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Central corneal thickness measurements with optical coherence tomography and ultrasound pachymetry in healthy subjects and in patients after photorefractive keratectomy

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PURPOSE. *To compare central corneal thickness measurements made using two different methods, optical coherence tomography (OCT) and ultrasound pachymetry, applied both in normal eyes and in eyes on which photorefractive keratectomy (PRK) had been performed. A second objective was to assess the intrasession variability of OCT measurements.*
METHODS. *In this prospective study, central corneal thickness was measured in 20 normal subjects (normal group) and in 20 PRK patients using the StratusOCT instrument model 3000 (Carl Zeiss Meditec), and also with an ultrasound pachymeter. Five OCT measurements were performed using the Fast Macular Thickness protocol. Corneal thickness data were obtained with the Scan Profile analysis protocol. The OCT measurement results were compared with the mean value of three ultrasound pachymetry measurements for the same eye.*
RESULTS. *The pachymetry–OCT correlation coefficients were 0.96 and 0.97 in the normal and PRK groups, respectively (p=0.14). Neither linear regression nor Bland-Altmann analysis revealed any significant systematic measurement error. Intrasession standard deviations in the normal and PRK groups were 4.9 µm and 3.8 µm, respectively.*
CONCLUSIONS. *Noncontact central corneal thickness measurements made using the StratusOCT instrument are accurate and reproducible, both in normal subjects and in post-PRK patients. The instrument system does not need any modifications to correctly detect and measure the center of the cornea. (Eur J Ophthalmol 2009; 19: 180-7)*

KEY WORDS. *Central corneal thickness, Pachymetry, Optical coherence tomography, Photorefractive keratectomy*

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INTRODUCTION

Measurement of central corneal thickness (CCT) is important when planning and evaluating keratorefractive procedures. It is also important when assessing glaucoma, since the CCT affects the results of applanation tonometry (1-3) and provides valuable information about glaucoma risk (1).
There are various different approaches for measuring CCT; these include ultrasound pachymetry (US pachymetry), ultrasound biomicroscopy (UBM), confocal microscopy, scanning slit topography (Orbscan; Bausch & Lomb) (4, 5), the rotating Scheimpflug camera (Pentacam; Oculus) (5), and optical coherence tomography (OCT). Ultrasound pachymetry is currently the most widely used gold standard method for measuring corneal thickness.
Optical coherence tomography is a noninvasive and noncontact technique which was originally designed for fun-

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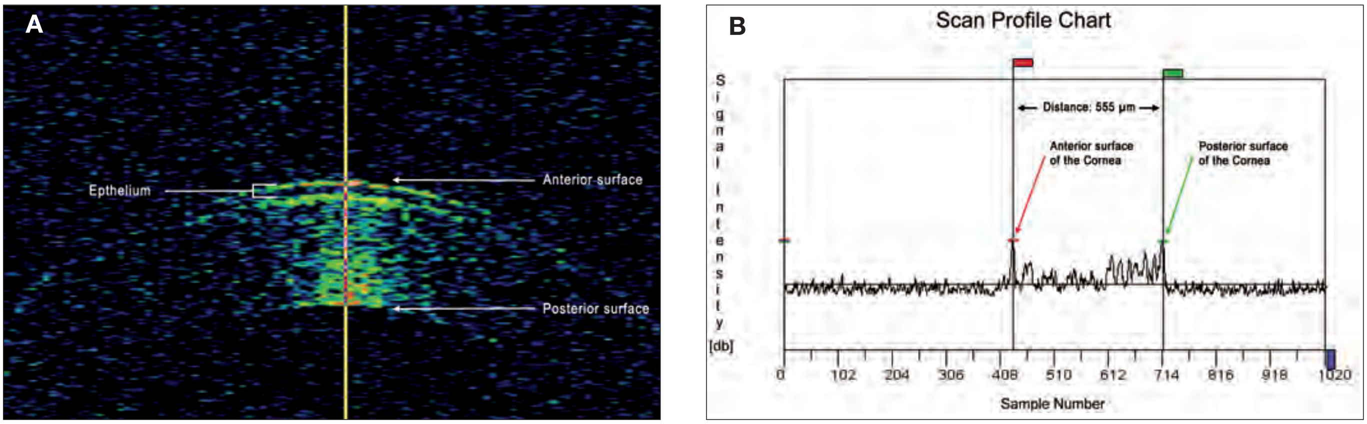

