Corneal Cross-Linking Pre-Operative Assessment using OCT Full-Field Corneal Pachymetry Compared to Ultrasonic Pachymetry.

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ABSTRACT

Purpose: This study compares single central corneal pachymetry measurements to the full-field ocular coherence tomography (OCT) pachymetry's minimal corneal thickness measurements to better identify patients who should be excluded from corneal cross-linking due to insufficient corneal thickness requirements.

Methods: A total of 32 eyes from 16 patients were identified. Inclusion criteria included patients with keratoconus who had both single central corneal ultrasonic pachymetry and full-field OCT – pachymetry measurements performed during pre-operative cross-linking evaluation.

Results: The mean central corneal thickness for single ultrasound pachymetry was 461.3 microns (95% CI 443- 479.6 microns) and for full-field OCT-pachymetry it was 415.4 (95% CI 391.1 - 439.7 microns). The difference was statistically significant (p = 0.000098) as calculated by a paired student's T test. Five of the 32 subjects (15.5%) had OCT full-field corneal pachymetry measurements less than 400 microns, while the single ultrasonic measurement was greater than 400 microns in all but 2 subjects.

Conclusions: A significant difference was noted in corneal pachymetry measurements comparing single ultrasound pachymeter to the minimal corneal thickness on full-field OCT pachymetry during the assessment for corneal cross-linking. Reliance on single ultrasound pachymetry measurements could lead to treatment of corneas with inadequate corneal thickness and result in endothelial cell damage during corneal cross-linking.

Key Words: Keratoconus, Pachymetry, corneal collagen cross linking, Corneal cross linking, CXL, Ultrasonic pachymetry, Ocular Coherence Tomography, OCT.

Keratoconus is a bilateral, progressive ectatic corneal disorder with an incidence of 1 in 2,000.[1-3] Corneal collagen cross-linking (CXL) has been used to structurally strengthen the corneal stroma and potentially halt the progressive ectasia seen in keratoconus patients. The procedure involves exposure to ultraviolet-A (370 nm) light after treating the cornea with a riboflavin solution. This process generates free radicals that cross-link adjacent collagen fibrils and strengthen the corneal stroma.[4-6] Prior to the advent of CXL, it was estimated that between 11 to 27% of keratoconus patients would go on to require corneal transplantation due to progressive ectasia, thinning and scarring.[7-8]

Multiple modalities exist to measure corneal thickness during the preoperative evaluation prior to CXL. Ultrasonic pachymetry typically measures a single point, usually performed in the center of the cornea. However, it is well known that, in keratoconus, the thinnest region of the cone is rarely in the central cornea[9-10] which could be missed with a single-point measurement. Ultrasonic single point pachymetry measurement is still a common component of the CXL pre-operative assessment.

Wollensak et al.[11] found that during their initial corneal cross-linking studies, UVA light transmission measurements following riboflavin treatment can be calculated that, in human corneas thinner than 400 microns, the cytotoxic endothelial UVA irradiance of 0.36 mW/cm2 is reached using the standard surface irradiance of 3.0 mW/cm2. This indicates that CXL treatment of corneas thinner

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than 400 microns, as those found in advanced keratoconus, could lead to irreversible endothelial cell toxicity and corneal decompensation. Dhaliwal and Kaufman[12] demonstrated that the standard CXL treatment in human corneas produces total cellular loss within the anterior 300 microns of the corneal stroma, while Kymonis et al.[13] showed that endothelial cell loss was found in 10.7% of 14 eyes with corneal pachymetry measurements between 350-399 microns after epithelial removal.

In this study we compare single central ultrasonic corneal pachymetry measurements to the full-field ocular coherence tomography (OCT) pachymetry's minimal corneal thickness measurements to better identify patients who should be excluded from standard corneal cross-linking due to safety concerns involving corneal endothelial cell damage in corneas with a pachymetry of less than 400 microns.

SUBJECTS AND METHODS

A retrospective chart review was performed for all patients who underwent pre-operative evaluation by one surgeon (SCK) for CXL at the Medical College of Wisconsin between July 2018 and May 2019. All patients had an established diagnosis of progressive keratoconus based on previous clinical examination and corneal topography. Only patients with both ultrasound pachymetry and full-field OCT pachymetry measurements were included in the study. Patient demographics are noted in Table 1. Data was collected following the tenants of the Declaration of Helsinki, in accord with the Health Insurance Portability and Accountability Act of 1996 and was approved by the Institutional Review Board at the Medical College of Wisconsin.

Full-field OCT-pachymetry measurements were obtained with the CIRRUS Anterior Segment OCT (Carl Zeiss Meditec, Inc., Jena, Germany). This device uses an 840 nm superluminescent diode to obtain approximately 100,000 A-scans per second with axial resolution of 5 µm and tangential resolution of 15 µm. A full field corneal thickness map was created (shown in Figure 1) from which the minimal corneal thickness is determined. OCT imaging was performed prior to ultrasonic pachymetry measurements to prevent any alterations induced by corneal contact with the ultrasonic probe.

