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The Relationship between central corneal thickness and intraocular pressure: A comparative study of normals and glaucoma subjects

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Summary

The purpose of the study is to determine whether central corneal thickness (CCT) is a better predictor than intraocular pressure (IOP) in early identification of those at higher risk of developing glaucoma. Sixtyfive subjects were categorized into normals, ocular hypertensives and glaucoma subjects based on clinical characteristics of ocular risk factors. The IOP was assessed with slit-lamp mounted Goldmann applanation tonometer. Prior to applanation tonometry, the central corneal thickness (CCT) of both eyes was assessed with Sonomed PacScan 300AP Biometric/ pachymeter. The difference in mean IOP between normals and glaucoma subjects was statistically significant (unpaired t-test; p<0.05). Similarly, there was a significant difference in mean CCT between normals and glaucoma subjects (p<0.05). The association between CCT and Age was not significant in normals but slightly significant in glaucoma subjects and the linear regression predicts a decrease of 7.0im in CCT for every 10 years. A strong association was found between CCT and IOP for ocular hypertensives with a prediction of increase of 0.70mmHg for every 10im corneal thickening. The association between CCT and IOP for glaucoma subjects was weak, with an indication of an increase of 0.35mmHg in intraocular pressure for every 10im corneal thinning. The central corneal thickness is a better predictor than intraocular pressure in identifying those at higher risk of developing primary open-angle glaucoma when combined with some ocular risk factors.

Keywords: Central corneal thickness, intraocular pressure, glaucoma, ultrasonic pachymetry, Goldmann applanation tonometry.

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Résumé

Pour déterminer si l'épaisseur de la cornee centrale est le meilleur predicteur que la pression intraoculaire dans l'identification précoce de ceux en risque de developer le glaucome. Soixante six sujets étaient catégorises in groupes normale, d'hypertension oculaire et de glaucome basé sur es caractéristiques cliniques des facteurs de risque oculaire. La pression intraoculaire était étudié a l'aide du sonomètre de Goldman ainsi que l'évaluation de l'épaisseur de la cornée centrale à l'aide du pachymétre ou Pacscan sonomed 300AP. La différence dans la moyenne de la pression intraoculaire entre les sujets normaux et de glaucome était statistiquement significative. Egalement il y avait une différence significative entre la moyenne de l'épaisseur de la cornee centrale chez les sujets normaux et de glaucome. L'association entre ECC et l'age n'était pas significative chez les sujets normaux et légèrement significatifs chez les sujets ayant le glaucome. La régression linéaire predict une réduction de 7.0im en ECC tous les dix ans. Il y avait une association significative entre ECC et PIO chez les groupes ayant l'hypertension oculaire avec une prédiction de croissance de 0.70mmHg pour tous les 10im d'épaississement de la cornée. L'association entre ECC et PIO chez le glaucome était faible avec une indication d'augmentation de 0.35mmHg en pression intraoculaire pour chaque 10im de cornée. En conclusion l'épaisseur de la cornée centrale est un meilleur predicteur que la pression intraoculaire pour identifier ceux a risque de développer le glaucome d'angle ouvert.

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by atrophy of ganglion cell axons from obstruction of axoplasmic flow at the level of the scleral laminal cribrosa. Structural changes to the optic nerve head and surrounding retinal nerve fibre layer have been shown to precede visual field defects in glaucoma [1]. The risk factors of glaucoma are elevated intraocular pressure (IOP), vertical elongation of optic nerve head, high cup-to-disc (C/ D) ratio, C/D asymmetry (between eyes), nerve fibre layer appearance (loss or defect of neuroretinal rim or notching) and thin cornea (lower values of central corneal thickness). If the disease is not diagnosed early, the irreversible damage to the optic head, retinal nerve fibre layer, ganglion cell axons, papillomacular bundle would result in visual impairment and blindness.

The intraocular pressure is the only modifiable risk factor of the glaucoma, and 'gold standard technology in its assessment is the Goldmann applanation tonometry [2,3]. The probe of the Goldmann applanation tonometer (GAT) is confined to the central 3.06mm diameter of the cornea where the maximum thickness is afforded. The early description of the applanation tonometer considered the possible influence of corneal thickness on the IOP as measured by the device. Studies have shown that intraocular pressure measuring using Goldmann applanation tonometer is affected by changes in the central corneal thickness (CCT) [3-11].

