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REVIEW

Central Corneal Thickness and Glaucoma Risk: The Importance of Corneal Pachymetry in Screening Adults Over 50 and Glaucoma Suspects

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Abstract: Glaucoma is a leading cause of preventable blindness, yet nearly half of those affected are unaware of their diagnosis. Individuals with glaucoma may present with "normal" or "lower" intraocular pressure (IOP) compared to typical glaucoma thresholds, due in large part to many of these individuals having thin corneas. Conversely, many with elevated IOP and thicker corneas may not necessarily have glaucoma. In this article, we review the importance of central corneal thickness (CCT) and corneal pachymetry devices in eye care. Additionally, we review the role of corneal thickness as a risk factor for glaucoma and glaucoma progression. PubMed and Web of Science databases were searched for articles and reviews on corneal pachymetry and its use in glaucoma, corneal biomechanics and refractive surgery, and glaucoma screening. The results of this review revealed that CCT is a risk factor for development of glaucoma, and in eyes suspected of glaucoma, corneal pachymetry can be performed by trained technicians to provide important information related to the risk of acquiring glaucoma and/or having other ocular diseases. Additionally, a lower CCT is associated with an increased risk of progression and faster rates of visual field loss in eyes with glaucoma. This review will provide evidence regarding the importance of performing corneal pachymetry on all persons over the age of 50 as part of a comprehensive eye examination to better identify those patients who have glaucoma or are glaucoma suspects.

Key Points:

- CCT has been shown to be a risk factor for the development of glaucoma in eyes suspected of glaucoma.
- CCT may act as a biomarker for tissues linked to glaucoma, including the lamina cribrosa and peripapillary sclera.
- A lower CCT is associated with an increased risk of progression and faster rates of visual field loss in eyes with glaucoma.
- By measuring age, CCT and IOP with the Laroche Glaucoma Calculator, there is a strong relationship for detecting persons at higher risk for glaucoma.
- Practitioners should consider measuring central corneal thickness in all patients over the age of 50, those at risk for glaucoma, as well as in those already diagnosed with the disease.

Keywords: glaucoma, corneal pachymetry, screening, corneal thickness

Introduction

Historically, the diagnosis of glaucoma has evolved significantly over time, moving from rudimentary observations to newer sophisticated technologies better capable of detecting higher risk patients. The historical progression of diagnosing glaucoma is marked by several key milestones.

Historical Background

Ancient civilizations, including the African Nile Valley and Greeks, noted symptoms like eye pain and vision changes, trauma and various remedies.[1] Similarly, early writing by Hippocrates and Galen described ocular conditions without

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specifically recognizing glaucoma.[1,2] By the medieval period, some physicians began to recognize the relationship between the appearance of the eye (such as changes in the sclera) and certain conditions, though glaucoma was not yet classified.[3] The development of the tonometer in the late 1800s marked a significant advancement. The first clinical tonometry measures began around this time, allowing practitioners to gauge intraocular pressure (IOP), a key indicator of glaucoma.[4] The invention of the ophthalmoscope in the 1850s allowed physicians to examine the interior structures of the eye, which enabled the observation of changes to the optic nerve characteristic in glaucoma.[5]

In the early 20th century physicians started to recognize that glaucomatous damage to the optic nerve was a critical factor in diagnosis and the examination of the optic disc became more prominent.[6] The introduction of visual field tests in the early 1900s allowed for the detection of peripheral vision loss associated with glaucoma. These tests helped clinicians identify functional impairments linked to the disease.[7] The late 20th century saw the development of automated tonometry devices, making it easier and more accurate to measure IOP. This was complemented by advancements in visual field-testing technologies. The use of gonioscopy to examine the anterior chamber angle became a critical part of glaucoma diagnosis, particularly in distinguishing between open-angle and closed-angle glaucoma.[8] Early uses of ultrasound pachymetry began in the 1950s and is used today to determine corneal thickness.[9] In the 21st Century, optical coherence tomography (OCT) has allowed for detailed imaging of the optic nerve and retinal nerve fiber layer, providing a non-invasive way to assess glaucomatous damage more accurately.[10] New technologies, including home tonometry devices and continuous monitoring systems, represent the latest advancements in glaucoma diagnosis, allowing for earlier detection and more personalized management.[11]

Corneal thickness is an important measurement that can assist in screening for glaucoma and identify patients at risk for progression.[12] This has become routinely used in patients with glaucoma; however, it has not been used routinely as part of a complete eye exam in normal patients. This article will make the case for the use of corneal pachymetry in all patients over the age of 50 and glaucoma suspects to help assist in identifying glaucoma patients earlier to reduce blindness from this insidious disease.

