeutic management of patients with keratoconus. Furthermore, OSI may be useful in clinical trials designed to compare interventions by reducing variability and objectifying retinal image quality as has been previously demonstrated.^{24, 31} With longitudinal follow-up, qualitative and quantitative analysis of the morphology of point spread function patterns such as those observed in

Figure 3A–E may help with early identification of patients with keratoconus and risk stratification during pre-operative assessment for elective excimer laser-assisted corneal procedures, such as LASIK.

In conclusion, this is the first study to explore the role of ocular light scatter in the staging of patients with keratoconus with double-pass retina point imaging technology. The ability of this technique to reconstruct the image projected on the patient's retina allows the clinician to directly evaluate retinal image quality in patients with keratoconus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Objective Scatter Index Values Stratified by Keratoconus Severity

OSI values of all keratoconus patients and lower severity topographic changes are plotted versus controls (A) and as stratified by clinical severity as determined by the Amsler-Krumeich (B) or Keratoconus Severity Score (C). Data were analyzed by two-tailed t-test with Welch's correction (A) or by one-way ANOVA with Holm-Sidak's correction for multiple comparisons (B, C). Asterisks denote groups that significantly differ from controls ($p < 0.05$). Center lines represent mean; error bars are SD.

Figure 2. OSI Differentiates Mild and Moderate Keratoconus from Controls and Eyes with Lower Severity Topographic Changes

Receiver operating characteristic (ROC) curves were constructed by plotting sensitivity versus 100% - specificity at varying cutoff values of OSI. Comparisons are made between control eyes and all eyes with topographic changes (A), control eyes and eyes with lower severity topographic changes (B), or control and keratoconic eyes only (C). Eyes with lower severity topographic changes (KSS 1–2) are compared to KCN eyes (KSS 3–4) in (D). For a list of the cutoff values used in construction of the curves and corresponding likelihood ratios, see Supplementary Tables 4–7. Area under the curve (AUC) $\pm$ standard error and p value are noted at bottom right of each panel.

Figure 3. OSI, Topography, and Tomography of Keratoconus by Stage

Two-dimensional point-spread function plots as determined as a function of double-pass retina point imaging (DPRPI)-derived ocular light scatter (A-E). OSI values are overlaid at the bottom right of each panel. The primary axis of scatter is displayed by a gray line and colors represent the relative intensity of light (scale in panel A). Placido disc topography displayed in (F-J). Scheimpflug tomography via Pentacam displayed in (K-O). Relative refractive strength is heat mapped by color using a standard 0.5 Diopter scale in the topography and tomography panels (F-O, legends in F, K). See Supplemental Figure 1 for an alternate heat map version of Panel 3O.

Table 1.

Patient Demographics

Group	Age		Gender		Total
	Years	p	# Male	p	n
Control	32.4		19		21
All Keratoconus	36.3	0.132	18	1.0	22
By Keratoconus Severity Score (KSS):					
KSS 1	34.0	0.740	3	N/A	3
KSS 2	29.0	0.561	4	N/A	6
KSS 3	41.0	0.030	7	N/A	9
KSS 4	38.3	0.428	4	N/A	4
By Amsler-Krumeich Scale (AK):					
AK 1	32.4	0.993	10	N/A	13
AK 2	38.7	0.457	2	N/A	3
AK 3	43.5	0.196	2	N/A	2
AK 4	33.0	0.993	4	N/A	4

A total of 43 eyes from 27 patients were enrolled in the study. Age was compared versus control by one-way ANOVA (subgroups) or unpaired t-test (all keratoconus). Gender was compared by chi-square analysis.