Fig. 1 - *Analysis of an individual corneal scan* **(A)** *using the built-in Scan Profile analysis protocol* **(A)** *of the StratusOCT. The bright vertical line intersecting the image in* **A** *represents the position of the analyzed A-scan shown in* **B**. *Various regions of the cornea are also labeled.*

dus imaging; however, many studies have shown its value in measuring corneal thickness (6-13). Most of these studies were done on the OCT2000 system (6, 8-10, 13) or used external analysis programs (7).

The purpose of the study was to compare CCT measurements using OCT and US pachymetry, both in normal eyes and in eyes that had undergone photorefractive keratectomy (PRK), without using any modification to the commercially available instrument system and using a built-in analysis protocol. A secondary objective was to assess the intrasession variability of the OCT measurements.

METHODS

The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki. Each participant was fully informed about the examinations, and provided written consent.

In this prospective study we enrolled 20 patients who had previously undergone PRK (PRK group), as well as 20 normal subjects (normal group). All participants were Caucasians. The normal subjects had best-corrected vision of 20/20 or better and no ocular history for the examined eyes. Eyes with any ocular history (except ametropia) were excluded from the study. Each participant underwent a complete ophthalmic examination including ocular history, best-corrected visual acuity, and slit-lamp biomicroscopy. The normal group comprised 12 women and 8 men; the mean age was 30 years (minimum 19, maximum 65 years). The PRK group comprised 10 women and 10 men, mean age 33 years (minimum 20, maximum 58 years).

Central corneal thickness was measured with the StratusOCT model 3000, software version 4.0.2 (0056) (Carl Zeiss Meditec Inc., Dublin, CA) and also with the Ultrasound Pachometer Model 855 (Humphrey Instruments Inc., San Leandro, CA)

In each case, the set of OCT scans was made first (always between 9:00 AM and 12:00 noon), and US pachymetry was performed a short time afterwards. This was always done within half an hour of the OCT measurements, to minimize any influence of diurnal variation of the corneal thickness (2).

Five OCT measurements were made with 5-minute latency. Each measurement used the Fast Macular Thickness scan protocol, which was originally designed for macular imaging; this protocol comprises six 6 mm radial scans (centered on the middle of the cornea) in 1.92 seconds. The focus point (set using the diopter adjustment knob) was set to lie on the front surface of the anterior segment.

We processed the data by analyzing each scan individually using the OCT software's built-in Scan Profile analysis protocol. In this process we selected the center of the cornea (highest point of the corneal scans; Fig. 1A). On this A-scan presentation the anterior and posterior surface of the cornea can be determined very precisely as the most reflective point in their respective surroundings, as shown in Figure 1B. The distance between these two points was calculated automatically by the software. We repeated this process for each of the six scans.

After analyzing the five OCT sessions we thus obtained a total of 30 corneal thickness values for each eye. The

OCT measurements and analyses were all performed by the same experienced operator (M.S.).

Ultrasound pachymetry was used as a gold standard comparison. Ultrasound measurements were performed immediately after anesthetizing the corneal surface using one drop of oxybuprocaine-hydrochloride 0.4% (Humacain 0.4%, TEVA Hungary Ltd., Budapest, Hungary). Three measurements were performed at the center of the cornea in an orientation perpendicular to the optical surface, and the three values were then averaged. The ultrasound measurements were all performed by the same experienced nurse practitioner.

For each eye, the six radial OCT scan measurements were summarized using three methods, namely as the mean, the trimmed mean, and the median. The best summarizing method was chosen according to measurement reliability. As left-right correlation of CCT for the eyes of a given subject is very high (meaning that intersubject variability of CCT is very large compared to the intrasubject left-right variability), only a single eye of each participant was included in the analysis. Preferably the right eye data were used in the analysis, but if this was not available, data from the left eye were used.