Initially, a normal CCT of 500ì m was assumed for the Goldmann applanation tonometry and no algorithm for correction of CCT variations has been established. Goldmann and Schmidt [12] noted that the measurement of IOP by Goldmann applanation tonometry assumes the CCT is 520ì m. Goldmann applanation tonometry is the most accurate at 520ì m, however the mean CCT for a normal corneal will vary among the population being tested. With the introduction of ultrasonic pachymetry, it became apparent that variations in corneal thickness are much more widespread than once believed. The ultrasound pachymetry is the most widely used technique for in vivo corneal thickness measurement [13]. Doughty and Zaman [14] reported mean corneal thickness of 5341 m for normal eyes with mean CCT of 530ì m for slit-lamp based pachymetry and 544ì m for ultrasonic pachymetry. Hoffman and colleagues [15] reported a range of central corneal thickness of 520-550ì m for normals.

Recent study [16] showed a mean CCT of 533 \pm 37.8ì m for blacks and 552 \pm 42.8ì m for whites and 95% confidence interval of 472-622ì m and 458-657ì m respectively. The risk factor that has the biggest impact on screening for glaucoma is central corneal thickness. Any measured intraocular pressure (mIOP) should be considered in the light of central corneal thickness and the combination of these factors (CCT and IOP) can help to identify those at a significantly higher risk of developing primary open-angle glaucoma (POAG) within the ocular hypertensive population [13]. In order to have a more comprehensive glaucoma screening program with good results in identifying those who are at higher

risk of POAG, measured intraocular pressure should be combined with C/D ratio and central corneal thickness. The changes in cup-to-disc ratio must have been observed overtime to ensure correlation with the disease. The relationship between measured intraocular pressure by applanation tonometry and central corneal thickness has been investigated by numerous studies [6,7,16,17].

A positive linear correlation between central corneal thickness and applanation tonometric estimates has been reported by many studies [18-20]. Significant variations in corneal thickness can play an important role in determining the true intraocular pressure. The measurement of CCT is useful for all ocular hypertensive patients to estimate their risk for progression to POAG. An improved ability to identify those at higher risk of developing the disease would lead to early and more effective management to ensure long-term preservation of vision. The aim of this study was to determine the variation of central corneal thickness with intraocular pressure in normals, ocular hypertensives and glaucoma subjects, as data on central corneal thickness with measured intraocular pressure in a predominantly black country like Nigeria are scanty to the best of our knowledge.

The study attempts to answer the following questions:

- (i) Is there any correlation between central corneal thickness and intraocular pressure in normals and glaucoma subjects?
- (ii) Can central corneal thickness values help in the early identification of those at higher risk of developing glaucoma?
- (iii) Is there a significant variation in central corneal thickness values in normals, ocular hypertensives and glaucoma subjects?

Materials and methods

A total of sixty-five (N=65) subjects consisting of males and females with M:F ratio of 35:30, between age range 22 to 62 years with mean age 46.0 ± 11.0 years were drawn from the patient population of the hospital within the period of study having consented to be part of the study. The subjects were carefully recruited with the inclusion criteria after detailed case history and eye examination. The criteria for inclusion in the study are: patients should not have active ocular diseases or maculopathy. They should neither be on antiglaucoma drugs nor contact lens wear. Those who were engaged on strenuous exercise, had history of ocular trauma or had undergone ocular surgeries were excluded from the study. Also excluded were subjects with corneal astigmatism of greater than 3.00D as measured with Autokeratometer because of the under-estimation of intraocular pressure in patients with astigmatism (with-the-rule astigmatism). The subjects were categorized into groups-normals, ocular hypertensives and glaucoma subjects based on the assessment of the vertical optic nerve head cupping, changes in visual field characteristics, Goldmann applanation tonometric reading, nerve fibre analysis and ultrasonic pachymetry. Each of these procedures were performed by different clinicians.