Glaucoma and Corneal Thickness

Glaucoma is the leading cause of irreversible blindness worldwide.[13] Characterized by optic nerve damage, it primarily affects peripheral vision, leading to optic neuropathy and vision loss. The progression of glaucoma is significantly dependent on the IOP.[14] While IOP is the most important modifiable risk factor for glaucoma, central corneal thickness (CCT) is a crucial factor in accurately interpreting IOP measurements. Corneal thickness heavily influences the biomechanics and structural properties of the cornea, thus CCT readings may have many clinical indications concerning eye health that should not be overlooked.[15] Based on the Goldmann applanation tonometry (GAT), the average CCT is approximately 530–540 µm.[16] With this in mind, abnormal CCT readings can be associated with the progression of glaucoma. For example, thinner CCT are strongly associated with the onset of primary open-angle glaucoma (POAG), independent of IOP levels.[12] In addition, variations in CCT can greatly affect IOP measurements and may lead to inaccurate readings. Patients with thicker corneas may have overestimated IOP readings, while patients with thinner corneas may have underestimated IOP readings, both of which can mask the patient's actual risk of developing glaucoma.[17] CCT measurements are an essential part of glaucoma evaluation, given its role in impacting accurate IOP measurements and acting as a biomarker for glaucoma risk.

Earlier Detection of Disease with Earlier CCT Measurement

Corneal pachymetry can be performed using ultrasounds or optically through a slit-lamp, however ultrasound pachymetry is more often used in clinical settings.[18] Corneal tomographers create a three-dimensional representation of the anterior segment and offer information about corneal thickness. One of the most utilized techniques for corneal tomography is Scheimpflug imaging, which involves a rotating Scheimpflug camera. Scheimpflug imaging produces cross-sectional images, which are then used to identify the anterior and posterior surfaces of the cornea.[19] Dedicated Anterior Segment-OCT devices are non-invasive and non-contact procedures. They rely on interferometry to detect minute differences in tissue depth and provide high resolution cross-sectional imaging of the cornea with both central and regional pachymetry.[20] Regardless of the specific type used, pachymetry may be utilized for disease examination or to measure corneal thickness before refractive surgery. It has also helped to prove the positive correlation between corneal thickness and intraocular pressure (IOP).[21]

Role of Pachymetry in Glaucoma Diagnosis

With the need for routine measurement of CCT for the management of patients with glaucoma, pachymetry can be essential. Pachymetry can have a significant effect on the management of patients with glaucoma or those suspected of having glaucoma, allowing physicians to perform less aggressive treatment of those with pseudo-ocular hypertension, modify target intraocular pressures, and detect elevated intraocular pressures in otherwise normal patients with thin corneas.[22] In a study evaluating the effectiveness of pachymetry in measuring corneal thickness when compared to Orbscan II (Bausch & Lomb, Orbtek Inc., Salt Lake City, UT) corneal topography, the standard deviation of measurements in Orbscan II was found to be much higher, showing less reliability when compared to ultrasonic pachymetry.[23]

Currently, there are several ways of performing corneal pachymetry including using ultrasound pachymetry (USP), non-contact tono/pachymetry, specular microscopy, biometry, Scheimpflug-based corneal topography, and optical coherence tomography (OCT). A study comparing these methods, using the mean difference and Bland-Altman analysis based on 95% limits of agreement.[24]

Glaucoma Screening: Laroche Glaucoma Calculator

Thin corneas are an important risk factor for glaucoma and, therefore, CCT assessment is highly important for glaucoma detection and evaluation. Glaucoma is described as a progressive loss of retinal ganglion cells with characteristic changes in the neuroretinal rim tissue of the optic nerve head, and visual field (VF) constriction.[25] Nearly half of the people with glaucoma in the United States do not know they have this disease, with an even higher percentage outside of the United States. Measuring corneal pachymetry in everyone over the age of 50 and glaucoma suspects will help identify patients with thin corneas who are at higher risk for glaucoma. Many patients with so-called "normal" pressures and glaucoma often go untreated because the thin nature of their cornea has not been identified. Additionally, there is also the risk that undetected glaucoma may lead to more vision loss. Therefore, early detection is key in the treatment of glaucoma, and corneal pachymetry is a critically important part of this.