Ultrasonic corneal pachymetry measurements were obtained using a DGH Pachmate 2 Handheld Pachymeter (DGH Technology Inc,, Exton, PA). Measurements were obtained in the central cornea after administration of topical anesthetic drops (Proparacaine hydrochloride 0.5%) and prior to any contact of the corneal surface with other devices or lenses. This pachymeter device takes 25 corneal measurements in rapid succession at a single location and calculates the average thickness and standard deviation. The average value was recorded in the chart and used for analysis in this study. All ultrasonic and OCT measurements were obtained in sequential fashion at the same visit to minimize diurnal variations or other factors such as corneal hydration.

Average and minimal corneal thickness measurements were recorded with standard deviation. Statistically significant differences in corneal thickness from ultrasonic and OCT measurements were evaluated with a paired student's t test. By convention, statistical significance was determined by a P value <0.05 and corresponding confidence intervals of 95%.

RESULTS

A total of 32 eyes from 16 patients met inclusion criteria and were included in the study. Patient characteristics are provided in Table 1. The average age was 31.9 years with a range from 18 to 60 years old. Twelve of the 16 participants were males (75%) while four (25%) were females. The mean central corneal thickness for single ultrasound pachymetry was 461.3 microns (95% CI 443- 479.6 microns) and for full-field OCT-pachymetry it was 415.4 (95% CI 391.1 - 439.7 microns). The difference was statistically significant (p = 0.000098) as calculated by a paired student's T test. Five of the 32 subjects (15.5%) had OCT full-field corneal pachymetry measurements less than 400 microns, while the single ultrasound measurement was greater than 400 microns (Table 2).

Table 1. *Summary of CXL patient characteristics and differences between ultrasonic pachymetry and OCT full-field pachymetry measurements.*

Characteristic	Value
Average Age	31.9 years [18-60]
Male	N = 12 (75%)
Female	N = 4 (25%)
Average Ultrasound Pachymetry and std deviation	461.28 ± 50.65 microns
Average Minimal Thickness OCT Pachymetry and std deviation	415.38 ± 67.49 microns

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Table 2. *Study data: subject and pachymetry data*

Subject/Eye	Age	Gender	Ultrasound Pachymetry	OCT Minimal Pachymetry
1	53	M	455	421
2	53	M	388	286
3	18	M	437	356
4	18	M	530	501
5	24	M	439	420
6	24	M	415	401
7	36	M	460	454
8	36	M	451	420
9	18	M	515	491
10	18	M	433	380
11	30	M	568	239
12	30	M	408	363
13	24	M	512	479
14	24	M	365	295
15	28	F	482	478
16	28	F	469	447
17	26	F	471	441
18	26	F	451	421
19	20	M	496	489
20	20	M	465	455
21	46	M	470	418
22	46	M	415	380
23	27	M	361	337
24	27	M	358	291
25	20	M	493	449
26	20	M	530	441
27	60	F	496	404
28	60	F	493	487
29	50	F	481	445
30	50	F	480	464
31	31	M	460	449
32	31	M	514	490

DISCUSSION

Accurate assessment of corneal thickness prior to corneal cross-linking is important since the treatment of corneas with inadequate thickness can lead to endothelial damage. Based on previous animal and human studies, a corneal thickness of greater than 400 microns is generally considered safe for conventional CXL.[5,12,14-16] Dhaliwal and Kaufman demonstrated that CXL produced an acellular region within the anterior stroma to a depth of 300 um in the treated cornea; thus, an additional "safety factor" of 100 microns is reasonable, which is why the 400 micron minimum corneal thickness in patients undergoing CXL is necessary.[12,13] However, advanced keratoconus can lead to progressive corneal thinning, with corneal pachymetry below 400 microns which may put patients at risk for endothelial cell damage during the CXL procedure. It may be possible that reports of posterior corneal haze after corneal cross-linking are, in actuality, the result of endothelial cell damage in a cross-linked cornea.[17] This study demonstrates that single point ultrasonic pachymetry often does not detect the true minimal corneal thickness, compared to full field OCT measurements, and reliance on this method may lead to misidentification of CXL candidates in certain cases.

Due to the ease of use, reproducibility of measurements[18] and relative cost/availability of handheld ultrasound pachymeters, this method has become common practice for evaluation of corneal thickness including in the pre-operative assessment for CXL. However, this method has its limitations. First, with single point measurements, the location of testing is critical and, as stated previously, could miss the often-eccentric thinnest region of the cornea. To our knowledge, many providers are not routinely mapping corneal thickness by testing multiple measurements in different meridians as was previously done with keratorefractive surgeries, such as radial keratometry.[19] This practice of corneal mapping could possibly increase the likelihood of detecting the minimal corneal thickness compared to central measurements alone but this has not been directly studied and may still be inferior to modern full-field OCT and other tomographic analysis methods. Figure 1 demonstrates an OCT full filed pachymetry map. In this example, the region of minimal corneal thickness is not in the central cornea. The table must be referenced to identify the thinnest pachymetry measurement. Another limitation of ultrasonic pachymetry is the direct corneal contact required for measurement. Non-perpendicular placement can lead to overestimation of corneal thickness and corneal indentation with the probe could disrupt the reflective surfaces, including displacement of the tear film[20] and cause thinning of the epithelium leading to inaccurate results. The lack of a set fixation target may make ultrasonic pachymetry less reproducible compared to OCT imaging, which uses a central fixation target to maintain central gaze and allows for more accurate identification of the central corneal surface.[21]

Our present study focuses on corneal thickness measurements from two separate devices that are commercially available and easy to use in the pre-operative assessment for cross-linking (figure 2).

