Int Ophthalmol (2019) 39:917–923
https://doi.org/10.1007/s10792-018-0895-1

ORIGINAL PAPER

Comparison of central corneal thickness measurements by ultrasound pachymetry and 2 new devices, Tonoref III and RS-3000

Thomas Desmond · Patricia Arthur · Kathleen Watt

Received: 26 September 2017 / Accepted: 16 March 2018 / Published online: 21 March 2018

Abstract
Purpose There is currently little evidence assessing the repeatability and accuracy of central corneal thickness measurements using the devices Tonoref III and RS-3000. This study aims to compare these devices against measurements by ultrasound pachymetry.
Methods Central corneal thicknesses were measured on 50 eyes. Measurements from two non-contact devices—Tonoref III (NIDEK CO., LTD, Gamagori, Japan) and RS-3000 (NIDEK CO., LTD, Gamagori, Japan)—were compared against ultrasound pachymetry, the gold standard. Ultrasound measurements were obtained using a 'Pachmate' device (DGH Technology, Inc, Exton, PA, USA). Repeatability was defined as the value that the difference between two consecutive measurements falls below 95% of the time. The within-subject standard deviation and repeatability values were calculated for Pachmate and Tonoref III by one-way ANOVA. Repeatability of RS-3000 was determined by nonparametric analysis. Agreement between Tonoref III and Pachmate was assessed by a Bland–Altman plot. Agreement between RS-3000 and Pachmate was assessed by nonparametric analysis.
Results The Pachmate, Tonoref III and RS-3000 had repeatability values of 16, 7.4 and 5 μm, respectively. The mean difference between Tonoref III and Pachmate was − 15 μm (95% LoAs − 31 to + 0 μm). The median value for the difference between RS-3000 and Pachmate was − 4 μm (95% of values within − 24 and + 4 μm).
Conclusion The Tonoref III and RS-3000 showed good repeatability when compared to ultrasound pachymetry. However, neither instrument agreed interchangeably with CCT measurements by ultrasound pachymetry. Practitioners should determine whether the level of agreement is sufficient to meet their clinical needs.

Keywords Pachmate · RS-3000 · Tonoref · Reproducibility of results · Repeatability · Agreement

T. Desmond (✉) · P. Arthur · K. Watt
School of Optometry and Vision Science, University of New South Wales, Sydney, NSW 2052, Australia
e-mail: t.desmond@unsw.edu.au

Reliable measurements of central corneal thickness (CCT) are an essential part of diagnosing and managing ocular conditions, such as glaucoma, keratoconus and corneal ectasia [1, 2]. They are also of primary consideration when assessing the suitability of an eye for ablative refractive surgery [3].

Several modalities exist to measure CCT. Ultrasound pachymetry (USP) remains the reference standard. It determines the CCT by measuring the time that is taken for an ultrasound wave to return after reflection from the corneal endothelium. It has several advantages, such as established repeatability, speed of use and portability. Considerable variation in

measurements is possible, because an accurate measurement is dependent on the operator placing the probe exactly perpendicular to the centre of the cornea. Furthermore, topical anaesthetic eye drops must be used, which has its own risks.

The Tonoref III (NIDEK CO., LTD, Gamagori, Japan) is a recently released device that combines the functions of an auto-refractor, keratometer, non-contact tonometer and non-contact optical pachymeter [4]. The pachymetry function measures CCT at the corneal apex by determining the distance between optical reflections from the front and back surfaces of the cornea.

The RS-3000 (NIDEK CO., LTD, Gamagori, Japan) images the cornea by ocular coherence tomography (OCT), a system that analyses optical reflectivity to provide scaled cross sections of ocular tissues. The practitioner may then extract an automatically measured CCT through either the corneal apex or pupil centre. This is also a non-contact technique. Both the RS-3000 and Tonoref III have greater patient safety and comfort compared with the Pachmate, as there is no contact made with the eye during measurement and no anaesthetic eye drops are required. The RS-3000 has an axial resolution of 4 μm, giving discrete CCT measurements as multiples of 4 μm.

