Original Article

Comparison of Six Methods of Central Corneal Thickness Measurement in Healthy Eyes

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Abstract

Objectives: Several methods of measuring central corneal thickness (CCT) have been compared, however, the data are still limited and conflicting. The aim of this study was to determine the agreement of CCT measurements performed in healthy eyes using ultrasound pachymetry (USP), non-contact tono/pachymetry, specular microscopy, biometry, Scheimpflug-based corneal topography, and optical coherence tomography (OCT).

Methods: All of the participants underwent a complete ophthalmological examination. The CCT of all of the eyes included was measured using 6 different methods. The agreement between the methods was analyzed using the mean difference and Bland-Altman analysis based on a 95% limits of agreement.

Results: A total of 64 patients with a mean age of 40.96±14.52 years (range: 20-78 years) were included in the study. The mean CCT value was 552.10±35.65 µm, 550.40±35.55 µm, 554.67±35.49 µm, 545.39±34.21 µm, 546.25±35.49 µm, and 552.64±33.59 µm using USP, non-contact tono/pachymetry, non-contact specular microscopy, biometry, Scheimpflug-based corneal topography, and OCT, respectively. The bias values determined by Bland-Altman plots were -1.70, -2.56, 6.71, 5.85, and -0.53 for tono/pachymetry, specular microscopy, biometry, topography, and OCT, respectively. OCT demonstrated the lowest bias compared to USP. The overall intraclass correlation coefficient was 0.961 (range: 0.945-0.974) with a 95% confidence interval.

Conclusion: All of the CCT measurements obtained using non-contact tono/pachymetry, non-contact specular microscopy, biometry, Scheimpflug-based corneal topography, and OCT were consistent with the USP measurements of healthy controls. Larger prospective studies to determine the interchangeability of different methods for CCT measurements in pathological conditions are warranted.

Keywords: Biometry, central corneal thickness, corneal topography, pachymetry, specular microscopy

Introduction

Central corneal thickness (CCT) measurements are commonly used to assess corneal endothelial function and to evaluate patients before and after keratorefractive surgery. CCT is also very important for the evaluation of intraocular pressure (IOP) measurements and a thinner cornea is associated with a greater risk of developing glaucoma (1,2). In addition, measurement of CCT is essential in excimer laser surgery, since photoablation with this laser may lead to considerable changes in CCT (3).

Currently, the gold standard for CCT measurement is ultrasound pachymetry (USP). However, the USP probe must be positioned carefully to avoid possible complications, such as corneal epithelial defects, irritation, or infection due to direct contact of the probe with the cornea (4,5). Therefore, other techniques of CCT evaluation, such as biometry, optical coherence tomography (OCT), and specular microscopy, have gained importance. It is essential to know if there is a discrepancy in CCT measurements obtained with different devices, especially for long-term follow-up and surgical decisions.

The results of previous comparisons of different devices used to perform CCT measurements have yielded limited and conflicting data. The objective of this study was to compare the CCT measurement of healthy eyes recorded using 6 different methods: UPS, non-contact pachymetry, specular microscopy, biometry, Scheimpflug-based corneal topography, and OCT, to determine the agreement between the techniques.

Methods

This prospective cross-sectional study was designed to evaluate the reproducibility, correlation, and agreement of CCT measurements in healthy individuals using 6 different methods. The study was approved by the institutional review board on January 15, 2019 (no: 33216249-604). Informed consent was obtained from all of the participants and the study was conducted in accordance with the Declaration of Helsinki.

A total of 64 patients were enrolled. The exclusion criteria were: age <18 years, poor cooperation during the examination or declining to participate, previous LASIK surgery, use of contact lenses within 2 weeks of the examination, or any chronic systemic and/or ocular disease (such as diabetes mellitus, malignancy, chronic renal failure, glaucoma, or dry eye disease).

All of the participants underwent a complete ophthalmological examination. The CCT of each eye was measured using all 6 methods.

The UPS device (P-1; Takagi Seiko Co. Ltd., Nagano, Japan) employed uses sound velocity at a frequency of 20 MHz and had a tip diameter of 1.5 mm. Five minutes before the measurement, 1 drop of 0.5% proparacaine hydrochloride was added to the cornea, and the patients were asked to look straight ahead when the probe was placed perpendicular to the corneal center. The median of 5 measurements was recorded.

Non-contact tono/pachymetry (NT-530P; Nidek Co., Ltd., Tokyo, Japan) was performed 3 times for each eye, and the average value was used for statistical analysis. The patients were positioned on the chinrest of the device and asked to look at the target.

