tvst

https://doi.org/10.1167/tvst.7.3.15

Article

Macular Choroidal Thickening in Keratoconus Patients: Swept-Source Optical Coherence Tomography Study

Rosa Gutierrez-Bonet[1], Jorge Ruiz-Medrano[1], Pablo Peña-Garcia[2], Muriel Catanese[3], Yalda Sadeghi[1], Katayoon Hashemi[1], Eric Gabison[4], and José M. Ruiz-Moreno[2,5]

[1] Jules Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne, Switzerland
[2] Castilla-La Mancha University, Albacete, Spain
[3] Medical Centre Griffon, Marseille, France
[4] Fondation Rothschild, Paris, France
[5] Puerta de Hierro-Majadahonda University Hospital, Madrid, Spain

Correspondence: Rosa Gutierrez-Bonet, Hôpital Ophthalmique Jules Gonin, Fondation Asile des Aveugles, Avenue de France 15, 1000 Lausanne, Switzerland. e-mail: rosagbonet@gmail.com

Received: 30 January 2018
Accepted: 30 April 2018
Published: 7 June 2018

Keywords: keratoconus; choroid; swept-source OCT; choroidal thickness; SS-OCT

Citation: Gutierrez-Bonet R, Ruiz-Medrano J, Peña-Garcia P, Catanese M, Sadeghi Y, Hashemi K, Gabison E, Ruiz-Moreno JM. Macular choroidal thickening in keratoconus patients: swept-source optical coherence tomography study. Trans Vis Sci Tech. 2018;7(3):15, https://doi.org/10.1167/tvst.7.3.15

Purpose: To determine the choroidal thickness (CT) profile in keratoconus (KC) patients using swept-source optical coherence tomography (SS-OCT).

Methods: This was a prospective, cross-sectional study. One hundred two eyes of 52 KC patients were studied using Pentacam and SS-OCT. The macular CT profile was created by manually measuring the distance between the retinal pigment epithelium and the choroid-sclera junction on horizontal b-scans at nine different macular locations. The results were compared to 93 eyes of 93 healthy controls.

Results: Mean age of the KC group was 34.9 $\pm$ 13.5 years and mean axial length (AL) was 24.1 $\pm$ 1.3 mm. Mean topographic KC classification (TKC) was 2.0; 39 eyes were classified as early KC (TKC <1–2), 34 eyes as moderate (TKC 2, 2–3), and 29 as advanced (TKC 3+). Mean subfoveal CT was 383.2 μm in KC patients and 280.5 μm in control group ($P < 0.001$). CT in KC patients was statistically thicker in all measure locations ($P < 0.001$). CT in KC eyes decreased with age, approaching control group at >45 years old, losing statistical significance ($P = 0.37$).

Conclusions: CT in KC patients is statistically thicker than in healthy population. After age 45, CT decreases approaching control group values.

Translational Relevance: This study describes changes in the CT profile of KC patients, a disease that was considered purely corneal. These choroidal changes argue that KC is a disease that likely involves several ocular structures other than the cornea, and could open new research lines related to the pathophysiology of KC.

Introduction

Keratoconus (KC) is a bilateral, asymmetric, noninflammatory disease that is characterized by the progressive ectasia, thinning, and increase of curvature of the cornea, inducing a conical shape and an eventual visual acuity loss. Although it is usually a sporadic disease, it has also been linked to other ophthalmological and systemic pathologies such as Down's and Turner's syndrome, Leber's congenital amaurosis, retinitis pigmentosa, mitral valve prolapse,[1] atopy, allergy,[2] sleep apnea, asthma,[3] and connective tissue disorders that include Marfan's and Ehlers Danlos' syndromes, osteogenesis imperfecta, and pseudoxanthoma elasticum.[1] This is suggestive of an association between KC and genetics.[1–3]

KC diagnosis and monitoring is currently based on clinical examination and topographic and pachymetry evaluation. Devices currently used in KC study have been used to classify and characterize the cornea based on shape, cone location, thickness, epithelial cell density, density of keratocytes, Bowman layer disruptions, stromal thinning, and scarring among others.[4,5]

The choroid is the middle layer of the eye; its high pigmentation and posterior location together with the light dispersion induced by the retinal pigment

epithelium (RPE) make more difficult to obtain good quality optical coherence tomography (OCT) images. Longer-wavelength, swept-source OCT (SS-OCT) provides deeper penetration and higher resolution images of the choroid, allowing a better determination of the choroidal thickness (CT), reaching the scleral tissue and even the orbital fat in certain patients such as those with high myopia.[5–11]

The purpose of this study is to evaluate the CT profile in eyes with KC.

Material and Methods

This prospective, cross-sectional study was carried out at the Jules-Gonin Eye Hospital, University of Lausanne, between the beginning of January and the end of February 2017. It followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Canton of Vaud, Switzerland (protocol number 2017-00257). Patients signed an informed consent form prior to the inclusion in the study. Inclusion criteria were a clinical and topographic diagnosis of KC, good quality images (Pentacam >95% validated data), and willingness to participate in the study. Patients with any history of ocular trauma, retinal diseases, eye surgery or other eye pathology were excluded from the study. Corneal cross-linking (CXL) was not considered an exclusion criterion as long as it had been performed at least 1 year prior to the CT measurement. Patients with axial length (AL) longer than 26 mm were also excluded due to the known negative correlation between AL and CT.[12] KC was diagnosed in patients presenting inferior-superior dioptric asymmetry over 1.2, maximum keratometry (Kmax) >47.2 diopters (D), and simulated keratometry >21 degrees.[13]

A total of 102 eyes from 52 patients with known history of KC underwent a complete ophthalmological examination including best-corrected visual acuity (BCVA), Goldman applanation tonometry, slit lamp, and fundus examination. Complementary tests included Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) to analyze topographic characteristics of the cornea, IOL Master 500 (Carl Zeiss Meditec, Jena, Germany) for the measurement of the AL, and Triton SS-OCT (Topcon Co, Tokyo, Japan) to study CT. This group was compared to 93 eyes from 93 age and gender-adjusted healthy controls recruited consecutively during the same period of time, with spherical equivalents from −3.00 to +3.00 D to avoid myopic patients who may have shown the already described choroid thinning, and with no ocular or systemic diseases. Four patients were excluded from the KC group for insufficient quality of their Pentacam images, and two more for low quality of the OCT b-scans that prevented an accurate measure of CT.

