

## **“Comparison of Corneal thickness measurements between Angiovue Optical Coherence Tomography, Ultrasound pachymetry and Ocular Biometry”**

### **Abstract**

**Purpose:** To compare central corneal thickness (CCT) measurements and their reproducibility when taken by Ultrasound Pachymetry, Ocular Biometry and Angiovue Optical Coherence Tomography (OCT).

**Methods:** Twenty-five healthy volunteers were recruited creating a sample size of 50 eyes. All subjects had pachymetric measurements by Ultrasound pachymetry (PachPen Handheld Pachymeter, Keeler Instruments Inc), Ocular biometry (IOL Master 700 Swept Source Biometry, Zeiss) and Angiovue Optical Coherence Tomography (Optovue Avanti RTVue XR Angiovue). Central corneal thickness measurements by the 3 methods, two sets of measurements were repeated by a single examiner for each method.

**Results:** The average measurements of central corneal thickness by Ultrasound pachymetry (PachPen Handheld Pachymeter, Keeler Instruments Inc), Ocular biometry (IOL Master 700 Swept Source Biometry, Zeiss) and Angiovue Optical Coherence Tomography (Optovue Avanti RTVue XR Angiovue) were 547.26 $\mu\text{m}$ , 551.36 $\mu\text{m}$ , and 536.42 $\mu\text{m}$ , respectively. The mean standard deviation (SD) of repeated measurements by Ocular biometry was 48.87 $\mu\text{m}$ , which was greater than the mean SD of 44.24 $\mu\text{m}$  and 40.35 $\mu\text{m}$  ( $P < 0.001$ ) by ultrasound pachymetry and Angiovue optical coherence tomography, respectively. There were statistically significant differences in the measurement results among the 3 methods (Ultrasound pachymetry vs. Ocular biometry  $P = 0.019$ ; Ultrasound pachymetry vs. Angiovue Optical Coherence Tomography;  $P < 0.001$ ; Ocular biometry vs. Angiovue Optical Coherence Tomography  $P < 0.001$ ). There was a significant linear correlation between the Ultrasound pachymetry and Ocular biometry ( $r = 0.945$ ,  $P < 0.001$ ), Ultrasound pachymetry and Angiovue Optical Coherence Tomography ( $r = 0.895$ ,  $P < 0.001$ ), and Ocular biometry and Angiovue Optical Coherence Tomography ( $r = 0.902$ ,  $P < 0.001$ ).

**Conclusion:** Central corneal thickness readings were comparable between PachPen Handheld Pachymeter, IOL Master 700 Biometry and Angiovue Optical Coherence Tomography; Angiovue optical coherence tomography gave significantly smaller values. The measurements of the 3 methods showed significant linear correlations with one another. All methods provided acceptable repeatability of measurements.

### **Introduction**

Corneal thickness is easy to measure and a sensitive parameter of corneal health and function. Knowing Central Corneal Thickness (CCT), is a very important parameter for the determination of corneal diseases such as Keratoconus and Fuch's dystrophy, for identifying the suitable patients for refractive surgery, so as for the detection of glaucoma patients and ocular hypertension [1].

Several traditional and new devices, are used for CCT measurements such as Ultrasound pachymetry (UP), Confocal microscopy, Optical Coherence Tomography (OCT), Scheimpflug imaging, Scanning slit lamp topography, interferometry and optical low coherence reflectometry [2]. Ultrasound pachymetry remains the gold standard in the measurement of CCT. It determines the CCT, by measuring the time that is taken for an ultrasound wave to return after reflection from the corneal endothelium [3]. Ultrasound pachymetry has a lot of advantages and disadvantages too. Disadvantages are the need of topical anesthesia, the corneal contact of the

probe that may cause epithelial erosion and infection and the dependency on examiner experience. A drop of topical anesthetic is essential before the measure of CCT, otherwise the technique becomes discomfort for the patient. The accuracy of this technique is dependent on the perpendicularity of the probe's application to the cornea and the reproducibility relies on precise probe placement. From the other side, Ultrasound pachymetry, offers the advantages of portability and is a relatively easy use technique. It is a simple, portable and cost-effective system.