All data were collected between 9.00am and 12.00noon to guide against diurnal variation in central corneal thickness [21] and intraocular pressure [22] The CCT was measured before applanation tonometry and dilated funduscopy. Note that the applanation tonometric values could not be highlighted for glaucoma categorization as there were instances of normal tension with considerable field changes and lower central corneal thickness values (thin corneae) of which normal tension glaucoma (NTG) was diagnosed.

Instrumentation

The Topcon slit-lamp biomicroscope with a three-mirror goniolens was used for external examination of the ocular adnexa and assessing anterior chamber angle. A slitlamp mounted Goldmann applanation tonometer was used to measure the intraocular pressure (after instilling 0.1% tetracaine hydrochloride and staining with wetted fluorescein strip). The magnitude of corneal astigmatism was assessed with Shinippon Autorefractor 9with inbuilt Autokeratometer), while dilated fundus examination was performed with Keeler ophthalmoscope after 10 minutes of instilling Mydriacyl 1.0% (tropicamide). The visual fields of the subjects were plotted using Humphrey visual field analyzer.

Procedure

The central corneal thickness of both eyes was taken using Sonomed Pac Scan 300AP pachymeters (ultrasound pachymeters/Biometric) with the eves in the primary position of gaze. The pachymeters was calibrated according to manufacturer's instruction. and recalibration was reassessed. The patient was comfortably seated and after anaesthetizing the eve by instilling topical 0.1% tetracaine hydrochloride. patient was asked to blink before CCT was measured to avoid any error as a result of corneal dryness. The patient was instructed to look straight ahead while the pachymeters probe was placed on the centre of the cornea ensuring perpendicularity of the probe to the cornea and the average of ten readings taken as the measured CCT to ensure reliability as well as reproducibility of readings. After five to 10 minutes of CCT measurement, the patient's tonometric readings were taken (after the application of 0.1% tetracaine hydrochloride and staining with wetted fluorescein strip). Three successive readings were taken for each eye and the average was recorded as the mIOP. Note that only the measured parameters of the right eye were used to avoid undue duplication of results. The data were analyzed using Kolmogorov-Smirnov z test, unpaired student t-test, and pearson's correlation coefficient. SPSS version 10.0 for personal computer (from United States of America) was the software used for data analysis.

Results

Based on clinical diagnosis of the ocular status obtained from a combination of ocular risk factors, three groups of normals, ocular hypertensives and glaucoma subjects were identified from the study

Table 1:	Characterisitics of	occular risk	factors fo	or the study	groups.
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Ocular risk factors	Normals	Ocular hypertensives	Glaucoma
CCT IOP Vertical C/D ratio	538-565ì m 12.5-14.0mmHg 0.1-0.6	581-628ìm 20.8-25.2mmHg 0.2 - 0.6	487-530ìm 12.4-24.2mmHg 0.4 - 0.8
(Mean vertical C/D ratio) C/D ratio symmetry between eyes Visual field	0.36 + 0.12 C/D ratio symmetry between both eyes No visual field changes	0.33+0.19 C/D ratio symmtery between both eyes No visual field changes	0.62+0.13 C/D ratio asymmetry ranging from 0.1 to 0.4 field changes ranging from Defects in Superior and inferior arcuate arcades of nerve fibre layer, neuroretinal rim pallor, inferior notching of optic nerve head, constricted fields.

This table highlights the factors that were used for the placement of the subjects in the respective groups.

population (Table1). The distribution of central corneal thickness and intraocular pressure was normal by kolmogorov-Smirnov z test. The difference in mean IOP between normals and glaucoma subjects was statistically significant (unpaired t-test: t=3.0, p<0.05).

 Table 2: Mean, standard deviation and 95% confidence

 interval CCT of normals, Ocular hypertensives and glau

 comas

Ocular status	Mean ± SD	95% confidence interval	
	CCT (ì m)	Mean ± SEM	
Normals	551.6 ± 44.5	538.0 - 565.0	
Ocular hypertensives	604.5 ± 14.4	581.0 - 628.0	
Glaucoma subjects	508.4 ± 33.8	487.0 - 530.0	

The ocular hypertensives have thicker corneae (higher CCC values), while thinner corneae were associated with glaucoma.

