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Accuracy, Repeatability and Reproducibility of Central Corneal Thickness Measurement by Optical Coherence Tomography Verses Ultrasound Pachymetry

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Abstract

Purpose*- To compare the accuracy, repeatability and intersession reproducibility of central corneal thickness measurements by Anterior segment optical coherence tomography and ultrasound pachymetry in normal subjects and glaucoma patients.*

Design*- Case- Control study*

Method- *A single observer measured central corneal thickness (CCT) in 60 eyes of 60 patients with Anterior segment optical coherence tomography (AS-OCT) and ultrasound pachymetry (UP) on two sessions with 15 days apart. In both methods, a set of three readings were taken and average was the final reading. Paired t- test was used to compare CCT measurement taken by AS-OCT and ultrasound pachymetry. The mean differences and level of agreement were calculated by Bland-Altmann plot within 95% LoA. Coefficient of repeatability (CoR) and coefficient of reproducibility was calculated.*

Results- *In normal subjects, the mean CCT measured by UP and AS-OCT was 534.04 ± 22.16 µm (486-610 µm) and 525.03 ± 23.63 µm (474-600 µm) respectively. The mean difference between ultrasound pachymetry and ASOCT measurements was -9.01 ± 7.65 µm and the 95% LoA were between -24 and 6 µm. The CoR of AS-OCT was 0.21% and of UP was 0.25%. The coefficient of reproducibility of AS-OCT and UP was 0.60% and 0.98% respectively.*

In glaucoma subjects, the mean CCT measured by UP and AS-OCT was 542 ± 21.34 µm (500-604 µm) and 534.80 ± 21.19 µm (480-599 µm) respectively. The mean difference between ultrasound pachymetry and ASOCT measurements was -7.70 ± 5.54 µm and the 95% LoA were between -18.6 and 3.2 µm. The CoR of AS-OCT was 0.21% and of UP was 0.33%. The coefficient of reproducibility of AS-OCT was 0.66% and of UP was 0.94%. In both study group, the CCT obtained by AS-OCT was highly correlated to UP.

Conclusion*- AS-OCT is a non-contact method hence there is no risk of infections, corneal trauma. The OCT scanner designed for retinal imaging, may be used to scan anterior segment with minor modifications. This study concluded that CCT measurements by ASOCT have a high degree of repeatability and intersession reproducibility and is comparable to the gold standard, ultrasound pachymetry so CCT measurements can used interchangeably in glaucoma and normal patients.*

Keywords: *Central corneal thickness; Ultrasound Pachymetry; Anterior Segment Optical Coherence Tomography*

Abbreviations

ASOCT (Anterior segment Optical Coherence Tomography)

UP (Ultrasound Pachymetry)

CCT (Central Corneal Thickness)

CoR (coefficient of Repeatability)

LoA (Limits of Agreement)

Introduction

Corneal pachymetry has an important role in the modern eye care such as refractive surgery screening **[**1**]**, corneal disease diagnosis such as ectatic dystrophies, contact lenses related complications, dry eye **[**2**]**, diabetes mellitus **[**3**]** and glaucoma management. Central corneal thickness (CCT) was found an independent risk factor for progression to glaucoma in ocular hypertension treatment study.**[**4**]** Accurate intraocular pressure (IOP) measurement has an important role in diagnosis and follow up of patients with glaucoma. Increased or decreased CCT lead to overestimation or underestimation of the true IOP. Higher IOP was recorded by Goldman Applanation Tonometry in thicker corneas and lower in thinner corneas. It has been reported in Ocular Hypertension Treatment Study (OHTS) that patients with a corneal thickness of 555 μm and less had a 3-fold higher risk of developing glaucomatous damage as compared to the patients with corneal thickness greater than 588 μm. The risk of developing glaucoma is increased by 70% when there is a decrease in corneal thickness of 40 μm and hence CCT has been considered as a powerful predictor in the development of primary open angle glaucoma among the ocular hypertensive eyes. **[**5**]** The principle of ultrasonic pachymetry, the gold standard is based on the measurement of the time delay of back-reflected sound at varying longitudinal distances (anterior and posterior surface of cornea) to determine the corneal thickness. The advantage of ultrasound pachymetry that make the instrument feasible to use in clinical practice are portability and relative affordability, but the technique is invasive because they contact with the cornea, hence there are chances of transmission of infection. The measurement of delay in low coherence infrared light reflected from various tissue structures is the principle of OCT (Optical Coherence Tomography). **[**6,7**]** The beam splitter of a Michelson interferometer split the low coherence infrared light into two components—one is directed to the object of interest in the sample arm and the other to a movable mirror in the reference arm. The signals reflected from these two components are then superimposed at the interferometer. The strength of reflected signal is a function of depth in the scan. However, the pigmented posterior layer of the iris hinders light penetration leads to poor visualization of ciliary

body. Although the commercially available OCT system was designed for retinal imaging, the image of anterior segment can be obtained by the OCT with few minor modifications.