IOL Master 500, is a noncontact optical device that provides an estimate of AL using partial coherence interferometry, which provides the distance between the corneal apex and the RPE. It also calculates keratometry values and anterior chamber depth.[14] AL was chosen instead of spherical equivalent as inclusion criterion due to the high astigmatism of KC patients.

Corneal topographic examination was performed always in the dark using Pentacam, which combines a slit illumination system with an automatically rotating Scheimpflug camera to reproduce a three-dimensional model of the anterior segment.[15] The following parameters provided by Pentacam were analyzed: minimal corneal thickness (MCT), mean keratometry, Kmax, and posterior elevation in the location of MCT.[16] The severity of KC was assessed based on the topographic keratoconus classification (TKC) as reported within the Pentacam HR software.

The same trained examiner performed all SS-OCT scans, and always during the afternoon to minimize diurnal variation.[17] A single-line scanning mode producing an OCT image of 12 mm containing 1024 axial scans, with acquisition time of 1 second. Two experienced examiners (RGB, JRM) independently in a masked fashion determined CT in both eyes by measuring the distance between the posterior limit of the RPE and the choroid-sclera junction just under the fovea, perpendicularly to the RPE (Fig. 1). Eight further measurements were performed every 1000 μm: five temporal to the fovea (T1–T5) and three more nasal to the fovea (N1–N3; Fig. 1). A 9 × 12 mm raster scan with automated retinal segmentation was also performed in order to verify retinal thickness. CT was also measured in 10 KC eyes both with and without scleral contact lenses, in order to establish whether high astigmatism might modify CT measurement.

Statistical Analysis

BCVA is recorded at our center in decimal format; therefore, the BCVAs were transformed to logMAR to calculate median values and the interquartile range (IQR). Normality of the samples was checked using the Kolmogorov-Smirnov test. The distribution of all variables in KC patients was found to be not normal.

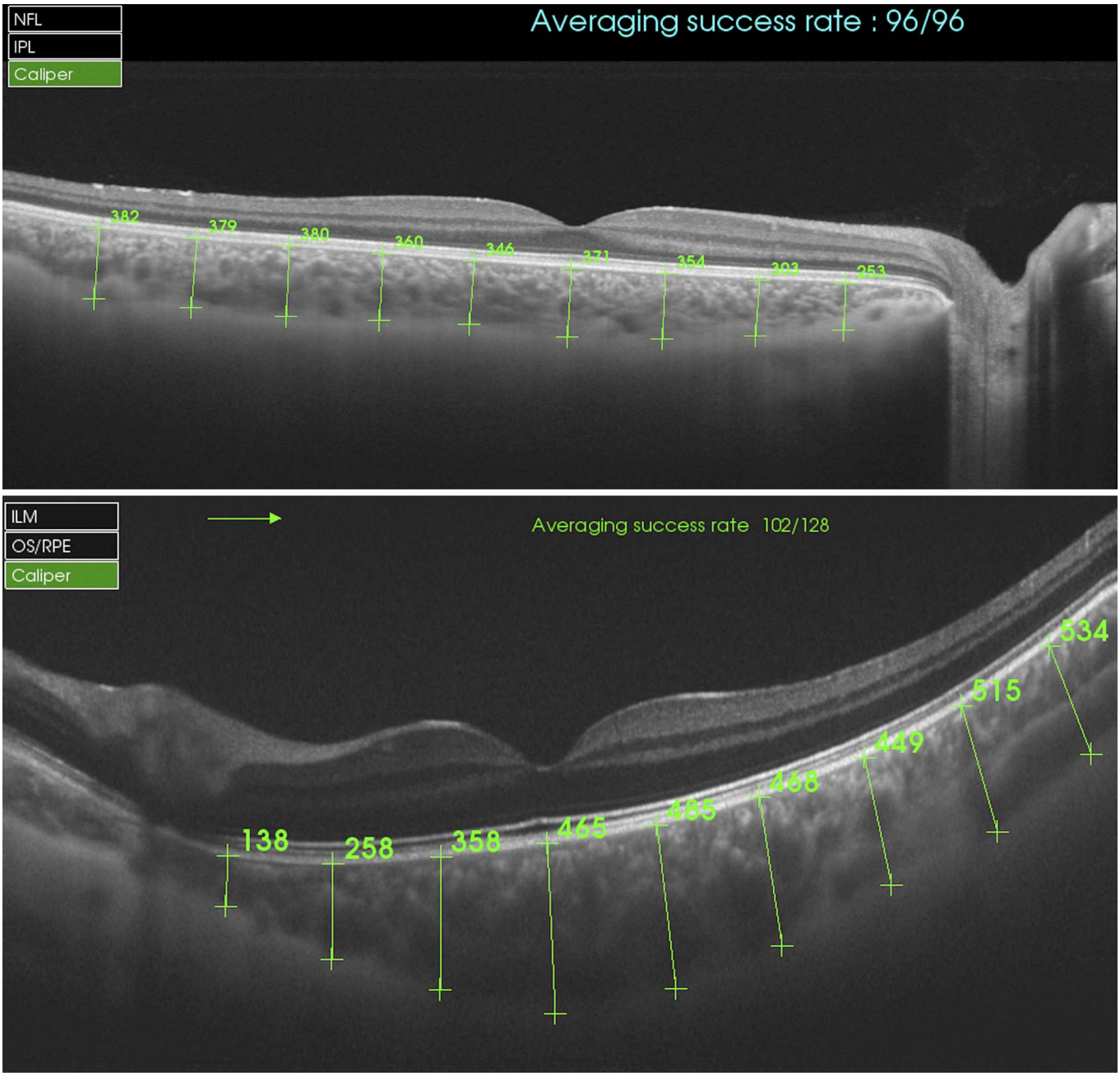

Figure 1. CT was manually measured from the posterior limit of the RPE to the choroid-sclera junction under the fovea in a healthy control (*top*) and in a KC patient (*bottom*). Eight further measurements were performed every 1000 μm: five temporal to the fovea (T1, T2, T3, T4, and T5) and three more nasal to the fovea (N1, N2, and N3).