Table 3:Mean, standard deviation, 95% confidenceinterval of IOP of normals, ocular hypertensives, andglaucomas

Ocular status	Mean \pm SD	95% confidence interval	
	IOP (mmHg)	Mean ± SEM	
Normals	13.3 ± 2.8	12.5 - 14.0	
Ocular hypertensives	23.0 ± 1.4	20.8 - 25.2	
Glaucoma subjects	18.3 ± 9.3	12.4 - 24.2	

Most of the mIOP was within normal and or slightly above the normal range of the intraocular pressure in the glaucoma subjects not significant to typify the group

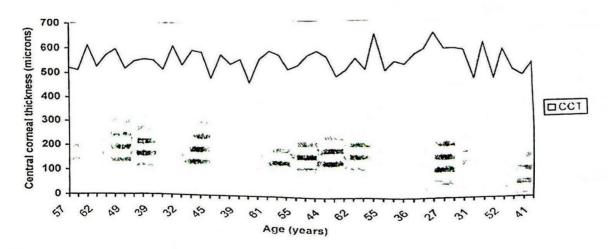
Similarly, the difference in mean CCT between normals and glaucoma subjects was significant (unpaired t-test: t=2.03, p<0.05). The mean CCT of glaucoma subjects (508.4 ± 33.8 im) was lower than that of normals (551.6 ± 44.5) m). However, the difference in mean CCT between males and females was not significant (p>0.05). Tables 2 and 3 show the mean, standard deviation and 95% confidence interval of the CCT and IOP of normals, ocular hypertensives and glaucoma subjects. Table 4 shows the mean, standard deviation and 95% confidence interval of CCT of males and females (normals). The association between CCT and age was not significant by pearson's correlation coefficient (P>0.05) for normals but there was a weak association between CCT and age in the glaucoma group and the regression equation (CCT=543-0.69Age) shows that for every 10 years, the central corneal thickness decreases by 7.0ì m which is clinically significant.

 Table 4:
 Mean, standard deviation, 95% confidence

 interval of CCT of normotensive males and females

Gender	Mean ± SD	95% confidence interval	
	CCT (i m)	Mean ± SEM	
Males(n=24)	556.4 ± 48.8	536.6 - 576.2	
Females(n=25)	543.2 ± 36.6	528.0 - 558.3	

The mean CCT of males was not different from that of females though the range for males was wider.



Interface Between Age and Central corneal thickness

Fig. 1: Interface of central corneal thickness (microns) and age (years in normal subjects

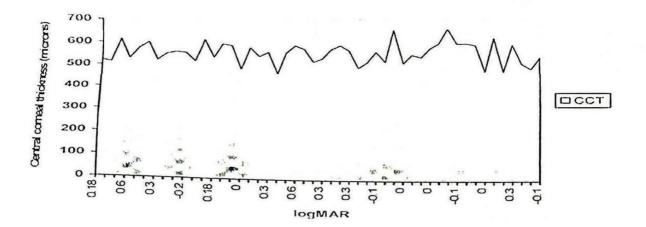


Fig. 2: Interface between central corneal thickness (im) and natural logarithm of minimum angle of resolution

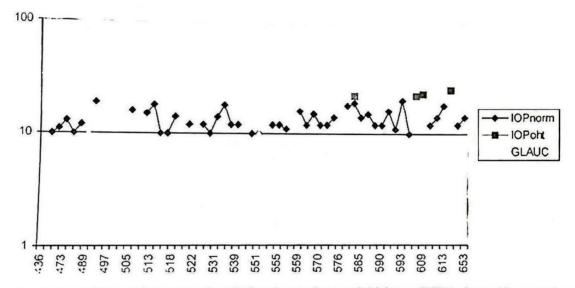


Fig. 3: Interface between intraocular pressue (mmHg) and central corneal thickness CCT (microns) in normals, ocular hypertensives and glaucoma subjects.