According to the Ocular Hypertension Treatment Study (OHTS), a thinner CCT is a predisposing factor to the onset of primary open-angle glaucoma (POAG) in those with ocular hypertension.[12] The study showed that a patient with the thinnest CCT (≤555 µm) or less had three times the risk of developing glaucoma within 5 years when compared to a patient with the thickest CCT (>588 µm), thus supporting the importance of CCT as a risk factor of glaucoma. Additionally, patients with glaucomatous damage are more likely to have thinner CCT.

Measurements of CCT have been used to predict the risk of glaucoma alongside other risk factors, including age and intraocular pressure. The Laroche glaucoma risk calculator uses these three variables as a risk stratification tool to predict the risk of glaucoma and inform the course of follow-up care.[26] Preliminary findings evaluating the discriminatory power of this calculator in detecting glaucoma found that compared to IOP alone (Area Under the Curve (AUC) = 0.72, p = 0.04) or CCT alone (AUC = 0.53), the glaucoma risk calculator (AUC = 0.81) that included age, IOP and CCT was significantly better at discriminating glaucoma patients from controls.[26] This data supports previously published findings that address whether corneal thickness is a true independent risk factor for glaucoma. As suggested by Brandt et al, CCT may serve as a biomarker for structural and physical factors affecting the pathogenesis of glaucoma and can be calculated individually alongside IOP.[27] As such, an adjustment formula to correct IOP for CCT was not shown to be necessary. The Laroche glaucoma risk calculator similarly calculated IOP and CCT individually, without adjustment formula corrections.[26] Unlike prior glaucoma risk calculator tools, the Laroche calculator was designed as an adjunct to the complete ophthalmic examination and can be used by non-physician trained medical personnel. In this way, IOP and CCT can be obtained quickly and efficiently using handheld tonometer's and pachymeters, respectively, to calculate glaucoma risk. Using this calculator, those with thinner corneas were assigned a higher point value, as the risk of glaucoma increases with thinner corneas. In addition to the points added for age, IOP, and CCT, those with a higher total point value of 6 or greater had an increased risk of glaucoma using this tool. More recent findings evaluating the efficacy of this calculator have demonstrated 92% sensitivity and 90% specificity in detecting glaucoma.[28] The use of this calculator demonstrates that the effect of corneal thickness as a predictive factor for glaucoma is not entirely from its effect on IOP measurement but further confirms that CCT independently affects glaucoma risk. The mean age of glaucoma is about 52 and most often due to age-related enlargement of the lens.[29]

Effects of Central Corneal Thickness on Intraocular Pressure Readings

Corneal thickness has been shown to impact IOP measurement readings. Patients with thicker corneas may have a measured IOP that is higher than their true IOP. Conversely, patients with thinner corneas have a measured IOP that is lower than their true IOP.[12] These findings may have adverse effects, especially in patients with thinner corneas. This is because an actual IOP that is higher than the measured IOP may leave patients susceptible to undetected glaucoma, as the prevalence of open-angle glaucoma increases with higher IOP.[30] On the other hand, patients with thicker corneas may be misclassified as having ocular hypertension.[27] Corneal thickness can therefore skew the accuracy of IOP readings and can conceal eye complications. Pachymetry, however, allows physicians to efficiently measure CCT and provides a more accurate IOP reading.

Intraocular Pressure and Corneal Compensation

Findings from the OHTS recognized CCT as a statistically independent risk factor for glaucoma, as eyes with ocular hypertension that also had thinner corneas had a higher risk of becoming glaucomatous.[12] The measurement of CCT is not as encompassing as corneal hysteresis in its measurement of the biomechanical response of the cornea. Despite this, CCT still represents an independent risk factor for glaucoma progression.

Additional Medical Conditions Associated with Corneal Thickness

Central corneal thickness is an important measurement for the management of ocular diseases, such as ocular hypertension and glaucoma. The average central corneal thickness is between 540 and 550 µm, however various studies have found different results. The OHTS found an average corneal thickness of about 573 ± 39 µm. Many of these patients had higher pressure readings and did not require treatment for Glaucoma. Glaucoma patients will often have a corneal thickness measurement of 511 µm with lower intraocular pressure readings that will need more careful monitoring.[21] With this in mind, different ocular conditions can present with varying measurements of corneal thickness.