For this reason, nonparametric statistic was used in this study. Mann-Whitney test was used to compare parameters between two groups. The level of significance considered was $P < 0.05$ for all comparisons. The statistical analysis was performed using SPSS 23.0 for Windows (SPSS, Inc, Chicago, IL). Spearman rho correlation coefficient was used to detect influential factors in CT.

Results

Baseline characteristics of the eyes with KC are in Table 1 for the whole group and for four age groups: less than 25 years, 25 to 35 years, 36 to 45 years, and more than 45 years. Mean age of the KC group was 34.9 ± 13.5 years and mean AL was 24.1 ± 1.3 mm.

Table 1. Baseline Characteristics of the KC Population

Age Group	Number of Eyes	TKC	TCT		Kmax		Kmean		Posterior Elevation	
<25	19	1.8	461.4	±51.5	53.4	±7.1	46.8	±3.9	44.1	±26.5
25–34	34	2.0	440.7	±83.9	56.0	±9.4	49.0	±6.5	58.6	±42.1
35–44	26	2.3	457.7	±53.4	56.2	±8.7	48.6	±6.5	45.1	±26.3
>45	23	1.8	487.4	±69.4	54.0	±10.2	48.0	±5.6	52.0	±39.4
Total	102	2.0	459.1	±69.4	55.1	±9.0	48.3	±5.9	51.0	±35.4

Kmax, maximal corneal curvature; Kmean, mean corneal curvature; TCT, thinnest corneal thickness.

In our study, 62.7% were males and had a median BCVA of 0.1 and IQR 0.0 to 0.1 logMAR. Mean age for the control group was 42.32 ± 19.04 years (range, 16–96), mean SE was −0.03 ± 1.26 D (range, −3 to +3), and 47.3% were women.

Table 2 summarizes the CT measures for each of the corresponding age groups in each of the nine eccentricities (−3000 microns nasally to +5000 microns temporal to the fovea). The coefficient of variation between observers for CT measurement was less than 3%. A statistically significant difference was noted in CT between healthy and KC eyes (ANOVA for repeated measures; $P < 0.001$) after adjusting CT for age in the control group. This corresponds to an increase in CT of 34% on average (ranging between 31% and 37 % across all eccentricities). However, this difference was less evident in older subjects (>45 years, 7%, ranging from −13% to 18%; Table 3; $P = 0.37$) and largest in younger age groups (<25 years, average increase of 40%, $P < 0.001$; 25–34 years, 23%, $P < 0.001$; 35–44 years, 29%; Table 3; $P < 0.0$). This change with age is summarized in Figure 2.

KC severity grading was provided by Pentacam HR proprietary software; TKC score goes from 0 to a score of 4. Scores of less than 2 were considered to denote early KC, TKC of 2 up to but not including 3 as moderate KC, and TKC of 3 or above as advanced KC (Fig. 3). Correlation between TKC and mean CT at each eccentricity was evaluated, and no significant correlation was detected ($0.149 > r > 0.10$, $0.141 < P < 0.918$, Spearmen test). Correlation between TKC and mean CT was neither significant ($r = 0.079$, $P = 0.430$, Spearmen test; see Supplementary Table S1).

Table 4 represents the correlation between baseline characteristics and CT in KC patients. Significant correlations with CT were found for AL, age, thinnest corneal thickness, and mean corneal curvature.

No difference was found between CT with or without rigid contact lenses. *P* values for the comparison of CT measurements with and without rigid contact lenses ranged from 0.108 to 0.866 (Wilcoxon test). Spearman's Rho correlation coefficient ranged from 0.895 to 0.999 in all variables analyzed, being >0.950 in seven out of nine of them. These results, together with the normal retinal thickness values obtained according to normative data, support our suspicions that astigmatism does not modify CT measurements using this device.

A correlation analysis between CT of right eye (RE) versus left eye (LE) of KC patients was

Table 2. CT for Healthy and KC Populations Across Nine Eccentricities

	Healthy Population by Age					KC by Age					
Eccentricity	<25	25–35	36–45	>45	Mean	<25	25–35	36–45	>45	Mean	*P* Value
−3 mm	125.8	177.5	144.9	139.6	142.7	208.9	214.4	214.4	121.0	192.3	0.001
−2 mm	188.9	242.3	208.4	193.0	200.5	281.0	305.3	293.2	181.2	269.7	0.001
−1 mm	250.7	300.6	266.7	244.5	255.3	345.7	369.3	372.2	246.0	337.9	0.001
0 mm	295.6	332.3	303.6	269.5	285.8	410.4	417.9	404.0	285.9	383.2	0.001
1 mm	298.6	333.7	304.0	259.2	280.5	402.0	414.5	381.4	289.6	375.6	0.001
2 mm	296.3	324.7	287.8	247.3	268.9	385.0	394.0	346.8	268.6	352.0	0.001
3 mm	283.3	323.9	270.4	234.4	256.2	374.6	379.9	334.9	268.3	342.3	0.001
4 mm	262.4	300.1	253.0	226.8	243.4	370.6	371.6	323.3	257.5	333.4	0.001
5 mm	231.2	267.2	257.2	209.0	227.5	336.8	334.8	300.6	246.0	306.4	0.001

Table 3. Percentage of CT Increase in Eyes With KC as Compared to Healthy Age-Adjusted Controls

Age	<25	25–35	36–45	>45	Mean	*P* Value
−3 mm	66%	21%	48%	−13%	35%	<0.001
−2 mm	49%	26%	41%	−6%	35%	<0.001
−1 mm	38%	23%	40%	1%	32%	<0.001
0 mm	39%	26%	33%	6%	34%	<0.001
1 mm	35%	24%	25%	12%	34%	<0.001
2 mm	30%	21%	21%	9%	31%	<0.001
3 mm	32%	17%	24%	14%	34%	<0.001
4 mm	41%	24%	28%	14%	37%	<0.001
5 mm	46%	25%	17%	18%	35%	<0.001
Total	40%	23%	29%	7%	34%	<0.001

performed (49 cases were bilateral). The concordance correlation coefficient (CCC) can be seen in Table 5. We considered the following limits of agreement for CCC: <0.90: poor; 0.90 to 0.95: moderate; 0.95 to 0.99: substantial; >0.99: almost perfect.