For non-contact specular microscopy (CEM-530; Nidek Co., Ltd., Tokyo, Japan) measurement, the patients were positioned with their chin placed in a cup and their forehead against the headband of the device. The CCT was measured 3 times for each eye, and the average was noted.

For biometrical CCT measurements (AL-Scan; Nidek Co., Ltd., Tokyo, Japan), the patients were instructed to rest their forehead on the headrest and focus on the blue light from the camera. A good-quality image was captured and biometric measurements were recorded.

Corneal topography (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy) was performed using the Sirius system, which is based on the combination of a Placido disc and Scheimpflug technology. All of the participants were asked to fix their eyes on the target. When the image was in focus, the device automatically performed the analysis, and the corneal curvature and anterior and posterior elevation values were determined. CCT was defined as the difference between the anterior and posterior elevations in the central cornea.

OCT is a non-contact, non-invasive imaging technique that exposes the layers of the cornea. In this study, the RS-3000 Advance OCT device (Nidek Co., Ltd., Tokyo, Japan) was used to capture high-resolution images of the cornea. The images were aligned with the corneal apex area to determine corneal reflection. The system obtained 5 different images, separated by 0.25 mm with 5 μm of axial resolution and 15 μm of transversal resolution. Once the image was saved, the caliper tool of the instrument was used to identify the corneal limits (epithelium and endothelium) to obtain the CCT values. The average CCT value was calculated for further analysis.

Only the right eye of the participants was examined, and the measurements were performed in sequence: non-contact tono/pachymetry, non-contact specular microscopy, biometry, Scheimpflug-based corneal topography, OCT, and USP. USP was performed last so as not to affect the results of the other examinations since it involved the use of a topical anesthetic (Alcaine; Alcon, Geneva, Switzerland). Since CCT may vary in the first hours after sleep, all of the measurements were performed between 2 pm and 5 pm. All of the measurements were performed by a single ophthalmologist.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY). The normality of data was confirmed using the Kolmogorov-Smirnov test. The results were compared using multivariate analysis of variance, linear regression, and Pearson's correlation analysis. The agreement between the devices was analyzed using the mean differences and Bland-Altman analysis based on a 95% limits of agreement (LoA) (6). The

LoA was estimated by the mean difference ± 1.96×SD of the differences, which provided an interval within which 95% of the differences between the measurements were expected to lie. A p value of <0.05 was considered statistically significant. Reliability was analyzed using the intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) values. In general, an ICC value of >0.8 is considered to indicate good repeatability, and a value >0.9 suggests excellent repeatability of measurements.

Results

Sixty-four patients (33 females and 31 males) with a mean age of 40.96±14.52 years (range: 20-78 years) were included in the study. The mean results of the 6 methods are summarized in Table 1. There was no significant difference in the mean CCT values (p=0.18). The lowest measurement was obtained with biometry while the OCT result was the highest.

Table 1. The mean central corneal thickness value determined with 6 different methods (μm)

Ultrasound pachymetry	552.10±35.65
Non-contact pachymetry	550.40±35.55
Specular microscope	554.67±35.49
Biometry	545.39±34.21
Corneal topography	546.25±35.49
Optical coherence tomography	552.64±33.59
p	0.18

All data are presented as mean±SD.

There were strong significant correlations between the CCT measurements recorded using all of the methods, with a significance level of 0.001 (Table 2). A comparison of the results is illustrated in scatter graphs presented in Figure 1.

Bland-Altman plots were drawn for each method compared with USP (Fig. 2). The bias values determined were -1.70, -2.56, 6.71, 5.85, and -0.53 for tono/pachymetry, specular microscopy, biometry, topography, and OCT, respectively (Table 3). OCT provided the lowest bias.

The ICC was calculated for the 5 methods examined compared with USP (Table 3). The overall ICC value was 0.961, and ranged from 0.945 to 0.974 at a 95% CI.

Discussion

This study was a comparison of USP and 5 other methods of measuring CCT. We determined that there was no significant difference between the results; the results were highly correlated, and the ICC values were >0.9.

An accurate evaluation of CCT measurement is very important in the follow-up of patients with or at risk to develop glaucoma, as well as preoperative and postoperative care of patients undergoing keratorefractive surgery. It has been recognized in recent years that studies of the reliability and interchangeability of CCT values measured using different methods are needed and of great value, especially in the follow-up of chronic conditions.