One research group has shown that CCT measurement taken with OCT correlates very well with the measurement obtained by ultrasound pachymetry.8 Other research group has investigated the accuracy of OCT in pachymetry for glaucoma patients and their result showed that both OCT and ultrasound pachymetry had high accuracy even done by different observer.**[**9**]** Muscat et al. studied the repeatability and inter-session and inter-observer reproducibility of corneal thickness measurement by OCT in normal subjects.**[**10**]**

The main purpose of the present study is to determine the repeatability and inter-session reproducibility of CCT measurement by OCT and ultrasound pachymetry in normal subjects and glaucoma patients and if AS-OCT could be possible substitute for ultrasound pachymetry in the measurements of CCT in glaucoma patients as AS-OCT has advantages of being non-contact, aseptic and without the risk of contact corneal trauma.

Materials and Methods

Study design and population

The study was conducted at Institute of Ophthalmology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh and the subjects for the study were taken from Eye Outpatient Department (OPD) and Glaucoma Clinic between November 2017 to November 2019. There were 2 study groups – group 1- normal subjects and group 2- primary glaucoma patients.

A total of 60 eyes of 60 patients with no anterior segment pathology were included in the study. In each study group, there were 30 patients. In each study group, there were 16 male participants and 14 female participants. The mean age of patients enrolled in group 1 was 46.77 ± 7.89 years and in group 2 was 51.53 ± 8.25 years.

Inclusion and exclusion criteria:

The inclusion criteria for normal subjects were intraocular pressure (IOP) ≤ 21mmHg, best corrected visual acuity- 6/6 with refractive less than +/- 6 dioptre. The inclusion criteria for glaucoma patients were intraocular pressure > 21 mmHg, glaucomatous optic disc changes, visual field changes (at-least two repeatable Humphrey visual field defect) and best corrected visual acuity- 6/6 with refractive less

than +/- 6 Dioptre. Smokers, dry eye syndrome patients, hypertensive and diabetic patients were also included in the study.

The exclusion criteria in the study included patients of anterior segment pathology like conjunctivitis, keratitis or anterior uveitis, history of contact lens use, refractive error more than +/- 6 diopter, history of trauma, pregnant women, instilling any ophthalmic eye- drop within 24 hours (for normal subjects), non- cooperative patient and patient not giving informed consent.

The study was conducted according to the Declaration of Helsinki and the research protocol was approved by institutional ethics committees. All participants had given informed consent after the nature and intent of the study has been fully explained to them. In each group, each eligible subject had a complete ophthalmic history including treatment and family history, time since diagnosis of glaucoma and precipitating factors. Visual acuity of patient was taken for each eye on Snellen's chart and slit lamp examination was done to look for any anterior segment pathology and fundus examination was done with 78D condensing lens. Applanation tonometry, gonioscopy and visual field analysis were done in the glaucoma patients.

In each case, central corneal thickness measurement was taken by anterior segment optical coherence tomography (ASOCT) followed by Ultrasound pachymeter. In both methods, a set of 3 readings were taken and average was the final reading. All scanning was performed during a specific period- 10:00 a.m. to 2:00 p.m. to minimize the effect of diurnal variation in corneal thickness. Measurements were taken at a second session after 15 days of the first session, keeping the time of day and order of testing for the second session same for each subject.

Scanning analysis

Anterior Segment Optical Coherence Tomography: The OCT scanner designed for retinal imaging (Visante, Carl ZEISS, Meditec, Inc) is used to scan anterior segment with anterior segment adapter lens. The patient was positioned on the OCT headrest and chin-rest, central corneal thickness (CCT) measurement was made at the apex of the cornea using anterior segment cube 512x128, cube analysis of the anterior segment 5 lines raster. The center of the cornea was identified by moving the scan navigators throughout the entire scan volume. The CCT measurement was taken at the intersection of the highest horizontal and vertical scans, using caliper on the horizontal scan. The position of the caliper was adjusted and the white horizontal lines of the caliper ends were placed on the anterior and posterior surfaces of cornea. The measurements were taken in micrometers.