Increased corneal thickness has been associated with increased IOP, increased body mass index, chronic kidney disease, and increased corneal curvature radius.[31] Elevated corneal thickness is also associated with corneal edema, where there is an accumulation of extracellular fluid in epithelium and stroma, leading to decreased corneal transparency. Corneal disease is also associated with thinned corneas, where CCT is decreased. The etiology behind many of these corneal thinning is generally unknown; however, they may be attributed to connective tissue disease, contact lenses, Down's Syndrome, and eye rubbing amongst other causes.[32] Keratoconus can arise from a reduced CCT. Keratoconus is characterized by a thinned cornea that bulges outward into a cone shape. Patients may experience symptoms of reduced visual acuity, image distortion, and increased light sensitivity.[33] There is an increase in people with myopia worldwide. People with myopia have thinner corneas. Some of these people will not be able to have traditional surgeries, including Laser in situ keratomileusis (LASIK), due to this and may be at higher risk for complications.

Inter-Instrument Variation of CCT

Corneal pachymetry is a technique used to measure the thickness of the cornea, which is important for various ophthalmic assessments, particularly in glaucoma diagnosis and management.[34] However, like other measurements in medicine, these readings can be influenced by variations due to different instruments and the observers taking the measurements. Here, we discuss inter-instrument variations and intra-observer variations in corneal pachymetry measurements.

The accuracy of a DGH corneal pachymeter can vary depending on the study and the pachymeter being used. A comparison study found that the DGH 1000 pachymeter had good agreement with Sonogage devices when measuring central corneal thickness. However, a different study found that the Pach-Pen pachymeter was more accurate than the DGH 1000, with measurements within 3 to 65 µm of the actual corneal thickness.[35] The Pachmate 2 is a handheld pachymeter that uses DGH's measurement algorithm to provide accurate and reproducible measurements. It can be used to measure corneal thickness for a variety of clinical applications, including glaucoma screening, keratoconus treatment, and preoperative evaluation of laser correction procedures.

Intra-Observer Variations

Intra-observer variation refers to the variability in measurements taken by the same individual at different times. This variability can be influenced by several factors including positioning of the Probe/Instrument. Variations in how the instrument is positioned or aligned can lead to different measurements, especially in contact methods. Central corneal thickness measurements were comparable with the use of hand-held and desk-mounted ultrasound units in glaucoma patients with good intraobserver reproducibility.[36]

Intra-observer variability with handheld corneal pachymetry can be measured by comparing repeated measurements of central corneal thickness (CCT).

Coefficient of reproducibility of measurements between observers was 5.08%. Accutome PachPen hand-held ultrasound pachymeters give excellent intra-observer repeatability and inter-observer reproducibility by personnel of different training grades.[37]

In one study, the mean difference between repeated measurements was 0.9 µm, with an intraclass correlation coefficient of 0.9934. Another study noted that the handheld pachymeter produced slightly higher measurements of CCT than Artemis-2, possibly due to lack of centration, oblique incidence, or the effect of topical anesthetic.[38] Other factors that can affect the accuracy of handheld pachymetry measurements include inaccurate placement of the probe and placing the probe obliquely.[39]

On the other hand, other factors that can affect pachymetry readings include observer fatigue; an individual's attention and focus may vary impacting measurement consistency, particularly in long sessions. Challenges in measurement conditions can include poor patient cooperation, patient movements, and blinking during measurements can lead to discrepancies. The application of topical anesthetics may improve patient comfort and behavior during measurements. Clinicians' varying degrees of skill and experience can also affect the precision and accuracy with which the measurements are taken. Recognizing these types of variations is critical for effective clinical practice. Clinicians should consider potential variations when interpreting pachymetry results, particularly when making decisions about diagnosis and treatment. Protocols for measuring corneal thickness should be standardized to minimize inter-instrument and intra-observer variability and enhance the reliability of results. Regular calibration of instruments and ongoing training for clinicians can help reduce discrepancies and improve measurement accuracy.

Inter-instrument and intra-observer variations in corneal pachymetry measurements are important factors that can influence clinical outcomes. Understanding and minimizing these variations through standardized procedures, calibration, and training can enhance the reliability of corneal thickness assessments and contribute to better glaucoma management and overall patient care.