Due to the limitations of Ultrasound pachymetry, other non-contact optical methods, such as Optical Coherence Tomography and Optical biometry are alternatives and provide rapid, reliable and objective measurements of the CCT. Optical Coherence tomography (OCT), is a non-contact technique that acquires pachymetry measurements based on optical interferometry [4]. OCT is able to discern sublayer detail and pachymetry and may be able to perform measurements on corneas with pathology that do not allow measurement by other techniques. This is because it has a high depth resolution and it can measure corneal thickness even in opacified corneas [5]. Optical biometry is commonly used for the calculation of intraocular lens (IOL) power and desired postoperative refraction. It can obtain multiple measurements of various biometric eye data such as CCT, anterior chamber depth, anterior aqueous depth, lens thickness, and axial length in a single capturing process [6].

CCT is becoming more routine in clinical examination and it is useful to understand the agreement and repeatability of CCT measurements between different instruments. The aim of this study is to evaluate and compare the intra-observer repeatability and quantify the agreement of CCT between Angiovue Optical Coherence Tomography (Optovue Avanti RTVue XR Angiovue), Ultrasound pachymetry (PachPen Handheld Pachymeter, Keeler Instruments Inc) and Ocular Biometry (IOL Master 700 Swept Source Biometry, Zeiss).

## **Methods**

The study population was composed of 25 healthy patients. Two measurements were taken from each patient, to secure the validation and accuracy assurance. All measurements performed as a part of routine ophthalmological examination, by the same ophthalmologist, at the same time of the day (9pm to 12 pm). Patients with pathological corneal features, contact lens wear and previous refractive surgery were excluded from the study. Both eyes were examined by Angiovue Optical Coherence Tomography (Optovue Avanti RTVue XR Angiovue), Ultrasound pachymetry (PachPen Handheld Pachymeter, Keeler Instruments Inc) and Ocular Biometry (IOL Master 700 Swept Source Biometry, Zeiss).

## **Statistical Analysis**

All data were analyzed by Statistical Package for Social Science software (SPSS version 22.0; IBM, Chicago, IL). Bland and Altman method were used to assess the repeatability and agreement of CCT measurements between the three methods. CCT measurements are presented as mean  $\pm$ SD. Mean difference  $\pm$ SD between measurements was calculated. The coefficient of repeatability and 95% limits of

agreement (LoA) as recommended by Bland and Altman method were used to assess repeatability between the paired measurements.

Comparison of the mean CCT values for the 3 devices was conducted by Student *t* test and the linear correlation between measurements by Pearson coefficient of correlation. P-Value was  $p=0.005$ .

### Results

The average measurements of central corneal thickness by ultrasound pachymetry (PachPen Handheld Pachymeter, Keeler Instruments Inc), ocular biometry (IOL Master 700 Swept Source Biometry, Zeiss) and Angiovue optical coherence tomography (Optovue Avanti RTVue XR Angiovue) were 547.26 $\mu$ m, 551.36 $\mu$ m, and 536.42 $\mu$ m, respectively. The mean standard deviation (SD) of repeated measurements by ocular biometry was 48.87 $\mu$ m, which was greater than the mean SD of 44.24 $\mu$ m and 40.35 $\mu$ m ( $P < 0.001$ ) by ultrasound pachymetry and Angiovue optical coherence tomography, respectively. There were statistically significant differences in the measurement results among the 3 methods (ultrasound pachymetry vs. ocular biometry  $P = 0.019$ ; ultrasound pachymetry vs. Angiovue optical coherence tomography;  $P < 0.001$ ; ocular biometry vs. Angiovue optical coherence tomography  $P < 0.001$ ). There was a significant linear correlation between the ultrasound pachymetry and ocular biometry ( $r = 0.945$ ,  $P < 0.001$ ), ultrasound pachymetry and Angiovue optical coherence tomography ( $r = 0.895$ ,  $P < 0.001$ ), and ocular biometry and Angiovue optical coherence tomography ( $r = 0.902$ ,  $P < 0.001$ ).