In addition to the aforementioned devices, there are other manners of testing corneal thickness including but not limited to Scheimpflug camera imaging, confocal microscopy and optical coherence pachymetry. Several studies show high correlation between central corneal thickness measure-

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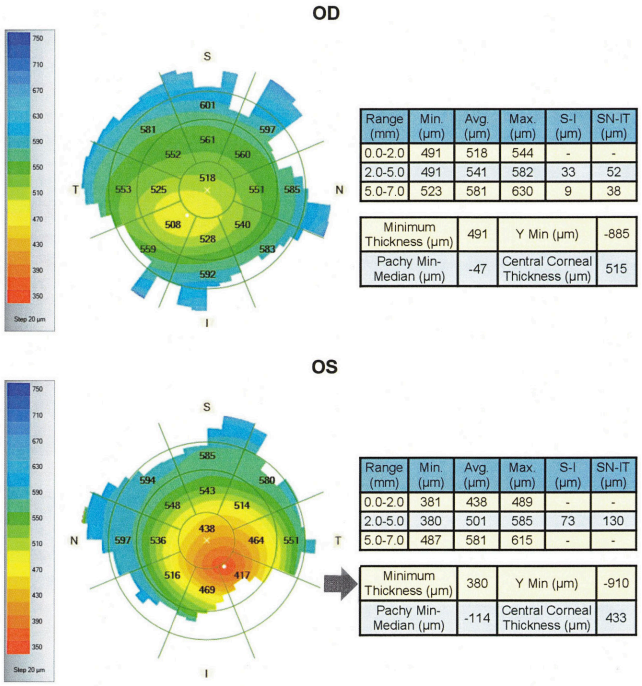

Figure 1. *This OCT full-field pachymetry demonstrates that the cone is not located in the central cornea in either eye. Furthermore, the thinnest corneal pachymetry (Black Arrow) is less than 400 microns in the left eye (OS). This would not have been detected by central Ultrasonic pachymetry.*

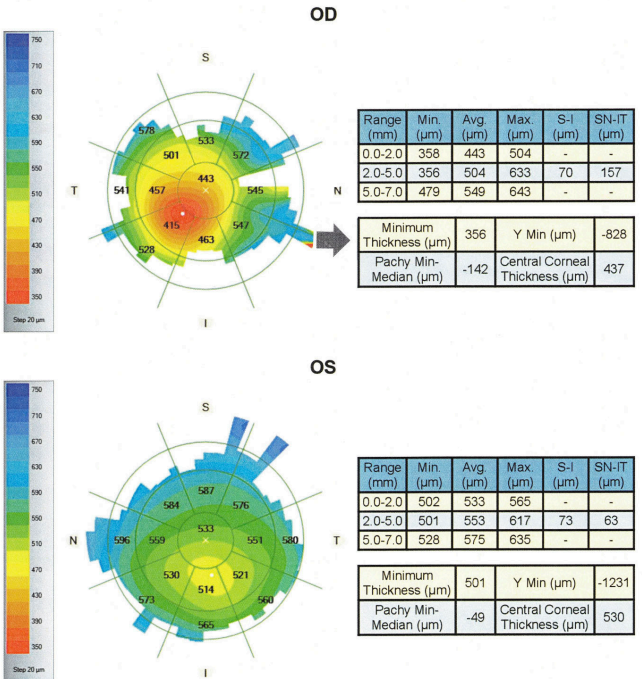

Figure 2. *Note the OD eccentric cone and the 356 micron thinnest pachymetry measurement (Black arrow) by OCT full-field pachymetry. The OD central pachymetry is over 440 microns and the OS minimum corneal thickness is greater than 500 microns.*

ments with various devices but raise the question of interchangeability of devices in clinical practice.[22-27] In regards to the devices used in the current study, ultrasound pachymetry has been found to consistently measure a higher central corneal thickness when compared to anterior segment OCT with values ranging between 7.5 - 49.4 microns higher.[27-30] Although there are limitations when comparing these measurements, including exact location of testing on the cornea, hardware/software used for analysis and methodological differences, the evidence suggests that there is a systematic difference between OCT and ultrasound.

The difference in corneal thickness, as measured with ultrasound and OCT, compounded by the fact that ultrasound pachymetry is not routinely checked in multiple corneal meridians, could lead to misidentification and treatment of corneas with inadequate thickness (less than 400 microns) during corneal cross-linking and result in irreversible endothelial damage. Full-field OCT pachymetry detected minimal corneal thickness more often than single measurement ultrasound pachymetry. We recommend full-field pachymetry during the pre-operative examination of prospective corneal cross linking patients.

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