Discussion

KC is understood to be a multifactorial disease,[18,19] although its specific pathogenesis has not

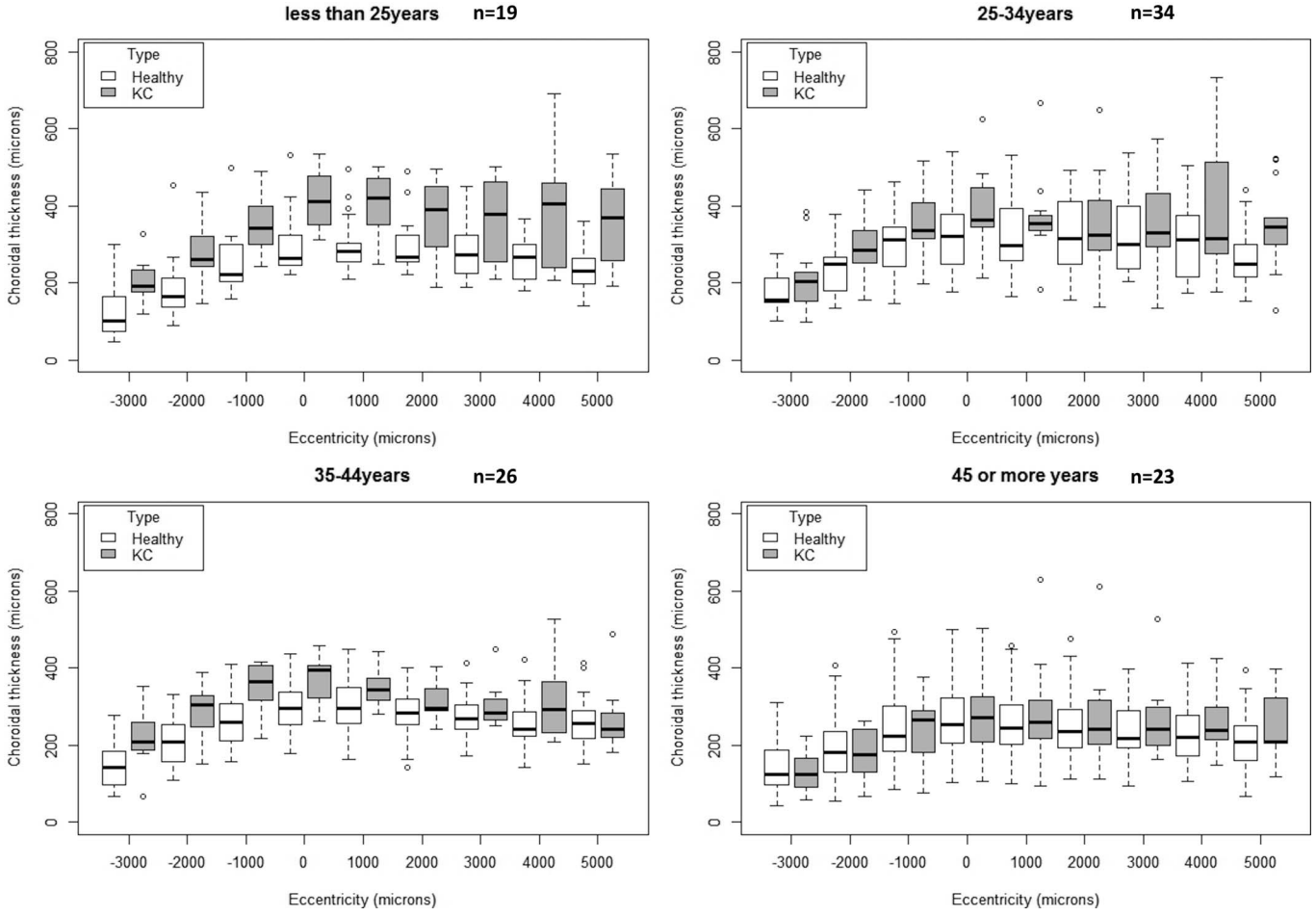

Figure 2. Analysis of CT for each of the corresponding age groups in each of the nine eccentricities (−3000 to +5000 microns) in KC patients versus aged and gender-adjusted healthy controls.