In the literature, data about different methods of CCT measurement are limited and conflicting. Maresca et al. (7) compared the agreement and reliability of a rotating Scheimpflug camera and USP and found a high correlation between

Table 2. The results of Pearson correlation analysis performed for the CCT results of different methods

	USP	Non-contact pachymeter	Specular microscope	Biometry	Corneal topography	OCT
USP	-	p:0.001	p:0.001	p:0.001	p:0.001	p:0.001
		r:0.977	r:0.973	r:0.974	r:0.940	r:0.976
Non-contact pachymeter	p:0.001	-	p:0.001	p:0.001	p:0.001	p:0.001
	r:0.977		r:0.975	r:0.967	r:0.937	r:0.962
Specular microscope	p:0.001	p:0.001	-	p:0.001	p:0.001	p:0.001
	r:0.973	r:0.975		r:0.952	r:0.919	r:0.965
Biometry	p:0.001	p:0.001	p:0.001	-	p:0.001	p:0.001
	r:0.974	r:0.967	r:0.952		r:0.971	r:0.984
Corneal topography	p:0.001	p:0.001	p:0.001	p:0.001	-	p:0.001
	r:0.940	r:0.937	r:0.919	r:0.971		r:0.959
OCT	p:0.001	p:0.001	p:0.001	p:0.001	p:0.001	-
	r:0.976	r:0.962	r:0.965	r:0.984	r:0.959	

r: Pearson correlation coefficient; p<0.05 was considered statistically significant; CCT: Central corneal thickness; OCT: Optical coherence tomography.
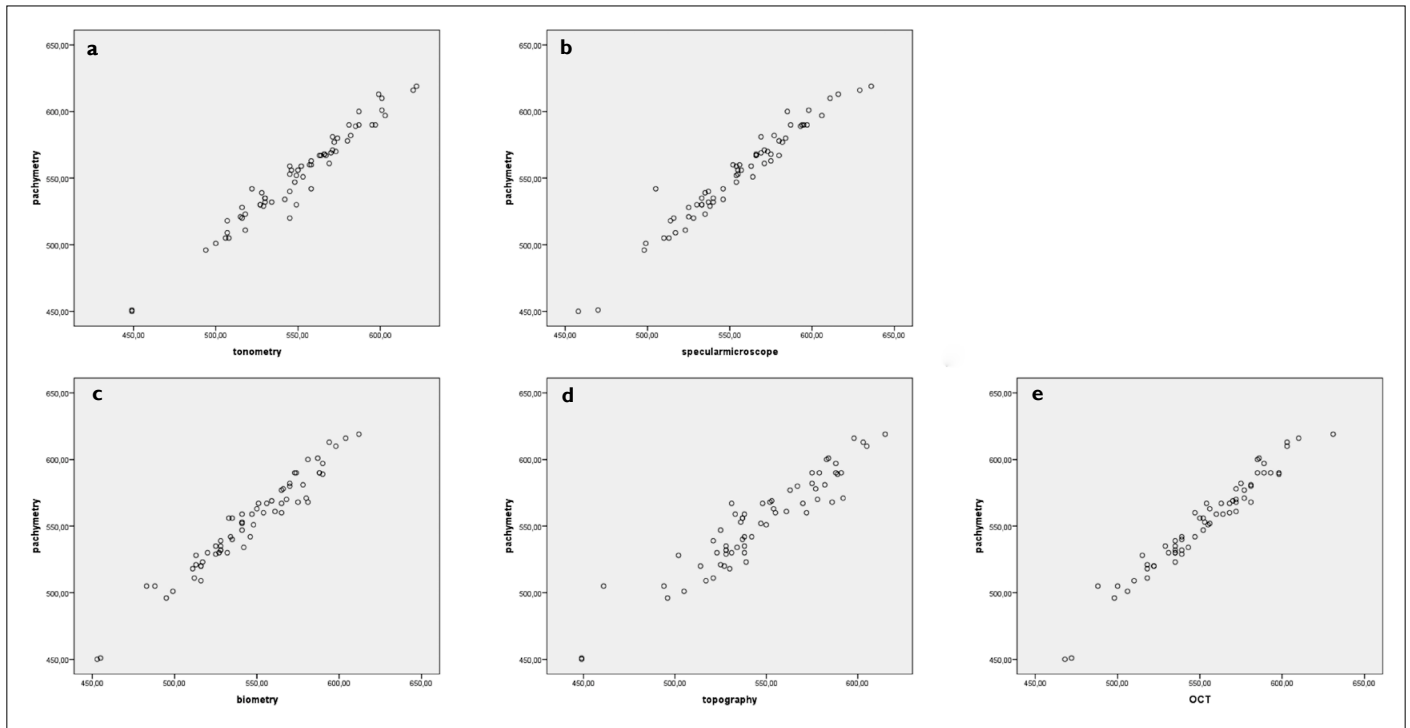
Figure 1. Scatter plot graphs showing the distribution of central corneal thickness measurement results. **(a)** Non-contact pachymeter and ultrasound pachymetry (USP), **(b)** specular microscopy and USP, **(c)** biometry and USP, **(d)** topography and USP, **(e)** optical coherence tomography and USP.