Before being widely adopted in practice, any new instrument should be assessed against the current standard technique for that measurement to ensure the optimal clinical outcomes and safety for patients. Any new device should have good agreement with or consistent variation to the reference device and have comparable repeatability. In the case of the Tonoref III and RS-3000, there are minimal data available, as they are relatively new technologies, and the authors are not aware of any study comparing them against USP. This study aims to assess the agreement and repeatability of the Tonoref III and RS-3000 against USP measurements to determine their utility for clinical practice. The Pachmate (DGH Technology, Inc, Exton, PA, USA) is a commonly used handheld USP and was used to provide the USP data for this study.

Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Measurements were taken from 50 eyes from 25 healthy volunteers. The participants gave written informed consent and had a median age of 23 years (range 22–67). Exclusion criteria included any known sensitivity to eye drops and any defect in corneal integrity. Participants with keratoconus, glaucoma, a history of ocular surgery, orthokeratology lens wear or pregnancy were not excluded. We did not collect data on the presence of these conditions from participants.

A single trained observer performed all measurements to minimise technical errors when performing USP. The observer was masked to any previous CCT measurements. CCT measurements were first taken using the Tonoref III, then RS-3000. This was followed by instillation of drops and measurements by the Pachmate. USP was performed last was to ensure that corneal integrity was not compromised by corneal contact that could potentially affect the non-contact measurements. USP is the gold standard, so measurements from the Pachmate were considered to be the reference CCT for each eye.

RS-3000

The device was set up for anterior eye measurements. The patient was instructed to look at the centre of the target, and the scan was aligned over the centre of the pupil. The default scan was used, which was the 12-line raster. This takes 12 line scans oriented radially around the centration point and gives an automated corneal thickness measurement at the apparent centre of each line scan, leading to a maximum of 12 measurements of CCT with each acquisition. Scans were taken in the right eye first and then in the left eye.

A reflex saturation beam at the peak of a line scan indicates that it has passed through the topographic centre of the cornea. Because the topographic centre of the cornea does not always coincide with the centre of the pupil, not all line scans had a reflex saturation beam at their apparent peak. Scans that did not show the reflex saturation beam were omitted from analysis.

Tonoref III

The device was set to pachymetry-only mode, in which the measurement occurs only when aligned correctly in front of the eye. Three measurements were taken in each eye. If there was a blink that led to a bad reading, that reading was disregarded, and another was taken until at least 3 good measurements were taken in each eye.

Pachmate

Participants had Alcaine 0.5% instilled in each eye. The Pachmate was set to take 20 measurements and give the average for each acquisition. The measurements were taken in the right eye, followed immediately by the left eye. Careful attention was paid to placing the probe as close and as perpendicular to the centre of the cornea as possible. The measurements were repeated for a total of 3 times and averaged to give the reference CCT.

Statistical analysis

Statistical analysis was carried out using GraphPad prism for Windows, version 7.03. Normality of results was checked visually when necessary by constructing a frequency histogram. Results from the RS-3000 did not follow a normal distribution for both the repeatability analysis and the between-device comparison. So, those analyses for the RS-3000 were performed nonparametrically.

The mean CCT, SD and SEM of each method of measurement were determined from the first measurement only from each device for each eye. This was to avoid artificially reducing the variance by averaging repeat measurements.

Repeatability

The within-subject (within-eye) standard deviation (Sw) was calculated for Pachmate and Tonoref III using one-way ANOVA. This is a measure of the repeatability of each device [5]. Independence of Sw from CCT was confirmed visually by plotting Sw against mean CCT.

Repeatability was defined as the value for which the difference between two consecutive measurements falls below 95% of the time. This can be determined as $\pm$ 2.77 $\times$ Sw [5]. A smaller number indicates better repeatability.

Repeatability for the RS-3000 was determined by assessing the differences between the first two measurements for each eye.

No measurements were omitted due to their being outliers. We do not anticipate outliers to greatly affect the results.

Between-device comparison

A Bland–Altman plot was used to assess agreement between the Tonoref III and Pachmate. This allows quick assessment of how well a test measurement predicts a reference measurement and is more suitable for a clinician than a correlation coefficient [6]. This gave the mean bias, SD and 95% limits of agreement (LoAs). The given SD was artificially small, because some measurement error was removed by averaging within-eye measurements [6]. The SD was modified to account for this and was used to determine modified 95% LoAs [6]. These LoAs then had their standard error assessed. The modified results represent a comparison between a *single* Tonoref III measurement and an average of 3 measurements by Pachmate (the reference CCT).