Systematic errors of the OCT-determined CCT (hereafter called OCT-CCT) were studied using a simple linear regression where confidence intervals of the intercept and slope were determined. Bland-Altman analysis was used to measure random error (and coefficient of variation) and the dependence of the error on CCT. In the US pachymetry–OCT comparison only the first OCT measurement of each session was used, since no repeated measurements are included in the proposed routine. As OCT-CCT may potentially have different accuracy in normal subjects as compared to PRK patients, accuracy was assessed in the two subject groups separately.

To assess the reproducibility of OCT measurements, intrasession variability of OCT-CCT was calculated as the within-patient standard deviation with analysis of variance (ANOVA). We compared CCT measurements of the PRK and normal group using the two-sample Student *t*-test.

Statistical analysis was done by the R system using the Sweave package (R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2005. Available at: http://www.R-project.org).

RESULTS

In the normal group, mean corneal thickness was 559 µm (mean 1 SD 30.69 µm) measured with US pachymetry and 560 µm (mean 1 SD 32.20 µm) measured with OCT. In the PRK group the corresponding values were 513 µm (mean 1 SD 45.61 µm) and 514 µm (mean 1 SD 47.48 µm), respectively, as seen in Table I.

As expected, using both measurement methods corneal thickness was significantly smaller in the PRK group than in the normal subjects ($p=0.0007$ for pachymetry and $p=0.0009$ for OCT-CCT, two-sample *t*-test with Welch correction). Using a backward stepwise linear regression model, age and gender did not show significant influence on CCT with either measurement method.

The left-right intraclass correlation coefficient of pachymetry CCT was 0.97 and 0.98 in the normal and the PRK groups, respectively; thus, use of data from only a single eye of each subject appears to be justified.

One of the aims of the study was to determine the most appropriate summarizing method for reducing the OCT measurements in the six scans to a single corneal thickness value. We found that the method of choice was the mean. Thus in the paragraphs below, the numeric CCT results correspond to the means of the six OCT scans. The reasons why the mean was chosen as the best method are discussed below.

TABLE I - SUMMARY OF US PACHYMETRY AND OCT MEASUREMENTS OF CCT

	US pachymetry, µm (mean ± SD)	**OCT-CCT, µm (mean ± SD)**	**Mean difference**	**95% CI**	**p value SE**	
Normal group	559±30.69	560±32.20	–1.41	–5.42; +2.58	0.48	2.02
PRK group	513±45.61	514±47.48	–0.30	–5.70; +5.10	0.91	2.73

US = ultrasound; OCT-CCT = central corneal thickness measured using optical coherence tomography; PRK = photorefractive keratectomy; SD = standard deviation; CI = confidence interval of the difference; SE = standard error.