Figure 2. Bland-Altman plots showing the comparison of central corneal thickness results between devices. **(a)** Non-contact pachymeter and ultrasound pachymetry (USP), **(b)** specular microscopy and USP, **(c)** biometry and USP, **(d)** topography and USP, **(e)** optical coherence tomography and USP.
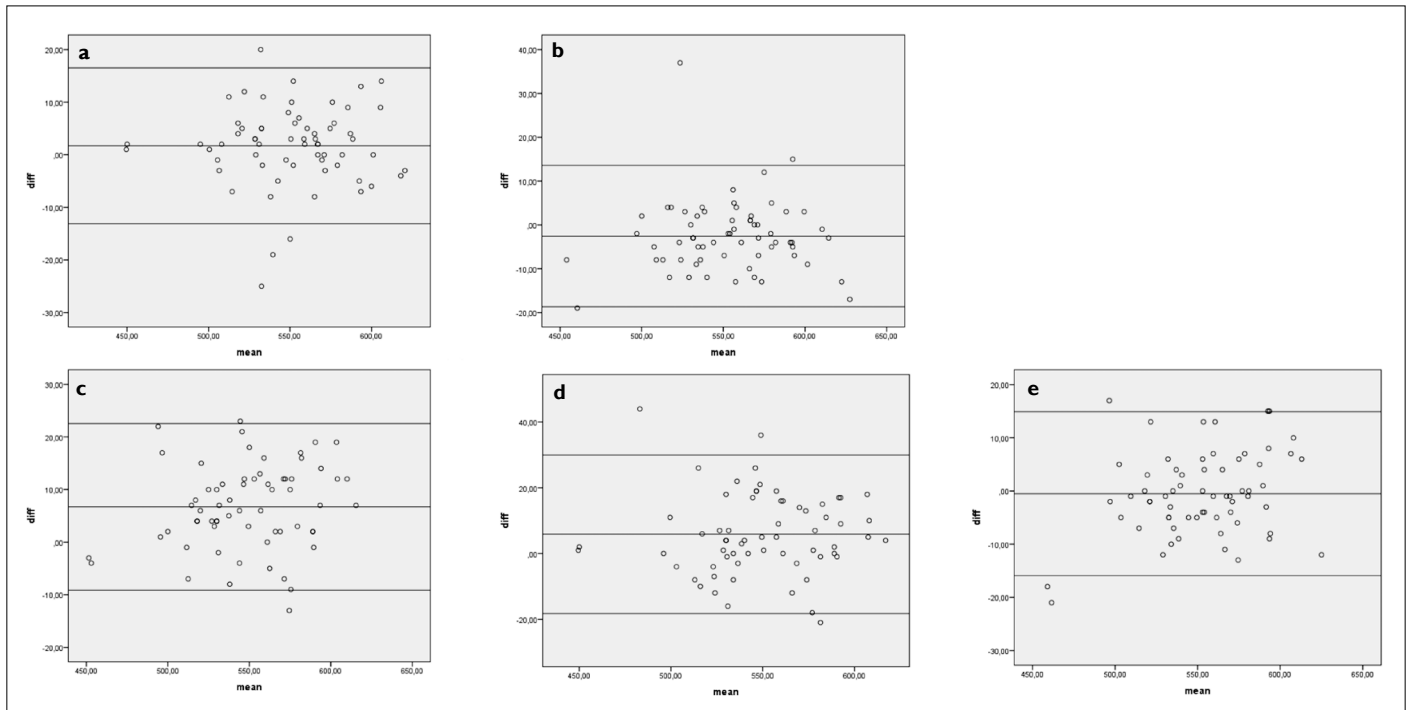
the 2 measurements, but as the difference between the 2 methods was statistically significant, the authors concluded that the 2 instruments could not be used interchangeably. Scotto et al. (8) performed CCT measurements using OCT, non-contact specular microscopy, and UPS, and reported an overall strong agreement between these 3 modalities. However, OCT tended to provide statistically significantly higher CCT readings than either alternative and had poorer