Ultrasound pachymetry: The ultrasound pachymeter (DGH 5100 e A- Scan/ Pachymeter combination unit) was used to measure central corneal thickness. One drop of topical anesthetic 0.5% proparacaine eyedrop was instilled in the lower fornix in eye and measurements were taken by gently placing the probe perpendicular to the corneal surface. Three values will be obtained from centre of cornea. A set of three readings were taken and the average was the final reading.

Statistical analysis

Central corneal thickness measurement between AS-OCT and ultrasound pachymetry was compared using paired t- test in normal subjects and glaucoma patients. Significance level was $p < 0.05$. To test agreement between the two different instruments, a Bland- Altman plot was performed. Mean differences and 95% limits of agreement (LoA) were calculated.

Repeatability of central corneal thickness measurements was assessed using alpha of Cronbach, intraclass correlation coefficient (ICC) and coefficient of repeatability (CoR). CoR was defined as the standard deviation (SD) of the difference from the mean of these repeated measurements divided by the average. The ICC ranged from a value of 0 to 1, with 0 indicating no agreement, and 1 indicating absolute agreement between repeated measurements.

The intersession reproducibility was calculated. As suggested by bland and Altman, the coefficient of reproducibility was defined as the SD of the differences between the pairs of measurements obtained during different sessions, divided by the average of the means of each pair of readings.

Results

In each study group, there were 16 male participants (16 eyes) and 14 female participants (14 eyes). The mean age of patients enrolled in this study in group 1 was 46.77 ± 7.89 years and in group 2 was 51.53 ± 8.25 years. (Table 1)

Parameters	Group 1: Normal Subjects (Age in Years)	Group 2: Glaucoma Patients (Age in Years)
Mean	46.77	51.53
Standard Deviation	7.89	8.25
Minimum	28	29
Maximum	64	69

Table 1: Mean (± SD) age in years in two study groups

Study group 1 – Normal Subjects

The mean CCT measurements ± SD was 525.03 ± 23.63 (474-600 µm) and 534.04 ± 22.16 (486-610 µm) for the anterior segment optical coherence tomography and ultrasound pachymetry respectively.

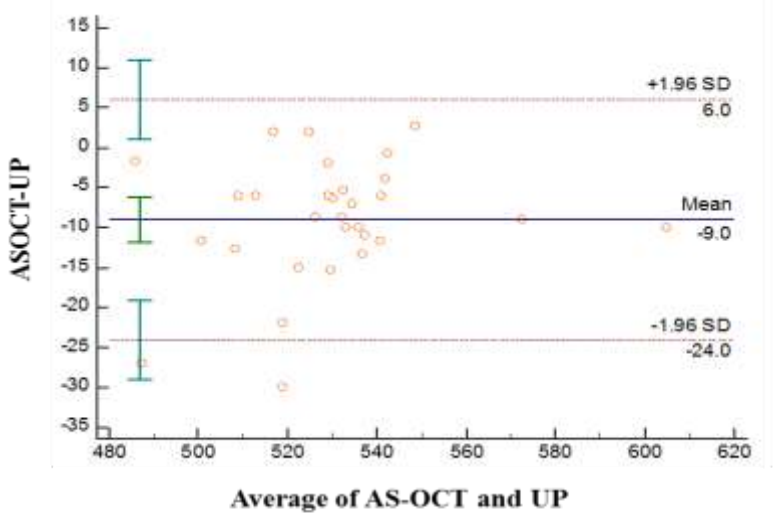

Figure 1: Bland-Altman plot for agreement between the instruments

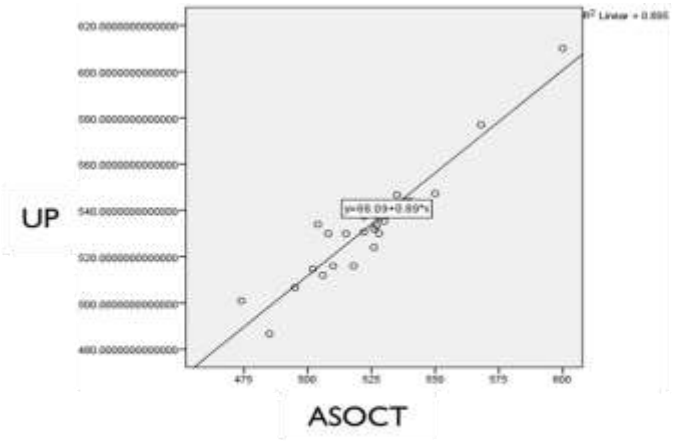

Figure 2: CCT correlation plot between Ultrasound pachymetry (UP) and AS-OCT

The mean difference between ultrasound pachymetry and ASOCT measurements was -9.01 ± 7.65 µm and the 95% LoA were between -24 and 6 µm (Figure 1). The central corneal thickness obtained by AS-OCT was highly correlated to ultrasound pachymetry (r=0.946). (Figure 2)

Instrument	Alpha of cronbach	Intraclass coefficient	Coefficient of repeatability
AS-OCT	0.993	0.992	0.21%
UP	0.987	0.986	0.25%

Table 2: Analysis of repeatability of central corneal thickness measurements obtained by both instruments.