Agreement of the RS-3000 against the Pachmate was determined by assessing the differences between the first measurement by RS-3000 against the average of 3 measurements by Pachmate for each eye.

Results

The mean CCT (SD) [SEM] for Pachmate was 552 μm (30) [4.2], for Tonoref III 538 μm (25) [3.7] and for RS-3000 548 μm (28) [3.9] (Fig. 1 for SEM data and Fig. 2 for SD data). The range of CCTs as measured by the Pachmate was 490–613 μm.

The repeatability off CCT measurements was evaluated for each device. The repeatability values of the Pachmate and Tonoref III were 16 μm (Sw, 5.6 μm) and 7.4 μm (Sw, 2.7 μm), respectively (Fig. 3). The distribution of differences between 2 consecutive measurements by the RS-3000 on each eye did not follow a normal distribution. The median value for the difference between two measurements

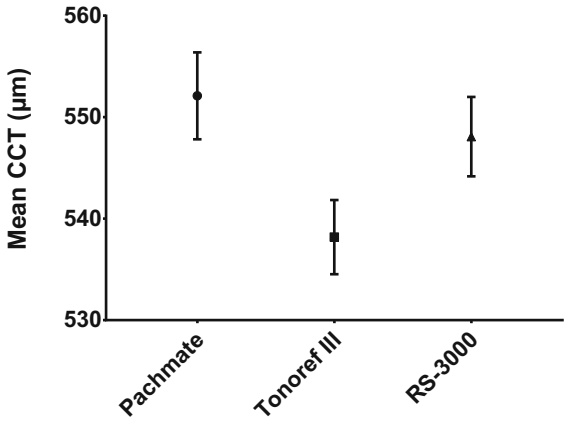

Fig. 1 Mean CCT for each device. Error bars show standard error of the mean

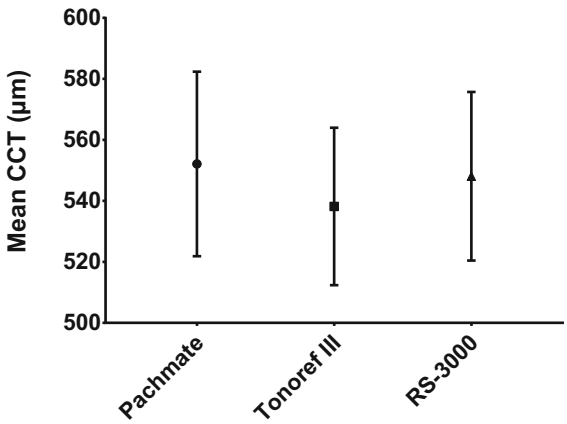

Fig. 2 Mean CCT for each device. Error bars show standard deviation of the mean

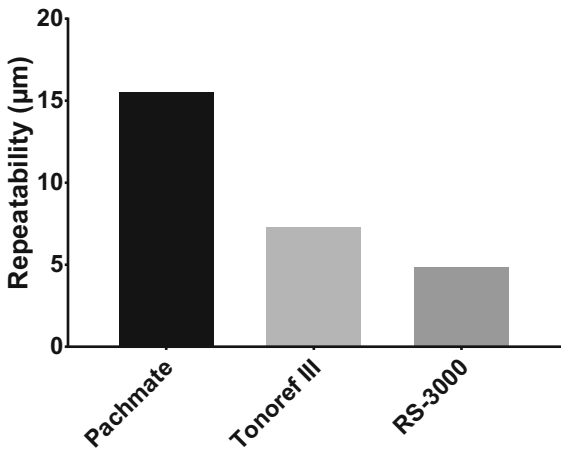

Fig. 3 Repeatability value for each device

was 0 µm (95% of values fell within 5 µm, 100% within 5 µm) (Fig. 3).

There was no relationship between Sw and the mean CCT measurement for either Pachmate or Tonoref III.