Table 3. The results of Bland-Altman analysis and the intraclass correlation coefficients calculated in comparison with USP

	Mean	LoA	Parameter	ICC	95% confidence interval
Non-contact pachymeter	1.70	16.53 and -13.1	Single measure	0.977	0.963-0.986
			Average of measures	0.989	0.981-0. 993
Specular microscope	-2.56	13.60 and -18.72	Single measure	0.973	0.956-0.984
			Average of measures	0.986	0.978-0. 992
Biometry	6.71	22.56 and -9.14	Single measure	0.972	0.955-0.982
			Average of measures	0.984	0.976-0. 991
Topography	5.85	29.99 and -18.29	Single measure	0.940	0.903-0.963
			Average of measures	0.969	0.949-0. 981
OCT	-0.53	14.89 and -15.95	Single measure	0.974	0.958-0.984
			Average of measures	0.987	0.978-0. 992

ICC: Intraclass correlation coefficient; LoA: Limits of agreement; OCT: Optical coherence tomography; USP: Ultrasound pachymetry.

Table 4. Summary of some reported results of different devices

	Methods	Difference	Correlation or repeatability	Conclusion
Maresca et al.[7]	Scheimpflug camera and USP	Significant	High correlation	Not interchangeable
Scotto et al.[8]	OCT, non-contact specular microscopy, and UPS	Significant	Poor repeatability	Not interchangeable
Binnawi et al.[10]	OCT, pachymetry, and TMS-5 topography	Significant	High correlation	Not interchangeable
Dogan et al.[11]	Scheimpflug-Placido topography, OCT, optical biometry, and USP	Significant	High repeatability	Not interchangeable
González-Pérez et al.[12]	USP, non-contact tono/pachymetry, Pentacam corneal topography, and OCT	Significant	High repeatability except tono-pachymetry	Interchangeable except tono/pachymetry
Gokcinar et al.[13]	OCT, corneal topography, optical biometry, specular microscopy, and USP	Significant	-	Not interchangeable
Teberik et al.[14]	Pentacam HR, Sirius topography, iPac, and Echoscan US-500	-	High consistency	Interchangeable
Mansoori et al.[15]	OCT, optical biometry, and Sirius anterior segment analysis	Significant	-	A high level of agreement between optical biometry and Sirius topography, but not OCT
Kiraly et al.[16]	IOL Master 700, Pentacam HR, and Cirrus HD-OCT	Significant		Not interchangeable
Ozyol and Ozyol[17]	SD-OCT with Scheimpflug system, optical biometry, and non-contact pachymetry	Non-significant	-	Interchangeable
Erdur et al.[18]	Ultrasonic pachymetry, SD-OCT, and non-contact specular microscopy	Non-significant	Strong correlation	Interchangeable
Calvo-Sanz et al.[19]	OCT, non-contact specular microscopy, and USP	Significant	-	OCT and USP offered highly comparable results, but not non-contact specular microscopy
Bayhan et al.[20]	SD-OCT, Sirius Scheimpflug-Placido topographer, Lenstar optical low-coherence reflectometry, and USP	Non-significant	Correlated closely	Interchangeable

HD-OCT: High-definition optical coherence tomography; OCT: Optical coherence tomography; SD-OCT: Spectral domain optical coherence tomography; USP: Ultrasound pachymetry.

repeatability indices. The authors concluded that CCT measurements using different instruments were not directly interchangeable. In another study, Maloca et al. (9) measured CCT values in 122 normal corneas using 7 different devices and reported high inter-device variations. They suggested that measuring CCT with only 1 device may lead to inappropriate clinical and surgical recommendations. Binnawi et al. (10) compared the CCT measurements of OCT, pachymetry, and Scheimpflug-Placido topography using the TMS-5 device (Tomey GmbH, Nürnberg, Germany) in 122 eyes and reported a statistically significant difference in the mean CCT value between the methods, although there was a significant and strong correlation between them. The authors reported that CCT measurements obtained with these 3 modalities were not directly interchangeable. Dogan et al. (11) compared CCT measurements obtained using Scheimpflug-Placido topography, OCT, optical biometry, and USP, and reported that the results of all 4 modalities were closely correlated and that the intra-examiner repeatability was excellent for all devices with an ICC of >0.90. However, they also noted that since there were significant differences between the results of different instruments, the measurements were not directly interchangeable. González-Pérez et al. (12) compared CCT values measured using USP, non-contact tono-pachymetry, a rotating Scheimpflug camera system (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany), and OCT, and reported that the ICC values demonstrated excellent reliability between pairs of methods, with the exception of non-contact tono/pachymetry. They determined that tono-pachymetry underestimated the CCT measurements while the remaining 3 modalities could be interchangeably used in healthy patients. Gokcinar et al. (13) compared CCT measurements obtained by OCT, corneal topography, optical biometry, specular microscopy, and USP, and reported a significant difference in the mean CCT values. The conflicting results reported may be associated with different patient characteristics.