The CoR (Coefficient of repeatability) of AS-OCT was 0.21%. The CoR (Coefficient of repeatability) of ultrasound pachymetry was 0.25%. The central corneal thickness measured by both instruments was highly repeatable. (Table 2)

Instruments	Mean Difference ± SD	Coefficient Of Reproducibility	P Value
AS-OCT	0.100 ±3.68 µm	0.60%	p<0.909
UP	-0.844 ± 5.281 µm	0.98 %	p< 0.388

Table 3: Analysis of intersession reproducibility of central corneal thickness obtained by both instruments.

The coefficient of reproducibility of AS-OCT was 0.60% and of ultrasound pachymetry was 0.98%. (Table 3)

Study Group 2- Glaucoma Patients

The mean CCT measurements ± SD was 534.80 ± 21.19 (480-599 µm) and 542 ± 21.34 (500-604 µm) in anterior segment optical coherence tomography and ultrasound pachymetry respectively.

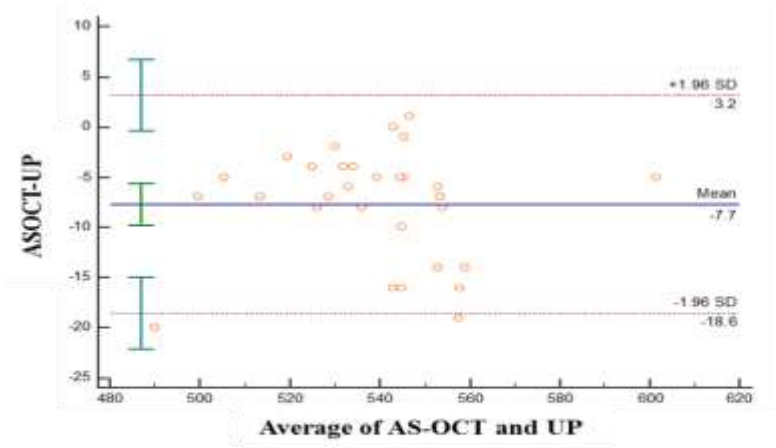

Figure 3: Bland-Altman plot for agreement between the instruments

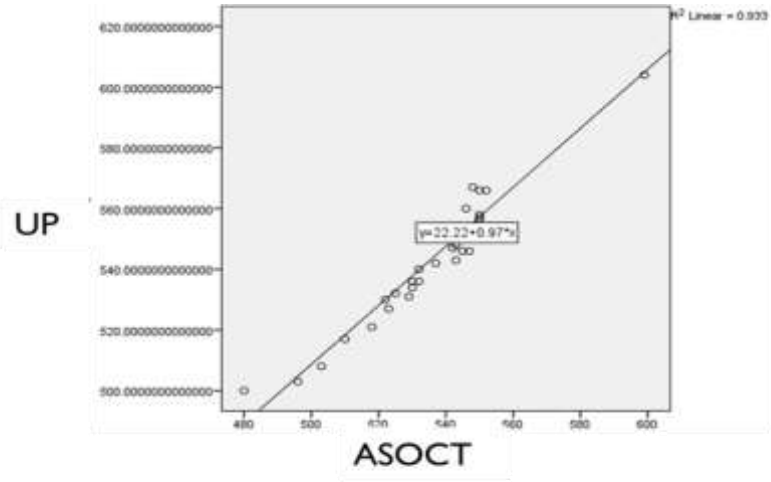

Figure 4: CCT correlation plot between Ultrasound pachymetry (UP) and AS-OCT

The mean difference between ultrasound pachymetry and ASOCT measurements was -7.70 ± 5.54 µm and the 95% LoA were between -18.6 and 3.2 µm (Figure 3). The central corneal thickness obtained by AS-OCT was highly correlated to ultrasound pachymetry (r=0.966, p<0.001) (Figure 4).