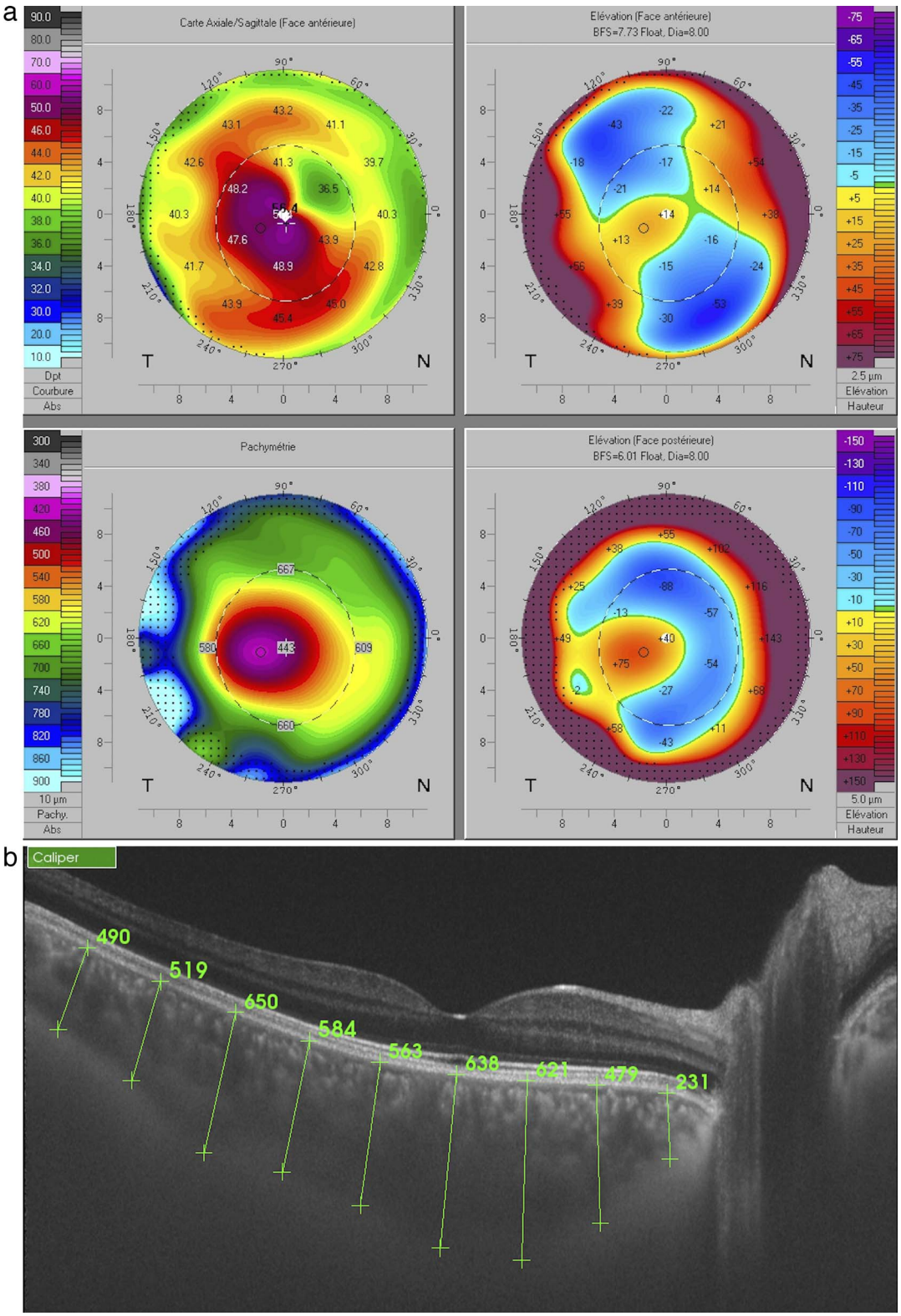

Figure 3. Corneal topography map from both right (grade II KC, a) and left eye (grade I–II, c) of patient with initials ATL provided by Pentacam and including the axial (*top left*) and pachymetric map (*bottom left*), and the anterior (*top right*) and posterior elevation (*bottom right*) of the cornea. Corresponding SS-OCT image of the same patient showing the measurements of CT of right (b) and left eye (d).

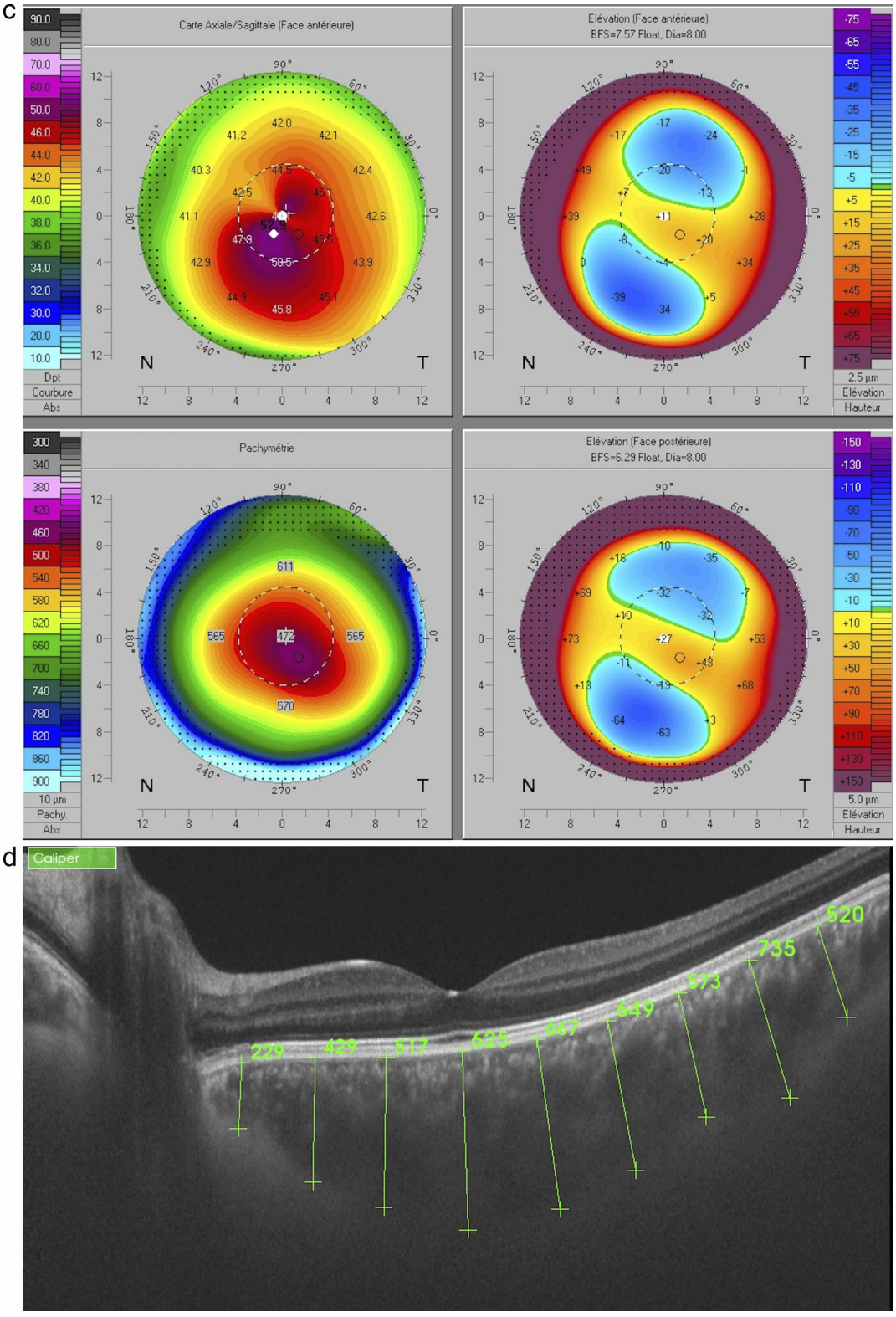

Figure 3. Continued.