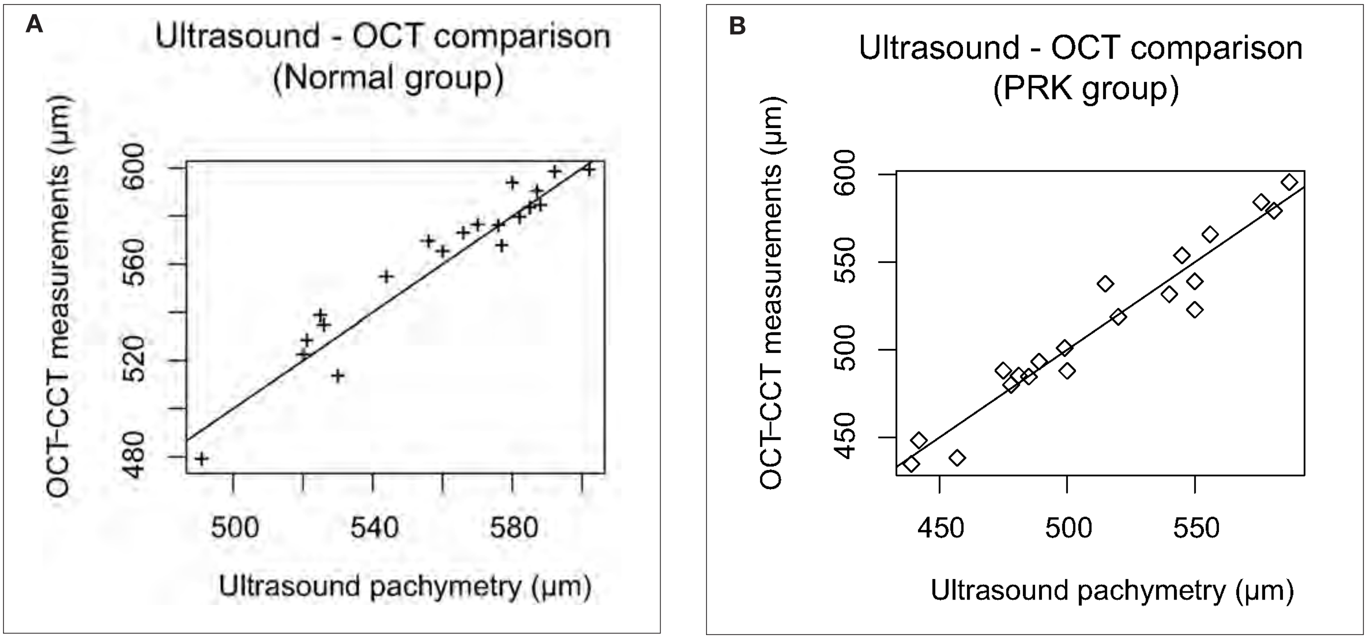

Fig. 2 - *Analysis of the relation between the ultrasound pachymetry and central corneal thickness measured using optical coherence tomography measurements in the normal group* **(A)** *and photorefractive keratectomy group* **(B)**.

Pachymetry-OCT comparison

The connection between the pachymetry CCTs and the corresponding OCT-CCT can be seen on the scatterplot (Fig. 2, A and B), which also shows the regression lines. The pachymetry–OCT correlations were 0.96 and 0.97 in the normal and PRK groups, respectively. The confidence intervals of the intercepts and slopes of the two regression lines were –26.4 to 114.1, 0.79 to 1.04 and –24.9 to 94.3, 0.82 to 1.05, respectively, both including zero intercept and slope of 1.0. The p values for intercept differing from 0 are 0.21 and 0.24, while the p values for slope differing from 1 are 0.19 and 0.23, respectively. Thus linear regression did not reveal any significant systematic measurement error.

In addition, we used Bland-Altman plots to compare the CCT data obtained from the OCT and pachymetry measurements. One common application of this method is to compare a new measurement method with a gold standard (14).

Bland-Altman analysis showed a measurement error of 8.5 μm (standard deviation) in the normal group. The measurement error did not significantly depend on the corneal thickness. The Bland-Altman difference-mean correlation was –0.18 (p=0.45), the confidence interval of the slope of the difference-mean regression line was –0.18 to 0.09 (p=0.45). The mean difference was –1.42 (confidence interval: –5.4 to 2.6), thus no significant shift in the measurement scale was detected. Largest positive and negative differences were 16.67 and –12.67, respectively. The standard deviation of the pachymetry-OCT difference shows no visible trend along the corneal thickness axis; the measurement error is virtually independent of the corneal thickness.

In the PRK group we observed similar results, SD = 11.5 μm, correlation = –0.16 (p=0.49), CI of the slope: –0.16 to 0.08 (p=0.49), mean difference = –0.30 (CI: –5.7 to 5.1), largest positive difference = 27.17, largest negative difference = –22.67. In this group also, no significant systematic error was detected, and the measurement error again appeared to be independent of the value of corneal thickness.

The above standard deviations of measurement errors correspond to coefficients of variations of 1.5% and 2.2% for the normal and PRK groups, respectively.