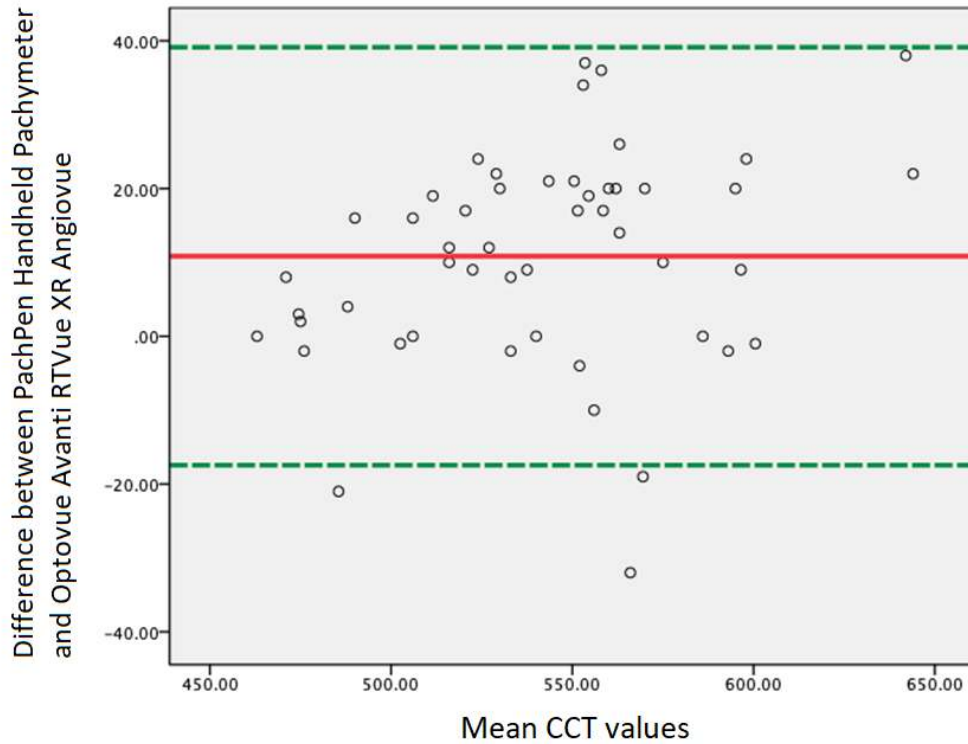
	N	Minimum	Maximum	Mean	Std. Deviation
PachPen	50	463.00	661.00	547.2600	44.24275
Zeiss IOL Master 700	50	417.00	663.00	551.3600	48.87792
Optovue Avanti RTVue XR	50	463.00	633.00	536.4200	40.35713
Valid N (listwise)	50				

**Table 1** The average measurements of central corneal thickness by the 3 devices

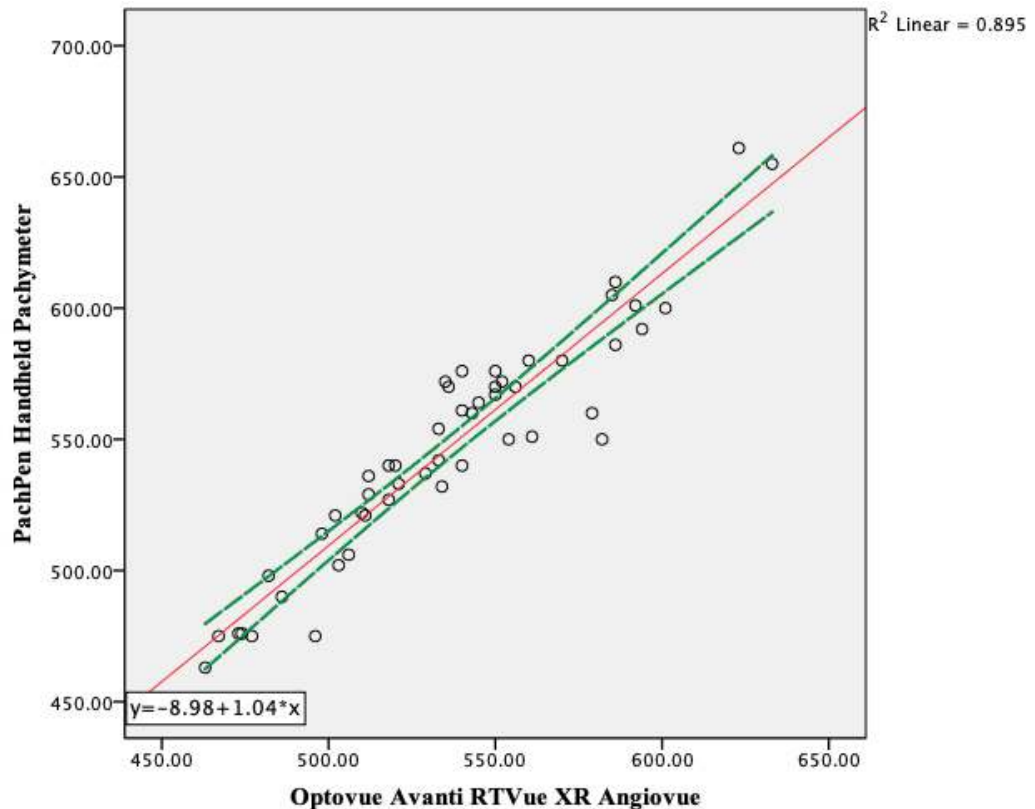
	Paired Differences	t	df	Sig.
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		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PachPen - Optovue Avanti RTVue XR	10.84	14.43	2.04	6.73	14.94	5.31	49	.000
Pair 2	Zeiss IOL Master 700 - Optovue Avanti RTVue XR	14.94	16.45	2.32	10.26	19.61	6.42	49	.000
Pair 3	Zeiss IOL Master 700 - PachPen	4.10	11.95	1.69	.70	7.49	2.42	49	.019