Table 4. Univariate and Multivariate Analysis of Correlations Between Baseline Characteristics and CT in Eyes With KC

Parameter	Univariate, *P* Value	Coefficient	Thinner CT Seen	Multivariate, *P* Value
Gender	0.001	−33.6	In men	0.26
AL	0.001	−34.3	In longer eyes	0.001
Age	0.001	−3.6	In older patients	0.001
TKC	0.002	12.7	Lower TKC score	0.001
CXL	0.04	23.9	Patients without CXL	0.19
K-mean	0.002	2.3	Lower Kmean	0.001
K-max	0.008	1.3	Lower Kmax	0.28
TCT	0.001	−0.41	Thicker TCT	0.34

Kmean, Mean corneal curvature; Kmax, maximal corneal curvature; TCT, thinnest corneal thickness.

been completely stablished. In the present study, statistically significant differences were found in the horizontal macular CT at all nine locations of KC patients when compared to normal healthy controls (subfoveal CT: 383.2 vs. 280.5 μm), which meant a mean increase of 34% (from 32%–37% depending on the location; Table 3). This difference in CT is progressively reduced from 40% in patients aged up to 25 years old and only 7% in patients over 45 years. While KC patients aged less than 25, 25 to 35, and 36 to 45 showed statistically thicker choroids when compared to healthy controls, those aged older than 45 did not. KC typically progresses over a period of 15 to 20 years from its diagnosis, usually during adolescence.[20] Our study indicates that KC patients show a statistically thicker choroid until 45 years of age, finding no differences in those aged >45 when compared to healthy controls.

Main changes in KC corneas are found at stromal level, finding reports about a decrease in the amount of extracellular matrix proteins, collagen types I, III, V, VI, and XII, being the collagen type I the main component of the stroma.[21] Whilst collagen fibers show a regular pattern in normal corneas, they are distributed in a more disorganized fashion in KC.[22] Since collagen type I is also the main component of the media and adventitia of vessel walls, and taking into account that the choroid is mostly made of vessels, modifications in the collagen that forms their walls could also be translated into structural variations. This may explain the choroidal thickening observed in KC eyes. Nevertheless, a collagen anomaly would not fully justify the results observed in KC patients older than 45. Other causes that could justify an increased CT would be hyperopia[23] (all our patients were selected according to AL and all mean SE of our control group was –0.03 to avoid this bias), young age[24] (CT was adjusted for age in the control group), hematologic causes such as intraocular lymphoma[25–27] (all our KC patients had no other ocular or systemic diseases), choroidal melanocytosis,[26] and noninflammatory disorders on the pachychoroid spectrum[28,29] (none of our patients showed RPE alterations, subretinal fluid, or pachyvessels on OCT).

Age-related choroidal thinning has been stablished, with an estimated reduction of 10 μm per decade.[30] Some conditions have been associated with a pathological increase of CT. During the acute phase of inflammation, Vogt-Koyanagi-Harada (VKH) patients show a thicker choroid when compared to control patients.[31] Moreover, Maruko et al.[32] described a marked reduction of CT after treatment, returning to normal values 1 month after intravenous methylprednisolone. Following this line of investigation, Kawano et al.[33] analyzed luminal and stromal components of the choroid of VKH patients. Vascu-

Table 5. Correlation Analysis of CT in Right Eyes Versus Left Eyes of KC Patients

Location	CCC	95% CI	*P* Value
N3	0.872	0.774–0.92	0.000
N2	0.862	0.756–0.92	0.000
N1	0.854	0.741–0.918	0.000
SF	0.788	0.623–0.880	0.000
T1	0.805	0.653–0.890	0.000
T2	0.759	0.572–0.864	0.000
T3	0.81	0.666–0.894	0.000
T4	0.832	0.702–0.905	0.000
T5	0.708	0.482–0.835	0.000

CI, confidence interval; N, nasal; SF, subfoveal; T, temporal.

lar dilation and stromal infiltration were both found to be responsible for the choroidal thickening and both were reduced after treatment, with the main variations taking place at the level of the choroidal stroma.[33] A similar situation can be seen in Behçet's disease.[34] Some systemic inflammatory disorders have also been linked to an increase of CT, such as ankylosing spondylitis or psoriasis.[35]

KC has classically been described as a noninflammatory ectasia, but latest findings contradict this theory.[35] KC is typically associated with a reduced corneal sensitivity, increased inflammatory levels in impression cytology, and increased rose Bengal staining, which are all indicative of an inflammatory component in this disease.[36] Furthermore, increased proinflammatory mediators have been observed in tear film analysis of KC patients, such as inflammatory cytokines, metalloproteinase, and cell adhesion molecules, all of which promote extracellular matrix degradation.[37–39] Several proteins such as transforming growth factor β, tumor necrosis factor α, interleukin 1 and 6, intercellular adhesion molecule 1, vascular adhesion molecule 1, and matrix metalloproteinase 9 (MMP9) and lactoferrin, among others, have been implicated in the stromal thinning.[39–42] Based on these findings, Shetty et al.[43] decided to treat KC patients with topical Cyclosporine A due to its anti-inflammatory properties, and the results showed not only diminished MMP9 tear levels, but also a KC stabilization.

Our results report a thinning of the choroid in KC patients aged 45 or older, levelling with CT values of age-adjusted healthy controls, around the same moment in time when KC progressively reaches stabilization.[20] Theories based on an inflammatory component of this disease might help explain this course of events, supporting the idea that inflammatory factors could potentially contribute to both KC activity and increase of CT. As explained before, a CT increase has also been described in other inflammatory diseases, including several different types of uveitis.[31–35] The poor CCC results found between RE and LE of KC patients (Table 6) favors this hypothesis. A high intereye concordance typical of healthy eyes[17,44] may lead to believe that CT is actually a function of the particular anatomy of the KC eye (not necessarily a by-product of inflammation). On the other hand, a higher disagreement between fellow eyes of KC patients (compared to CT concordance between control eyes) would favor an inflammatory etiology as the authors and others in the KC field have proposed. Should these results be confirmed by further, larger studies, CT could potentially become a new clinical marker for disease activity in KC patients.