Inter-method comparison

A Bland–Altman plot was created to compare the Tonoref III against the Pachmate (Table 1 and Fig. 4). The upper LoA was + 0 µm (SEM, ± 2.0 µm), the lower LoA was − 31 µm (SEM, ± 2.0 µm) and the width of the LoAs was 32 µm. The agreement decreased at larger CCTs. Due to this non-uniform difference, a regression approach is also presented to better predict the CCT by Pachmate. The line of best fit had the equation $y = -0.16 + 72$. This approach gave a slightly improved width of LoAs of 27 µm.

The distribution of within-eye differences between measurements from Pachmate and RS-3000 did not follow a normal distribution (Fig. 5). The median value for the difference between devices (RS-3000–Pachmate) was − 4 µm (IR − 10–0 µm; 95% of values within − 24 and + 4 µm).

Discussion

CCT measurements are becoming an increasingly important part of clinical evaluation. The assessment of glaucoma risk in patients is particularly relevant. A thinner cornea is associated with lower intraocular pressure readings and is an independent risk factor in the development of primary open angle glaucoma (POAG) [1, 2]. The ocular hypertension treatment study found that for each 40 µm reduction in CCT, there was a 71% increase in risk of developing POAG over a median time of 72 months. This effect was independent of the IOP measured [1].

This paper analyses CCT measurements from 2 new devices utilising optical pachymetry and OCT. There are still other technologies to determine CCT not analysed in this paper, including rotating Scheimpflug imaging and slit scanning tomography. When assessing a device's suitability for measuring CCT, regardless of mechanism, it needs to measure the true CCT reliably or do so with an acceptable amount of predictable error. This is a clinical decision that should

Table 1 Agreement of Tonoref III and Pachmate

Simple approach (Tonoref III–Pachmate)	
Mean Bias (μm)	− 15 ± 1.1
SD of bias (μm)	8.1 ± 0.8
95% LoA's (μm)	− 31 to 0 ± 2.0
Regression approach (Tonoref III–Pachmate)	
Estimated bias (μm)	− 0.16*CCT + 72
SD of estimated bias (μm)	6.9
95% LoA's (μm)	Estimated bias ± 13

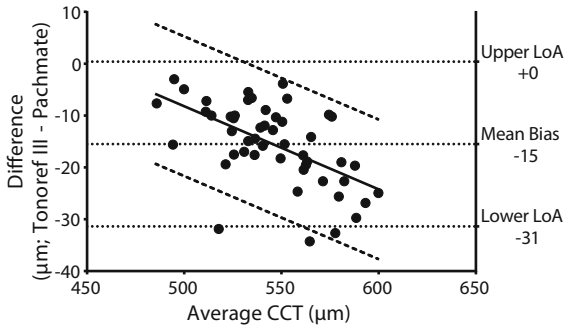

Fig. 4 Bland–Altman plot to assess the agreement of CCT by Tonoref III and Pachmate (horizontal lines, simple Bland–Altman comparison; descending lines, regression approach to determine more accurate LoAs)

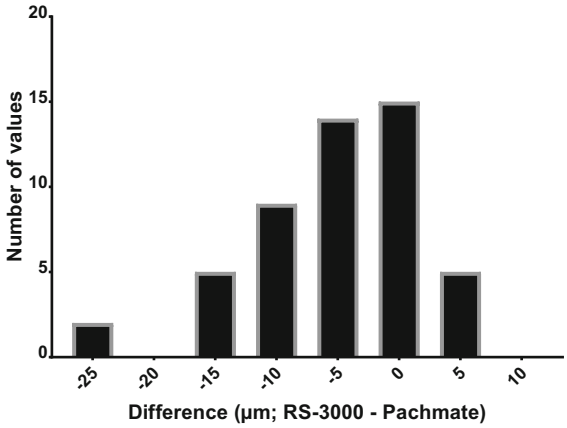

Fig. 5 Frequency histogram to demonstrate the spread of differences in CCT (RS-3000–Pachmate)

be determined with regard to the intended use of the measurement [7].

Re-analysis of various studies on USP devices has shown repeatability values of approximately 18 μm (Humphrey model 855) [8], 7.3 μm (Tomey SP-2000) [9], 18 μm/26 μm (Allergan-Humphrey 850) [10, 11] and 5 μm (Quantel Medical Pocket II) [12]. Our study demonstrated a repeatability value of approximately 16 μm, which is consistent with other studies.