**Table 2** Statistical analysis -paired t-test by 3 the devices



**Figure 1.** Bland-Altman plots of the mean differences between the first and second measurements against the mean CCT values by PachPen Handheld Pachymeter and Optovue Avanti RTVue XR Angiovue in comparison with the mean difference between the 2 measurements.



**Figure 2** Scatter Chart of CCT measurements between PachPen Handheld Pachymeter and Optovue Avanti RTVue XR Angiovue.

## Discussion

There are a lot of studies in scientific literature, referring to CCT measurements with new devices and technology specially before and after refractive surgery [7] or at different stages of keratoconus [8]. In the present study we measured the central corneal thickness by ultrasound pachymetry (PachPen Handheld Pachymeter, Keeler Instruments Inc), ocular biometry (IOL Master 700 Swept Source Biometry, Zeiss) and Angiovue optical coherence tomography (Optovue Avanti RTVue XR Angiovue). The repeatability of CCT measurements was high with all instruments and this has already proven with a lot of studies [9-11].

At the same time, there was an agreement between the results, too. The statistical analysis proved that CCT measurements was  $547.26 \pm 44.24\mu\text{m}$  with ultrasound pachymetry (PachPen Handheld Pachymeter),  $531.36 \pm 48.87\mu\text{m}$  with optical biometry (Zeiss IOL Master 700) and  $536.42 \pm 40.35\mu\text{m}$  with the anterior segment Optical Coherence Tomography (Optovue Avanti RTVue XR Angiovue). The average measurements of CCT, with ultrasound pachymetry (PachPen Handheld Pachymeter) was lower at about  $10.84 \pm 14.43\mu\text{m}$  than the CCT measurements with anterior segment OCT (Optovue Avanti RTVue XR Angiovue) ( $p < 0.001$ ).

Correspondingly, the average of optical biometry (Zeiss IOL Master 700) was higher at about  $14.94 \pm 16.45\mu\text{m}$  in comparison with the measurements of anterior segment OCT (Optovue Avanti RTVue XR Angiovue) ( $p < 0.001$ ) and at about  $4.10 \pm 11.95\mu\text{m}$  comparatively to ultrasound pachymetry measurements (PachPen Handheld Pachymeter). The mean difference between the three devices was about 4 to  $14\mu\text{m}$ . These differences in measurements, are due to the different structure and method of use, of the three instruments.

Measuring the CCT with PachPen Handheld Pachymeter is usually the method of choice of most examiners, due to its already established reliability, ease of use and low cost of the machine compared to the other two devices. However, the measurement with ultrasound pachymetry requires a contact examination in the patient's corneal epithelium, which can be annoying for the patient. For the correct calculation it is necessary to place the probe as vertically as possible at the top of the cornea, so that the measurement corresponds to the central area.

Results from other studies have shown that measuring the central thickness of the cornea using ultrasound pachymetry (PachPen Handheld Pachymeter) provides excellent repeatability between measurements [12]. A similar observation was made by Gunvant et al. [13], demonstrating that ultrasound pachymetry provided excellent repeatability and reliability between observations. At the same time, this technique was reported to be easy to use and required minimal patient cooperation compared to other techniques. In addition, Miglior et al. [14] showed that even a well-trained operator may not be able to take reliable measurements of CCT using ultrasound pachymeter. At this point it should be noted that although ultrasound pachymetry has been reported to have good repeatability, a deviation of about  $-2.4\mu\text{m}$  [15] has been observed among examiners [16]. Finally, a difference of up to  $49\mu\text{m}$  has been reported in the measurements of the central thickness of the cornea using different kind of ultrasound pachymeters [17].