This study has several limitations. The main one is that CT was manually measured; however, other studies using the same device have shown a correlation between observers from 96.6% to 98.8%, which corresponds well with our results (97%).[17,30] Another limitation was the fact that CT was studied using a single-line, fovea-centered scan protocol, so isolated alterations in the macular CT profile could have been missed. The possibility that optical alterations due to the high astigmatism shown by these patients may have led to altered measurements of CT was discarded, as retinal thickness was among normal limits in all our patients, per information given by volume retinal scans and no difference was found between CT measures with or without rigid contact lenses. The limited sample size could also be considered a limitation, but the fact that KC is a rare disease should be taken into account. We did not analyze extra-ocular confounders in any group, such as cigarette smoking or microvascular disease that might alter both CT and corneal rigidity. When possible, both eyes of KC patients were included, while Ray and O'Day[45] state that it is more accurate to include one eye only for statistical reasons. However, given that KC is considered a rare and, most important, an asymmetric disease, we chose to include all eyes that met the inclusion criteria.

The results of our study showed that the macular CT profile of KC patients is statistically thicker than that of aged-adjusted healthy controls. The difference in CT over normative values was most prominent in young patients losing statistical significance in those over 45 years. CT measured using OCT technology could potentially be a new biomarker for KC stability, should these results be confirmed by further studies.

Acknowledgments

Our gratitude to Ciara Bergin for her valuable help during the first series of statistical analyses of our data.

Rosa Gutierrez-Bonet and José M. Ruiz-Moreno contributed to the conception and design of the work/project. Rosa Gutierrez-Bonet, Jorge Ruiz-Medrano, and Yalda Sadeghi contributed to the acquisition of data. Rosa Gutierrez-Bonet, Jorge Ruiz-Medrano,

and José M. Ruiz-Moreno contributed to the conceptualization of the manuscript and review and synthesis of the literature. Rosa Gutierrez-Bonet, Pablo Peña-Garcia, and José M. Ruiz-Moreno contributed to the analysis and interpretation of data. Rosa Gutierrez-Bonet, Jorge Ruiz-Medrano, José M. Ruiz-Moreno, Muriel Catanese, Eric Gabison, Yalda Sadeghi, Pablo Peña-Garcia, and Katayoon Hashemi contributed to the critical review and revision of the manuscript. Rosa Gutierrez-Bonet and Jorge Ruiz-Medrano contributed to the drafting of the manuscript. Rosa Gutierrez-Bonet, Jorge Ruiz-Medrano, José M. Ruiz-Moreno, Muriel Catanese, Eric Gabison, Yalda Sadeghi, Pablo Peña-Garcia, and Katayoon Hashemi contributed to the final approval of the version to be published.

Disclosure: **R. Gutierrez-Bonet,** None; **J. Ruiz-Medrano,** None; **P. Peña-Garcia,** None; **M. Catanese,** None; **Y. Sadeghi,** None; **K. Hashemi,** None; **E. Gabison,** None; **J.M. Ruiz-Moreno,** F (Topcon, Co)

References

1. Kalkan Akcay E, Akcay M, Uysal BS, et al. Impaired corneal biomechanical properties and the prevalence of keratoconus in mitral valve prolapse. *J Ophthalmol*. 2014;2014:402193.
2. Gomes JA, Rapuano CJ, Belin MW ARJ. Global consensus on keratoconus diagnosis. Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. *Cornea*. 2015;34:359–369.
3. Woodward MA, Blachley TS, Stein JD. The association between sociodemographic factors, common systemic diseases, and keratoconus an analysis of a nationwide heath care claims database. *Ophthalmology*. 2016;123:457–465.
4. Grieve K, Georgeon C, Andreiuolo F, et al. Imaging microscopic features of keratoconic corneal morphology. *Cornea*. 2016;35:1621–1630.
5. Copete S, Flores-Moreno I, Montero JA, Duker JS, Ruiz-Moreno JM. Direct comparison of spectral-domain and swept-source OCT in the measurement of choroidal thickness in normal eyes. *Br J Ophthalmol*. 2014;98:334–338.
6. Spaide RF, Koizumi H, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2008;146:496–500.
7. Gabriele ML, Wollstein G, Ishikawa H, et al. Optical coherence tomography: history, current status, and laboratory work. *Invest Ophthalmol Vis Sci*. 2011;52:2425–2436.
8. Huang D, Swanson E, Lin C, Schuman J, Stinson W, Chang W. Optical coherence tomography. *Science*. 1991;254:1178–1181.
9. Lim H, de Boer J, Park B, Lee E, Yelin R, Yun S. Optical frequency domain imaging with a rapidly swept laser in the 815-870 nm range. *Opt Express*. 2006;14:5937–5944.
10. Huber R, Adler D, Srinivasan V, Fujimoto J. Fourier domain mode locking at 1050 nm for ultra-high-speed optical coherence tomography of the human retina at 236, 000 axial scans per second. *Opt Lett*. 2007;32:2049–2051.
11. Unterhuber A, Povazay B, Hermann B, Sattmann H, Chavez-Pirson A, Drexler W. In vivo retinal optical coherence tomography at 1040 nm-enhanced penetration into the choroid. *Opt Express*. 2005;13:3252–3258.
12. Flores-Moreno I, Lugo F, Duker JS, Ruiz-Moreno JM. The relationship between axial length and choroidal thickness in eyes with high myopia. *Am J Ophthalmol*. 2013;155:314–319.
13. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. *J Refract Surg*. 1995;11:371–379.
14. Kurian M, Negalur N, Das S, et al. Biometry with a new swept-source optical coherence tomography biometer: repeatability and agreement with an optical low-coherence reflectometry device. *J Cataract Refract Surg*. 2016;42:577–581.
15. Mohammadpour M, Mohammad K, Karimi N. Central corneal thickness measurement using ultrasonic pachymetry, rotating scheimpflug camera, and scanning-slit topography exclusively in thin non-keratoconic corneas. *J Ophthalmic Vis Res*. 2016;11:245–251.
16. Flynn TH, Sharma DP, Bunce C, Wilkins MR. Differential precision of corneal Pentacam HR measurements in early and advanced keratoconus. *Br J Ophthalmol*. 2016;100:1183–1187.
17. Ruiz-Medrano J, Flores-Moreno I, Pena-Garcia P, Montero JA, Duker JS, Ruiz-Moreno JM. Asymmetry in macular choroidal thickness profile between both eyes in a healthy population measured by swept-source optical coherence tomography. *Retina*. 2015;35:2067–2073.
18. Bykhovskaya Y, Margines B, Rabinowitz YS. Genetics in keratoconus: where are we? *Eye Vis*. 2016;3:16.