Influence of CCT in Refractive Surgery

Laser in situ keratomileusis (LASIK) is a surgical procedure done to correct visual refractive errors by reshaping the cornea. The target tissue in reshaping the cornea is the stroma. During LASIK surgery, a corneal flap is created and folded to expose the stroma and an excimer laser is focused onto the pupil to ablate the stroma.[40] Upon ablation completion, the flap then covers the stromal bed. This procedure can also be used to accurately determine the thickness and diameter of the corneal flap. LASIK surgery can allow the eye to properly refract light by flattening the corneal curvature, correcting myopia.[40] Central corneal thickness plays a vital role in LASIK surgery. Thinner corneas are contraindicated in LASIK. To successfully create the cornea flap, patients must have a certain amount of corneal thickness. A safe and effective stromal bed corneal thickness is at least 250 µm.[41] Since the cornea is thinned through the surgical procedure, an adequate thickness is required for the reshaping of the cornea. The cornea should be thick enough to support the corneal flap to avoid any further complications, such as keratoconus, a type of corneal ectasia characterized by worsened vision due to thinning and bulging of the cornea.[33]

Pachymetry can be utilized before LASIK surgery to ensure that the patient's cornea is thick enough for refractive surgery to be safely performed. Ultrasound Pachymetry, amongst other tests such as Optical coherence tomography, was found to be an effective tool in measuring CCT in pre- and post-operative LASIK procedures.[41] Pachymetry mapping can also be utilized to reveal abnormal corneal patterns, such as keratoconus and pellucid marginal degeneration.[42] Therefore, through pachymetry, corneal thickness can be measured to ensure that it is within the safe limits for LASIK surgery.

Biomechanics of the Cornea and Its Association with Glaucoma

The biomechanical properties of the cornea, particularly corneal hysteresis, provide insight on how the cornea functions in a healthy and diseased state. Hysteresis refers to the mechanical property of the cornea that reflects its ability to absorb and disperse light. The corneal tissue has complex viscous and elastic qualities that allow it to respond to the loading and unloading of an applied force.[43] Clinical instruments with applanation have been utilized to measure the biomechanics of the cornea as it deforms in response to an air puff.[44] Corneal hysteresis is quantified as the measurable difference as the cornea changes configurations, which despite being informative, is an expensive measurement. Therefore, corneal thickness should also be considered.

Results from the Ocular Hypertension Treatment Study[45] and Early Manifest Glaucoma Trial[46] have suggested an increased risk for development and progression of glaucoma in individuals with thin corneas. Eyes with primary open angle glaucoma have been shown to have lower corneal hysteresis in comparison to those with ocular hypertension, glaucoma suspects, and normal controls.[47,48] This was demonstrated in a study by Susanna et al, in which a 20% higher risk of developing visual field defects was associated with each 1 mmHg lowering of corneal hysteresis.[49] Thin corneas detected with corneal pachymetry can help detect those patients at higher risk for glaucoma.

More recent findings have shown that movement and thickening of the lamina cribrosa is related to corneal hysteresis. The study found that eyes with lower corneal hysteresis had less displacement of the lamina cribrosa, supporting the hypothesis that a lower hysteresis is related to scleral stiffening.[50] Without the ability to displace, the lamina cribrosa will have increased strain and lead to more glaucomatous damage to the optic nerve head.[43] As a more affordable option, measurement of corneal thickness can provide more insight into this.

Limitations of Corneal Hysteresis

As Corneal Hysteresis Is a Dynamic Measurement of the Eye, It Can Continue to Change Over Time. Contrastingly, Measurements Using CCT Remain Relatively Stable Uniquely the Laroche Glaucoma Calculator Accounts for Higher Risk Numbers With Age That Correlates With Dynamic Changes of Corneal Hysteresis Over Time.[51]

Conclusion

The diagnosis and progression of glaucoma, as well as its severity, has been associated with central corneal thickness. The relatively normal range of IOP observed in some glaucomatous eyes may be explained by thin corneas and an understanding of corneal biomechanics. It may also explain why some eyes progress faster than others. Thin corneas are a powerful risk factor for glaucoma. Just as we check intraocular pressures in all patients as a part of a complete eye examination, the central corneal thickness should be measured in all patients over 50, as well as glaucoma suspects in younger patients. When the three parameters of age, central corneal thickness and intraocular pressure are entered into the Laroche glaucoma calculator, you have a 92% sensitivity and 90% specificity towards identifying normal patients without glaucoma compared to glaucoma suspects and patients with glaucoma. This can help to identify patients earlier with "normal" intraocular pressures but thin corneas, who are unaware of their risk for glaucoma. Ophthalmologists and practitioners should consider measuring central corneal thickness in all patients over the age of 50, those at risk for glaucoma, as well as in those already diagnosed with the disease. This will help identify both glaucoma patients and glaucoma suspects earlier.

Disclosure

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