In another comparative study of PachPen Handheld Pachymeter with the anterior segment optical coherence tomography (AS-OCT) and the spectral microscopy (specular microscopy), several similarities but also differences were observed in the measurement of CCT. Specifically, the value of the thickness of the central cornea with PachPen ultrasound pachymetry was  $544.43 \pm 36.61\mu\text{m}$ , while with the anterior segment optical coherence tomography (AS-OCT) it was  $527.09 \pm 35.54\mu\text{m}$  and with the specular microscopy  $533.17\mu\text{m}$ , with a statistically significant difference between these three devices ( $p = 0.002$ ). CCT value measured by PachPen ultrasound pachymeter was significantly higher than the other two groups. In conclusion, the value of central corneal thickness measured by PachPen ultrasound pachymeter is highest than the measurements with the anterior segment optical coherence tomography (AS-OCT) by  $11.23\mu\text{m}$  [18]. In the present study there is an overestimation of Central Cornea Thickness measured by PachPen at  $10.84\mu\text{m}$  compared to that measured by Optovue Avanti RTVue XR Angiovue. A study by Laszll Kiraly et al. [19] comparing central corneal thickness measurements with three different devices (IOL Master 700, Pentacam HR, and Cirrus HD-OCT) found repeatability and good internal consistency of Zeiss IOL Master 700 measurements,

with a mean value of central corneal thickness of  $543.20 \pm 31.69\mu\text{m}$  and  $542.75 \pm 31.34\mu\text{m}$  for the optical coherence tomography Cirrus HD - OCT Model 400, with a non-statistical difference between them ( $p = 0.519$ ) [19]. In the present study the measurements with optical biometry (Zeiss IOL Master 700) and with the anterior segment optical coherence tomography (Optovue Avanti RTVue XR Angiovue) showed a statistically significant difference of  $14.94 \pm 16.45\mu\text{m}$ . The difference between the two studies could be attributed to the number of participants in each study, but also to the different characteristics that the anterior segments OCT devices have.

Woo Beom Shin et al. compared ultrasound pachymetry (USP) with optical biometrics (Zeiss IOL Master 700) to measure central corneal thickness [20]. The mean values of the measurements using the USP and the IOL master 700, were  $554.4 \pm 37.4\mu\text{m}$  and  $551.1 \pm 37.1\mu\text{m}$ , respectively, showing that the IOL master 700 gave statistically significantly smaller measurements than the USP with a p-value  $<0.001$ . According to Pearson correlation test, the mean values from the measurements of the central corneal thickness with the two test devices were found to have a fairly positive correlation ( $r = 0.977$ ,  $p < 0.0001$ ), an observation with which the present study agrees as it was found that the correlation by Pearson optical biometrics (Zeiss IOL Master 700) and ultrasound pachymetry (PachPen Handheld Pachymeter) were very strong ( $r = 0.972$ ,  $p < 0.001$ ) and statistically significant.

It could be expected that measurements of central corneal thickness with anterior segment optical coherence tomography (Optovue Avanti RTVue XR Angiovue) would give higher values than ultrasound pachymetry measurements (PachPen Handheld, non-tactical) while the ultrasound probe causes displacement of the lacrimal layer. In a comparative study by Haitao Li et al., concluded 50 normal eyes, the mean thickness of the central cornea was  $550.3 \pm 31.1\mu\text{m}$  for ultrasound pachymetry measurements while for anterior segment optical coherence tomography, it was  $535.7 \pm 30.2\mu\text{m}$ . In other words, there was a difference of  $14.6\mu\text{m}$  in the mean value of the central thickness of the cornea, with a smaller value corresponding to the anterior segment optical coherence tomography [21]. In the same study, is observed that measurements taken manually by anterior segment optical coherence tomography gave higher values ( $1.9\mu\text{m}$ ) than ultrasound measurements, although they were not statistically significant. This difference between automatic and manual shooting was attributed to the observation that the anterior corneal margins were outlined slightly lower than the anterior corneal surface, leading to an underestimation of thickness [20]. Haitao Li et al. [21] conducted a comparative study of corneal thickness with three different devices: classical ultrasound pachymeter, Visante AS-OCT and Orbscan II. The average central thickness values for the three machines were respectively  $553.5 \pm 30.26\mu\text{m}$ ,  $538.79 \pm 26.22\mu\text{m}$  and  $553.22 \pm 25.47\mu\text{m}$ . Visante AS-OCT underestimated corneal thickness in relation to ultrasound pachymetry. It also underestimated both central and eccentric measurements in relation to Orbscan. It should be noted that the Bland - Altman graphs for the comparison between Orbscan ultrasound pachymetry and Visante AS OCT revealed that the difference in the corneal central thickness measurements varied according to the actual thickness. It was therefore observed that for the thinner corneas ( $<500\mu\text{m}$ ) the Orbscan tended to overestimate the central corneal thickness. A larger data scatter was observed too, indicating less agreement