19. Cremona FA, Ghosheh FR, Rapuano CJ, et al. Keratoconus associated with other corneal dystrophies. *Cornea*. 2009;28:127–135.
20. Feder RS, Neems LC. Noninflammatory ectatic disorders. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *CORNEA Fundamentals, Diagnosis, and Management*. 4th ed. New York, NY: Elsevier; 2017:820–843.
21. Chaerdaky R, Shao H, Pandey A, Jun A, Chakravarti S. The keratoconus corneal proteome: loss of epithelial integrity and stromal degeneration. *J Proteomics*. 2013;87:122–131.
22. Akhtar S, Bron AJ, Salvi SM, Hawksworth NR, Tuft SJ, Meek KM. Ultrastructural analysis of collagen fibrils and proteoglycans in keratoconus. *Acta Ophthalmol*. 2008;86:764–772.
23. Jin P, Zou H, Zhu J, et al. Choroidal and retinal thickness in children with different refractive status measured by swept-source optical coherence tomography. *Am J Ophthalmol*. 2016;168:164–176.
24. Ruiz-Moreno JM, Flores-Moreno I, Lugo F, Ruiz-Medrano J, Montero JA, Akiba M. Macular choroidal thickness in normal pediatric population measured by swept-source optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54:353–359.
25. Shields CL, Arepalli S, Pellegrini M, Mashayekhi A, Shields JA. Choroidal lymphoma shows calm, rippled, or undulating topography on enhanced depth imaging optical coherence tomography in 14 eyes. *Retina*. 2014;34:1347–1353.
26. Shields CL, Pellegrini M, Ferenczy SR, Shields JA. Enhanced depth imaging optical coherence tomography of intraocular tumors: from placid to seasick to rock and rolling topography—the 2013 Francesco Orzalesi Lecture. *Retina*. 2014;34:1495–1512.
27. Arias JD, Kumar N, Fulco EA, et al. The seasick choroid: a finding on enhanced depth imaging spectral-domain optical coherence tomography of choroidal lymphoma. *Retin Cases Brief Rep*. 2013;7:19–22.
28. Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. *Retina*. 2013;33:1659–1672.
29. Pang CE, Freund KB. Pachychoroid neovasculopathy. *Retina*. 2015;35:1–9.
30. Ruiz-Medrano J, Flores-Moreno I, Peña-García P, Montero JA, Duker JS, Ruiz-Moreno JM. Macular choroidal thickness profile in a healthy population measured by swept-source optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2014;55:3532–3542.
31. Fong AHC, Li KKW, Wong D. Choroidal evaluation using enhanced depth imaging spectral-domain optical coherence tomography in Vogt-Koyanagi-Harada disease. *Retina*. 2011;31:502–509.
32. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness after treatment of Vogt-Koyanagi-Harada disease. *Retina*. 2011;31:510–517.
33. Kawano H, Sonoda S, Yamashita T, Maruko I. Relative changes in luminal and stromal areas of choroid determined by binarization of EDI-OCT images in eyes with Vogt-Koyanagi-Harada disease after treatment. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:421–426.
34. Ishikawa S, Taguchi M, Muraoka T, Sakurai Y, Kanda T, Takeuchi M. Changes in subfoveal choroidal thickness associated with uveitis activity in patients with Behcet's disease. *Br J Ophthalmol*. 2014;98:1508–1513.
35. Türkcü FM, Sahin A, Yüksel H, et al. Evaluation of choroidal thickness in psoriasis using optical coherence tomography. *Int Ophthalmol*. 2016;36:851–854.
36. Dogru M, Karakaya H, Özçetin H, et al. Tear function and ocular surface changes in keratoconus. *Ophthalmology*. 2003;110:1110–1118.
37. Ionescu C, Corbu CG, Tanase C, et al. Inflammatory biomarker profile as microenvironmental expression in keratoconus. *Dis Markers*. 2016;2016:1243819.
38. Pásztor D, Kolozsvári BL, Csutak A, et al. Tear mediators in corneal ectatic disorders. *PLoS One*. 2016;11:1–14.
39. Lema I, Sobrino T, Durán J a, Brea D, Díez-Feijoo E. Subclinical keratoconus and inflammatory molecules from tears. *Br J Ophthalmol*. 2009;93:820–824.
40. Jun AS, Cope L, Speck C, et al. Subnormal cytokine profile in the tear fluid of keratoconus patients. *PLoS One*. 2011;6:1–8.
41. Galvis V, Sherwin T, Tello A, Merayo J, Barrera R, Acera A. Keratoconus: an inflammatory disorder? *Eye*. 2015;29:843–859.
42. Lema I, Brea D, Rodríguez-González R, Díez-Feijoo E, Sobrino T. Proteomic analysis of the tear film in patients with keratoconus. *Mol Vis*. 2010;16:2055–2061.
43. Shetty RR, Ghosh AA, Lim RR, et al. Elevated expression of matrix metalloproteinase-9 and inflammatory cytokines in keratoconus patients

is inhibited by cyclosporine A. *Invest Ophthalmol Vis Sci*. 2015;56:738–750.
44. Chen FK, Yeoh J, Rahman W, et al. Topographic variation and interocular symmetry of macular choroidal thickness using enhanced depth imaging optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53:975–985.
45. Ray W, O'Day D. Statistical analysis of multi-eye data in ophthalmic research. *Invest Opthalmol Vis Sci*. 1985;26:1186–1188.