Similarly, there was a slight association between CCT and IOP of normals (r=0.2), but the linear regression (IOP=6.832 + 0.012CCT) was not significant. In the same vain no linearity could be predicted for glaucoma subjects as the linear regression (IOP=36.3-0.035CCT) was not significant, although there was an indication of an increase of 0.35mmHg in IOP for every corneal thinning of 10i m. For ocular hypertensives, there was a strong correlation between CCT and IOP (r=0.77, p<0.05) and the linear regression (IOP=-21.4 + 0.074CCT) was significant and as such there was a prediction of 0.70mmHg increase for every 10i m increase in central corneal thickness. Although there was a slight association between CCT and Visual acuity (r=0.25), the linear regression was not significant. Note: The visual acuity (VA) was the natural logarithm of the minimum angle of resolution (log MAR), where the MAR is the reciprocal of the Snellen's acuity. The mean C/D ratio for normals, ocular hypertensives and glaucoma subjects were 0.36 ± 0.12 , 0.33 ± 0.19 and $0.62 \pm$ 0.13 respectively. Fig.1 shows the interface between central corneal thickness and Age in normals while Fig. 2 shows the interface between central corneal thickness and log MAR for normals. Fig.3 shows the composite graph of IOP versus CCT for normals, ocular hypertensives and glaucoma subjects

Discussion

This study has shown that the central corneal thickness evaluation is a better predictor than intraocular pressure in identifying those at higher risk of developing glaucoma. One factor that was initially considered important by many clinicians involved in providing vision care services was the intraocular pressure. This was because of its significant influence on the diagnosis and follow-up of ocular hypertension (OHT) and glaucoma patients. Grisson and colleagues [13] described ocular hypertension as intraocular pressure greater than two standard deviations above the mean 21.0mmHg by population studies in the absence of optic nerve damage or visual field loss. However, OHT based on the findings of this hospitalbased study is a term used to describe IOP greater than one and half standard deviation above the mean 23.0mmHg and a mean CCT of 604.5i m. The measured CCT values consistently acted as distinct representations of the respective groups than the intraocular pressure.

Glaucoma causes progressive painless loss of vision which is irreversible due to damage to the ganglion cell axons (which form the optic nerve), nerve fibre layer and papillomacular bundle to varying degree depending on the stage of the disease. Early identification of those at higher risk of the disease followed with proper management would help in the preservation of vision. Glaucoma is the major cause of blindness among black Americans but only the fifth cause of blindness in persons of European descents or "white" Americans populations [23]. Other population- based or epidemiological studies also support glaucoma as a major cause of blindness in black population. More significantly, blacks were found to have a 4.7 times higher prevalence of POAG compared to Whites [24]. Glaucoma has been documented as one of the leading causes of blindness in Nigeria and sub-Sahara Africa [25-33]. Hoffmann et al [15], reported a range of 520 to 550i m CCT for normals, while Asensio and colleagues [34] in their study found a mean CCT of 547 ± 5.0 m. Shimmyo et al [17] showed that blacks relatively have thinner central corneal thickness than Whites, Asians or Hispanics with mean CCT of 535.51 m as against 551.61 m obtained in this study. The mean CCT of 533ì m obtained in the study of Semes et al [16], for blacks was not different from the mean CCT values from other studies [13,14] but different from that obtained in our study with mean CCT of $551.6 \pm$ 44.5ì m and 95% confidence interval of 538 - 565ìm in a predominantly black population. The difference in mean CCT between normals and glaucoma

subjects was statistically significant, the mean CCT of the glaucoma subjects being 43.21 m thinner than that of normals. With the mean IOP of 18.3 ± 9.3 mmHg for glaucoma subjects, the risk factor that could have the biggest impact on glaucoma screening is central corneal thickness as shown in this study.