Reproducibility

In order to assess the intrasession variability of the OCT method, the five consecutive OCT-CCT measurements

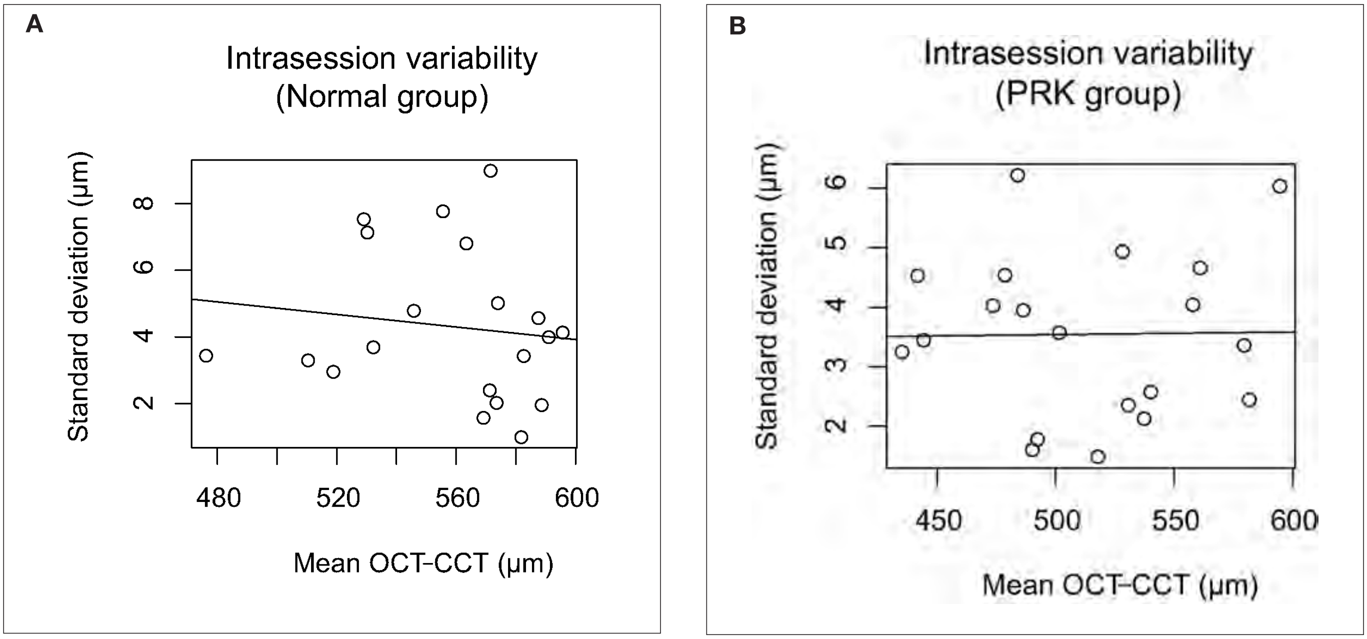

Fig. 3 - *Analysis showing the intrasession standard deviations and the means of optical coherence tomography measurements in the normal group* **(A)** *and photorefractive keratectomy group* **(B)**.

were compared among themselves. We determined the intrasession standard deviation for each eye, and plotted it against the corresponding mean CCT (Fig. 3).

We found that the intrasession standard deviation was independent of the CCT. The individual intrasession SD values ranged from 1.0 to 9.0 µm in the normal group, and from 1.5 to 6.2 µm in the PRK group.

The overall intrasession standard deviations in the normal and PRK groups were 4.9 µm and 3.8 µm, respectively, corresponding to coefficients of variation of 0.87% and 0.74%. The difference between the intrasession standard deviations was not significant (p=0.14).

Choice of summarizing method for the six OCT scans

The regression, Bland-Altman, and intrasession variability analyses were repeated using two further calculation methods (i.e. trimmed mean, median), to enable us to choose the most robust method of summarizing the six OCT scans. The numeric results were very similar to the above figures corresponding to the mean OCT values.

There were no noteworthy differences in the results of the regression analyses. The Bland-Altman analyses showed that random measurement errors were smallest using the mean, slightly larger using the trimmed mean, and again slightly larger using the median, but the differences were very small (intrasession variabilities, healthy group 8.5, 8.5, 8.5; PRK group 11.5, 11.7, 11.7, respectively). Thus, intrasession variabilities showed a slight increasing trend moving from the mean through trimmed mean to the median. On the strength of the above small differences between the summarizing formulas we chose the mean as the most accurate method (Fig. 4).