Kiraly et al. (14) similarly reported that CCT measurements performed using IOLMaster 700 (Carl Zeiss AG, Oberkochen, Germany), Pentacam HR, and Cirrus HD-OCT (Carl Zeiss AG, Oberkochen, Germany) were not interchangeable due to the low agreement between the results of these devices. Our results did not support these data (Table 4).

Other studies have reported results similar to our findings. Teberik et al. (15) investigated the consistency of the average scores of CCT measurements using the Pentacam HR, Sirius topography, iPac (Reichert Technologies Inc., Depew, NY, USA) and Echoscan US-500 (Nidek Co., Ltd., Tokyo, Japan) devices, and determined that the high level of consistency indicated that they could be used as alternatives to one another. Mansoori et al. (16), who compared CCT measurements of OCT, Sirius optical biometry, and

anterior segment analysis, concluded that although there was a high level of agreement between optical biometry and Sirius topography, there was a low level of agreement between OCT and the other methods. In a sample of 45 healthy controls, Ozyol and Ozyol (17) reported that spectral-domain OCT with a Scheimpflug system, optical biometry, and non-contact pachymetry were interchangeable. Erdur et al. (18) compared CCT measurements performed using ultrasonic pachymetry, spectral-domain OCT, and non-contact specular microscopy, and demonstrated the presence of a strong correlation between these methods. Furthermore, although USP and specular microscopy were found to provide comparable CCT measurements, the values obtained using OCT were lower than those of the other methods. Calvo-Sanz et al. (19) analyzed CCT measurements obtained with OCT, non-contact specular microscopy, and USP, and reported that while OCT and USP offered highly comparable results, non-contact specular microscopy resulted in lower mean CCT values compared with the other 2 methods. Bayhan et al. (20) compared SD-OCT, Sirius Scheimpflug-Placido topography, Lenstar optical low coherence reflectometry (Haag-Streit AG, Koeniz, Switzerland), and USP in terms of agreement and repeatability of CCT measurements and reported that there was a close correlation between all 4 modalities. In the current study, we determined that the 5 methods compared with USP provided very similar results, and that OCT had the lowest bias.

All of the measurements used in this research were carefully performed by a single ophthalmologist, which may have contributed to our results. Moreover, patients with chronic disease that can affect CCT were excluded from this study, which may also lend strength to this study.

The main limitation of this work is the small number of patients. Also, we compared results in healthy eyes, and it is important to determine the interchangeability of these methods in myopic eyes or those with glaucoma, which may be a subject for future studies. Various other factors, such as corneal edema, corneal opacity, and corneal surface irregularity, may have affected our measurements using different instruments. In addition, we did not compare the repeatability of the methods examined, which is important in defining agreement. Lastly, the wide age range of the patients included may be another limitation to the study.

In conclusion, we determined that the results of CCT measurements by non-contact tono/pachymetry, non-contact specular microscopy, biometry, Scheimpflug-based corneal topography, and OCT were interchangeable with USP in healthy controls. Therefore, USP may no longer be the gold standard for CCT measurement. Although some studies in the literature have concluded that different devices cannot

be used interchangeably, there are also publications supporting our findings. Different device models and patient characteristics may affect results. Technological developments may mean that the difference between devices will decrease even more and we can obtain more precise measurement results. Larger prospective studies are warranted to determine the interchangeability of different methods for CCT measurements in pathological conditions such as keratoconus cornea and post-refractive surgery cases.

Disclosures

Ethics Committee Approval: The study was approved by the local ethics committee and conducted in accordance with the principles of the Declaration of Helsinki (Ethics Committee Number: 33216249-604, Date: 01.15.2019).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (TU, Eİ); preparation and review of the study (TU, YK, NGT); data collection (TU, AU); and statistical analysis (HY, MD).

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