Instrument	Alpha Of Cronbach	Intraclass Coefficient	Coefficient Of Repeatability
AS-OCT	0.990	0.989	0.21%
UP	0.925	0.925	0.33%

Table 4: Analysis of repeatability of central corneal thickness measurements obtained by both instruments

The CoR (Coefficient of repeatability) of AS-OCT was 0.21% and of ultrasound pachymetry was 0.33%. The central corneal thickness measured by both instruments was highly repeatable in the study group 2. (Table 4)

Instruments	Mean Difference ± SD	Coefficient Of Reproducibility	P Value
AS-OCT	0.13 ±3.56 µm	0.66%	P<0.839
UP	0.66 ± 5.11 µm	0.94 %	p< 0.944

Table 5: Analysis of intersession reproducibility of central corneal thickness obtained by both instruments in study group 2

The coefficient of reproducibility of AS-OCT was 0.66% and of ultrasound pachymetry was 0.94%. (Table 5)

Discussion

In both the study groups, the CCT measurements obtained by the AS-OCT were slightly lower than ultrasound pachymetry. Ramesh et al. **[**11**]**, Wells et al.1, Zhao et al. **[**12**]**, Kim et al. **[**13**]** and Neri et al. **[**14**]** also reported higher values of CCT measurements by ultrasound pachymetry in comparison to AS-OCT. The results of present study comparable with their studies. The possible reason for the difference may be the use of topical anaesthetic which cause corneal epithelial edema **[**15,16**]** resulting in overestimation of the corneal thickness taken with ultrasound pachymeter. Secondly, the placement of the probe in the paracentral regions of the cornea may lead to overestimation of central corneal thickness.

In both the study groups, the CCT measurement by the AS-OCT and Ultrasound pachymetry was also found highly correlated, and the mean difference between the AS-OCT and ultrasound pachymetry was statistically significant but clinically not significant. The CCT values between these devices can be used interchangeably in normal and glaucoma patients.

Other studies much like our study were conducted by Garcia-Medina et al. **[**17**]** and Çomçalı et al. **[**18**]** (included glaucoma and normal patients) found similar results. A similar study was reported by Bechmann et al. **[**8**]** which included normal and corneal edema patients. In our study, we found that AS-OCT uses low-coherence interferometry scanning with high penetration, lower absorption and low scattering. It also provides high resolution cross section images in vivo.

However, Ayala and Strandas [9] reported higher CCT by AS-OCT compared to ultrasound. On the other hand, no significant difference in CCT measured by AS-OCT and ultrasound pachymetry was observed in glaucomatous eyes which was similar to findings of present study.

Repeatability and Reproducibility of AS-OCT and ultrasound pachymetry

In both study groups, the coefficient of repeatability and inter-session reproducibility was excellent in AS-OCT and was comparable to the standard ultrasound pachymetry.

While similar results were reported by Chen et al. [19] and Bechmann et al. [8] regarding repeatability and reproducibility among normal patients. Li et al. [20] reported that pupil-centration provided better repeatability than vertex centration.

The studies conducted by Kim et al. [13], Muscat et al [10], Gokcinar et al.[21], Piotrowiak et al.[22], Wongchaisuwat et al.[23] and Correa-Pérez et al.[24] concluded good inter-observer reproducibility of the results obtained by the devices.

Similar results reported concerning reproducibility in keratoconus patients in a study conducted by Prospero Ponce et al. [25], in post-PRK patients by Schneider et al. [26], in eyes with corneal edema done by Wongchaisuwat et al. [23] and in glaucoma patients reported by Ayala and Strandas [9].

AS-OCT is considered a promising non-contact instrument for evaluating pachymetry. AS-OCT uses low-coherence interferometry scanning with lower absorption, low scattering and high penetration. It also provides high- resolution cross-sectional images in vivo and localize and quantify the corneal scars and edema. It also allows to examine anterior chamber angle and provides relevant clinical data regarding iris pathology, corneal pathology, tear film pathology.

Conclusions

AS-OCT is a non-contact method hence there is no risk of infections, corneal trauma. We can acquire AS-OCT by using anterior segment adapter lens in retinal OCT instruments and patient's data can be retrieved easily for comparison on subsequent follow-up. The repeatability and reproducibility of AS-OCT is comparable to the gold standard, ultrasound pachymetry so CCT measurements can used interchangeably in glaucoma and normal patients.

Limitations

The Sample size was small in the present study and only normal subjects and glaucoma patients were included. Inter-observer reproducibility was not determined. Further studies are required in order to evaluate the accuracy, repeatability, and reproducibility of AS-OCT in patients who undergo kerato-refractive surgeries, patients having corneal pathologies. Research is also required for evaluation of accuracy, repeatability, and reproducibility of AS-OCT in peripheral corneal thickness measurements.

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