Using backward stepwise linear regressions, neither the OCT-CCT to US pachymetry differences, nor the OCT intrasession standard deviations, showed any significant relationship with age, gender, or PRK treatment (OCT-pachymetry differences: gender eliminated at p=0.98, age at p=0.56, PRK p=0.73; intrasession SDs: gender eliminated at p=0.17, PRK at p=0.15, age p=0.19).

DISCUSSION

The first use of the OCT for imaging the cornea was reported by Izatt et al (15) in the 1990s. Later, Hirano et al (8) demonstrated the capabilities of the OCT2000 instrument for imaging the cornea in various corneal diseases. Subsequently, Muscat et al (9) were able to show a high

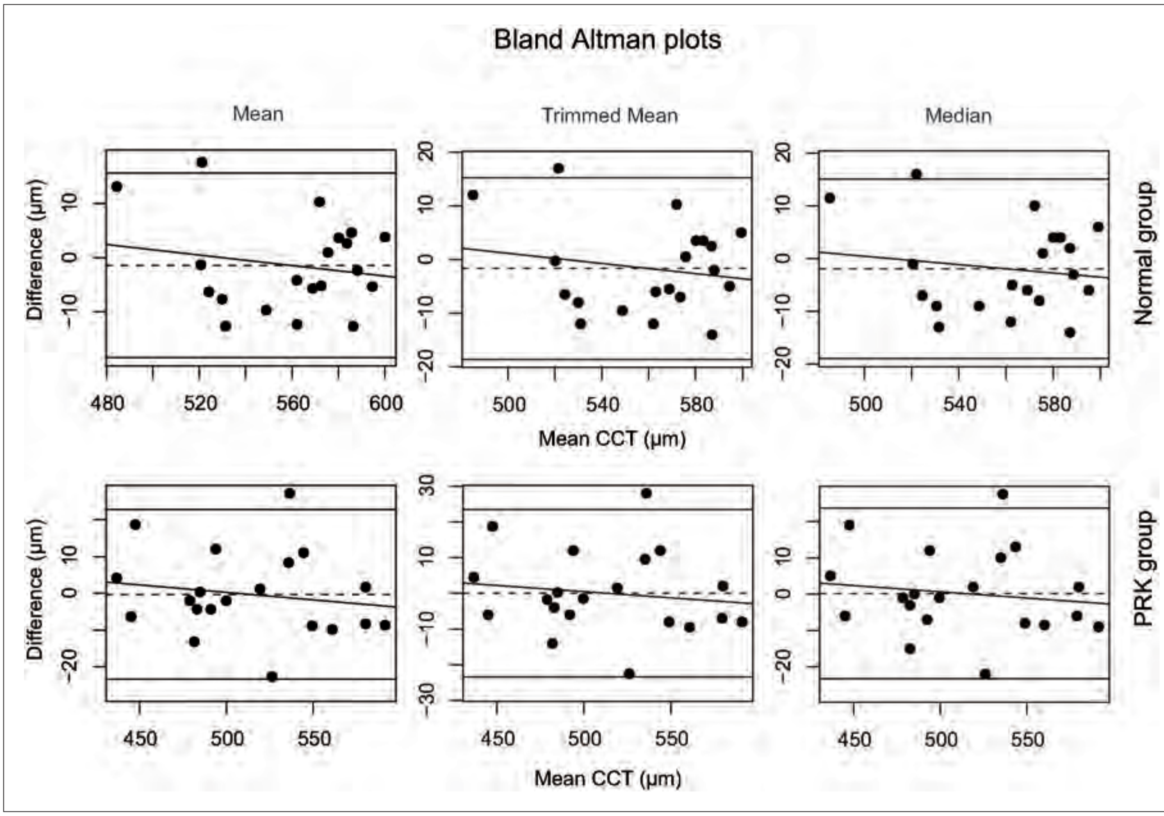

Fig. 4 - *Composite diagram of 2x3 Bland-Altman plots of central corneal thickness (CCT) of two groups (healthy volunteers and photorefractive keratectomy treated patients) with ultrasound (US) pachymetry compared to three optical coherence tomography (OCT) measurement methods: mean CCT from six radial OCT scans, their trimmed mean, and their median. Individual plots show the means and the differences between US pachymetry and combined OCT-CCT measurements. There is a very good agreement between OCT-CCT and pachymetry for all of the three summary methods of OCT scans; measurement errors are below clinical relevance level. Means of OCT scans were chosen as our summary method as no outlying OCT measurements were present and means showed slightly smaller variabilities than trimmed means or medians when compared with OCT-CCT.*

degree of repeatability and reproducibility of CCT as measured with OCT, although their system required a few special modifications. Wong at al (10) compared the accepted standard, US pachymetry, with OCT2000 and Orbscan measurements, and found significant correlation between the techniques. Bechmann and coauthors (6) compared CCT measurements made with US pachymetry and with OCT, and demonstrated excellent accordance between the two methods, with the results showing a constant difference. More recently, Fishman et al (7) evaluated CCT as measured using the OCT3 and Orbscan instruments, and found a high level of agreement between US pachymetry and OCT3, as well as good repeatability with OCT3. Most recently, Sin and Simpson (13) examined within and between session repeatability of OCT imaging for anterior segment morphometry. Their findings suggest very good repeatability of corneal thickness measurement. They also pointed out that it is important to optimize each OCT scan and also average multiple scans to maximize intersession repeatability.

In our present study, we measured CCT with OCT on healthy subjects and also in patients after PRK without making any modification to the instrument system, and also using no external analysis programs, only the built-in protocols of the StratusOCT instrument.