between ultrasound and Orbscan in thin corneas. At the same time, the anterior segment optical coherence tomography was found to be less underestimated in thin corneas, while the smaller dispersion of the measurements indicated a better agreement between the two machines in thin corneas [22].

In the present study, we observed better agreement and less measurements dispersion between ultrasound pachymetry and optical biometry with a difference of  $4.10 \pm 11.95\mu\text{m}$  ( $p < 0.019$ ). Therefore, the optical biometry (Zeiss IOL Master 700) may be more suitable for measuring corneal thickness, especially in thin corneas, as it is in better agreement with ultrasound pachymetry, which is the golden rule, compared to anterior segment optical coherence tomography.

This observation is particularly important in determining the suitability of patients with thin corneas for refractive surgery. One possible excuse could be the fact that a flattening effect that the ultrasound contact technique can cause is more obvious on the thin corneas and thus lead to a greater deviation in the measurements between the three machines. At the same time, topical anesthetic drops, particularly proparacaine, have been reported to cause local corneal swelling and change of CCT [23]. It is reported that the use of proparacaine in the cornea causes an increase in its thickness up to  $8.9\mu\text{m}$  [23]. In contrast, Herse et al. and Lam et al. suggest that the use of a single drop of anesthetic does not cause a significant change in the central thickness of the cornea [24,25]. It is not entirely clear whether measurements with PachPen Handheld Pachymeter or optical biometry (Zeiss IOL Master 700) or anterior segment optical coherence tomography (Optovue Avanti RTVue XR Angiovue) reflect better the real thickness of the cornea. It is possible that differences in the software analysis of each machine contribute to the discrepancy of the measurements. Clinically, the systematic errors of the machines should be taken into account when measuring the central corneal thickness. In this study, the differences in the measurements of the central corneal thickness between the three machines were less than  $14.94\mu\text{m}$ . A meta-analysis by Doughty and Zaman showed that a 10% difference in the central thickness of the cornea could lead to a difference in intraocular pressure of up to 3.4 mmHg. They calculated that for every  $10\mu\text{m}$  difference in the central thickness of the cornea, a change of 0.2mmHg is introduced in the intraocular pressure measurements [26]

More recently, Kniestedt et al. observed that the effect of central corneal thickness on level tonometry covers a wide range, with changes in intraocular pressure measurements ranging from 0.11 to 0.71 mmHg for each  $10\mu\text{m}$  of central corneal thickness [27].

An alternative approach to investigating the relationship between central corneal thickness and tonometer measurements can be made using a manometer in the anterior chamber. In one of the largest recent studies, Böhm, A. et al. used a manometer to measure intraocular pressure and found that the tonometer measurements may be increased or decreased by 0.4 mmHg for every  $10\mu\text{m}$  change above or below the reference point. This point is the central corneal thickness at which the flattening tonometer measurements are identical to the real intraocular pressure [28].

In addition to the effect that central corneal thickness has on the Goldman level tonometer, it has been reported to affect other tonometry methods, such as the Tonopen and the air tonometer [29-30].



The importance of central corneal thickness, however, is not only clinically important in calculating true intraocular pressure. The role of the central corneal thickness in the selection of patients to undergo refractive surgery is also important.

Although underestimation of central thickness may lead to the exclusion of potentially suitable patients for refractive surgery, overestimation in patients who appear eligible for refractive surgery could lead to catastrophic complications of secondary keratectasia.

Finally, it should be noted that the thickness of the central cornea is considered an aggravating factor for the development of glaucoma. In the ocular hypertension treatment study, for every 40µm reduction in central corneal thickness, there was a 1.71 risk of developing primary open-angle glaucoma in ocular hypertensive eyes [31, 32].

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