Tonoref III

The Tonoref III was found to have an excellent repeatability value of approximately 7 μm. However, its measurements were an average of 15 μm thinner than the Pachmate. The variability of this measurement led to relatively large 95% LoAs, with the Tonoref III expected to measure up to 31 μm thinner than the Pachmate. This is a comparatively large disagreement, and whether this is acceptable should be determined for the clinical purpose and accuracy required [7]. Larger-scale trials would be required to be able to assign a conversion factor. The Bland–Altman plot (Fig. 4) clearly demonstrates a correlation between the CCT and the measured bias. However, at larger CCTs there is a greater disagreement between the Tonoref III and the Pachmate; thus, care should be taken when interpreting the given LoAs, because a lower LoA will be too wide for thinner CCTs and too narrow for larger CCTs [7]. The Tonoref III is easy to use, fast, safe and convenient to administer as part of an array of entrance tests. Before a practitioner decides to use it for CCT measurements, they should understand that its results are not directly interchangeable with USP measurements.

RS-3000

The RS-3000 also demonstrated an excellent repeatability value of approximately 5 μm. This is very close to its axial resolution of 4 μm and caused many repeat measurements that were identical or exactly 4 μm different. As a result, the measurements of the RS-3000 fail to follow a normal distribution, necessitating the nonparametric analysis.

Re-analysis of various studies on CCT measurements by OCT devices has shown repeatability values of approximately 13 μm (Cirrus HD-OCT, Carl Zeiss Meditec, Inc., Dublin, CA) [13], 5 μm (RTVue, Optovue, Inc., Fremont, CA) [12], 16 μm (Heidelberg SL-OCT, automatic, Heidelberg Engineering, Heidelberg, Germany) [14] and 14 μm (Zeiss Visante OCT, automatic, Carl Zeiss Meditec, Dublin, CA) [14]. Studies assessing the agreement of CCT measurements by OCT devices and USP have shown larger 95% LoAs of − 30 μm (RTVue) [15], − 54 μm/− 22 μm (Heidelberg SL-OCT) [14, 16] and − 33 μm (Zeiss Visante OCT, automatic) [14]. It should be noted that there is some methodological heterogeneity between these studies. Some took measurements over pupil centre, some over corneal vertex and for some it is not clear. We are unsure if this will cause a clinically significant error.

The largest expected difference between the RS-3000 and Pachmate for a single measurement was − 24 μm. Although not directly comparable, the repeatability and agreement of RS-3000 compares favourably to the alternate OCT devices.

In this study, the Tonoref III and RS-3000 both showed measurements that were thinner than those from the Pachmate. Explanations for the discrepancy include transient swelling following topical anaesthetic [17], uncertainty of the speed of sound in the cornea and uncertainty of the index of refraction of light used in OCT [16].

This study had exclusion criteria that were atypical compared to most studies that have assessed the quality of CCT measurements. We only excluded participants if there were safety concerns of compromised ocular surfaces or a history of adverse reactions to eye drops. We suspect that eyes that were undergoing orthokeratology, had glaucoma or keratoconus, had undergone refractive surgery or belonged to pregnant women would have CCTs that were abnormal. USP measurements may vary in these eyes if they are oedematous, affecting the speed of sound through the cornea [18, 19]. Similarly, optical pachymetry is affected by degraded corneal reflections [20]. OCT devices appear less prone to these effects [19].We are aware that several of our participants wore orthokeratology lenses, but we did not formally account for this. Nevertheless, we anticipate that CCT measurement devices should still give accurate measurements in these cases and reflect patients in a real-life testing situation. Future studies could compare the accuracy of these devices in ocular surgery cases to confirm their utility in those circumstances.

Utilising only one observer to take the measurements allowed for comparisons to be made between the instruments only. However, future studies should use multiple observers to better assess inter-observer agreement and repeatability for the Tonoref III and RS-3000 and enhance the data for the Pachmate. They could also compare against more established non-contact pachymeters such as anterior segment OCT devices and Scheimpflug imaging devices.