We found that the mean CCT values as determined with OCT and, separately, with ultrasound correlated very well. Our intraclass correlation coefficients of 0.97 and 0.98 (in the normal and PRK groups, respectively) between the results using the two methods are comparable with those reported in other studies (6, 7, 9, 10). From a clinical point of view, the random measurement errors are within acceptable limits.

No significant systematic errors were detected during the comparison of the US pachymetry and OCT-CCT methods. We have given confidence intervals which constrain these errors between upper and lower limits, and the width of these confidence intervals could be further narrowed by an extended study examining a larger number of patients.

When we selected the summarizing method for combining the results of the six OCT scans on a given eye, we chose the mean as being the most accurate method. However, the accuracies of all three potential methods were in fact very similar. In this context, an important point to note is that in our study the OCT measurements were always successfully performed in each of the six scans, without any artefacts. Although the mean was in this situation slightly more accurate than the trimmed mean or median, if other studies including more patients were to reveal artefacts, then one of the latter two methods would have to be chosen as they are more robust against outlier datapoints.

Measurement of CCT with OCT offers many advantages over the ultrasound technique: it is noninvasive, noncontact, and does not require topical anesthesia. It can be particularly helpful when direct contact with the cornea is not possible because of various corneal pathologies. The patient can fixate a target during the measurement, and real-time infrared-camera monitoring allows the proper placement of the center of the scanning lines.

OCT also generates high-resolution cross-sectional images of the cornea, which along with the measurement data and a photograph of the cornea can be stored and later retrieved for further analysis or follow-up.

The disadvantage of this technique is that the light beam of the OCT has to be perpendicular to the corneal surface, therefore peripheral corneal thickness measurements may be difficult to perform. Our study focused on CCT measurements only; peripheral measurements with OCT might need further investigations.

Our proposed everyday routine protocol is as follows: one Fast Macular Thickness measurement well centered to the cornea; Scan Profile analysis and measurement of the CCT on all scans; and average of the six obtained sets of measurement data. If any part of the obtained data is questionable, the image acquisition can be repeated.

In summary, our study demonstrated that noncontact CCT measurements using the StratusOCT instrument are accurate and reproducible, both in normal subjects and in post-PRK patients. The instrument system does not need any modifications to correctly detect and measure the center of the cornea, but a useful further enhancement could be an automatic CCT-measuring module integrated within the software.

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