To conclude, the Tonoref III and RS-3000 devices provide a fast and safe method of measuring CCT. This study has shown them to have good repeatability. However, their measurements are not directly interchangeable with those from USP. A single CCT measurement from the Tonoref III and RS-3000 may read 31 and 24 μm lower, respectively, than those obtained by USP. Practitioners should consider whether this error and uncertainty is acceptable before adopting them for a specific clinical use.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (UNSW Sydney) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Gordon MO, Beiser JA, Brandt JD et al (2002) The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 120:714–720
2. Chihara E (2008) Assessment of true intraocular pressure: the gap between theory and practical data. Surv Ophthalmol 53:203–218
3. Randleman JB, Woodward M, Lynn MJ, Stulting RD (2008) Risk assessment for ectasia after corneal refractive surgery. Ophthalmology 115:37–50
4. Auto Ref/Kerato/Tono/Pachymeter TONOREF^{TM} III| Auto Refractometer/Auto Keratometer/Non Contact Tonometer/Pachymeter| NIDEK CO.,LTD. https://www.nidek-intl.

com/product/ophthaloptom/refraction/ref_auto/tonoref3.html. Accessed 30 Nov 2016
5. Bland JM, Altman DG (1996) Statistics Notes: measurement error. BMJ 313:744
6. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 327:307–310. https://doi.org/10.1016/S0140-6736(86)90837-8
7. Bland JM, Altman DG (1999) Measuring agreement in method comparison studies. Stat Methods Med Res 8:135–160
8. Marsich MM, Bullimore MA (2000) The repeatability of corneal thickness measures. Cornea 19:792–795
9. Lackner B, Schmidinger G, Pieh S et al (2005) Repeatability and reproducibility of central corneal thickness measurement with Pentacam, Orbscan, and ultrasound. Optom Vis Sci 82:892–899
10. O'Donnell C, Maldonado-Codina C (2005) Agreement and repeatability of central thickness measurement in normal corneas using ultrasound pachymetry and the OCULUS Pentacam. Cornea 24:920–924
11. De Sanctis U, Missolungi A, Mutani B et al (2007) Reproducibility and repeatability of central corneal thickness measurement in keratoconus using the rotating Scheimpflug camera and ultrasound pachymetry. Am J Ophthalmol 144:712–718
12. Nam SM, Im CY, Lee HK et al (2010) Accuracy of RTVue optical coherence tomography, Pentacam, and ultrasonic pachymetry for the measurement of central corneal thickness. Ophthalmology 117:2096–2103. https://doi.org/10.1016/j.ophtha.2010.03.002
13. Correa-Pérez ME, López-Miguel A, Miranda-Anta S et al (2012) Precision of high definition spectral-domain optical coherence tomography for measuring central corneal thickness reliability of cirrus HD-OCT pachymetry. Invest Ophthalmol Vis Sci 53:1752–1757. https://doi.org/10.1167/iovs.11-9033
14. Li H, Leung CKS, Wong L et al (2008) Comparative study of central corneal thickness measurement with slit-lamp optical coherence tomography and visante optical coherence tomography. Ophthalmology 115:796–801
15. Ishibazawa A, Igarashi S, Hanada K et al (2011) Central corneal thickness measurements with Fourier-domain optical coherence tomography versus ultrasonic pachymetry and rotating Scheimpflug camera. Cornea 30:615–619
16. Kim HY, Budenz DL, Lee PS et al (2008) Comparison of central corneal thickness using anterior segment optical coherence tomography vs ultrasound pachymetry. Am J Ophthalmol 145(228–232):e1. https://doi.org/10.1016/j.ajo.2007.09.030
17. Nam SM, Lee HK, Kim EK, Seo KY (2006) Comparison of corneal thickness after the instillation of topical anesthetics: proparacaine versus oxybuprocaine. Cornea 25:51–54
18. Simon G, Small RH, Ren Q, Parel J-M (1993) Effect of corneal hydration on goldmann applanation tonometry and corneal topography. Refract Corneal Surg Thorofare 9:110–117
19. Bechmann M, Thiel MJ, Neubauer AS et al (2001) Central corneal thickness measurement with a retinal optical coherence tomography device versus standard ultrasonic pachymetry. Cornea 20:50
20. Tam ES, Rootman DS (2003) Comparison of central corneal thickness measurements by specular microscopy, ultrasound pachymetry, and ultrasound biomicroscopy. J Cataract Refract Surg 29:1179–1184. https://doi.org/10.1016/S0886-3350(02)01921-1