Grisson et al [13] claimed that the risk of an African-American male developing POAG is as high as 50% if he is over 60 years old, C/D ratio greater than 0.5, IOP of more than 26.0mmHg and CCT of less than 555i m. If the C/D ratio is greater than 0.5, the IOP is within normal range of 10-21mmHg and CCT less than 555i m and age 50 years and above. normal tension glaucoma is suspected. From this study, the mean vertical C/D ratio for the OHT group was 0.33 ± 0.19 , 0.36 ± 0.12 for normals and $0.62 \pm$ 0.13 for glaucoma subjects. A 50-year-old Nigerian male with CCT less than 538ì m, C/D ratio of 0.6 .C/ D ratio asymmetry of 0.2 between both eyes, and intraocular pressure greater than or equal to 18.3mmHg in the absence of visual field defects may have more than 50% chance of developing primary open-angle glaucoma. Quigley and colleagues [35] have shown that up to 20% of the optic nerve is lost in glaucoma before automated perimetry can detect a visual field defect. Central corneal thickness was not affected by gender (unpaired t-test: P>0.05). Mean CCT of 556.4 ± 48.8 i m for males and 543.2± 36.6ì m for females and 95% confidence interval of 536.6 - 576.2i m and 528 - 558.3i m respectively. This was not consistent with the findings of Lleo et al [18] who reported a significant difference between the CCT of males and females $(542.34 \pm 43.84i \text{ m})$ and females $(551.34 \pm 40.58i \text{ m})$ with 95% confidence interval of 536.85 - 547.83 and 546.32 -556.37ì m respectively.

There was no correlation between CCT and Age (p>0.05) in normals and this was consistent with the claims of Lleo and colleagues. However, there was a weak association between CCT and age in the glaucoma group and the regression line showed that for every 10 years, the cornea gets thinner by 7.0i m. The association between CCT and VA was weak but the linear regression was not significant. Patients with early to moderate glaucoma will not typically exhibit reduction in visual acuity attributable to optic nerve head and visual field changes. The retention of macular function, as measured by Snellen's acuity chart, until very late in the glaucomatous disease process is the reason many of such patients do not seek care because of poor vision.

An increase of 0.12mmHg for normals and 0.70mmHg for ocular hypertensive subjects was

predicted for every 10i m increase in central corneal thickness while 0.35mmHg increase in intraocular pressure for every 10im decrease in CCT for glaucoma subjects which makes the inclusion of ultrasonic pachymetry an important procedure in the accurate identification of those at higher risk of developing primary open-angle glaucoma as lower values of CCT (thinner corneae) are indicative of the disease. Previous studies suggested a range of error for Goldmann applanation tonometer between 0.11 and 0.71mmHg for every 10i m of deviation from a normal 520i m. Herndon et al [39] in their study showed a modification to Doughty and Zaman [40] correction table of IOP for deviation from the mean CCT. They theorized that the true IOP is measured when the mean CCT is 545.5im, and a correction factor of 0.5mmHg decrease in IOP for every 10i m increase in CCT was proposed. Whitacre and Stein [4], however posited that it was not necessary to recalculate IOP based on regression formula of applanatory IOP versus CCT as there may be other sources of error for IOP differences. They claimed that factors such as corneal rigidity and hydration are likely to affect IOP readings. The increased corneal rigidity due to increased CCT results in more force being applied to applanate the cornea. This additional force is registered by the instrument as an increase in IOP. Technically, this explains the mechanism of ocular hypertension as typified by higher values of CCT and IOP. Studies [3,16] have revealed that patients with ocular hypertension have thicker cornea than normals and those with normal tension glaucoma have thinner corneae than normals as determined by ultrasonic pachymetry. This is consistent with measurements obtained in this study (551.6 ± 44.5) m for normals, 604.5 ± 14.4 m for OHT and $508.4 \pm 33.8i$ m for glaucoma subjects). Recently, ultrasonic pachymetry was recommended as an addition to the armamentarium of eye care practitioners in Nigeria as it would enhance the chances of identifying early those at higher risk of developing glaucoma [41].

In conclusion, this study although hospitalbased has shown that the central corneal thickness assessment is a better predictor than intraocular pressure in identifying those at higher risk (especially when combined with C/D ratio, C/D ratio asymmetry) among people with seemingly healthy eyes who are about 50 years old. It is now clear that ultrasonic pachymetry is important in glaucoma screening in a predominantly African population.

We want to therefore recommend that broad-based epidemiological study of Nigerians in

different geographical zones (so as to have larger sample size) be carried out to ascertain the variation of intraocular pressure with central corneal thickness combined with C/D ratio, C/D ratio asymmetry, in correctly identifying and classifying those at higher risk of the disease in our country which is the most populous in Africa.

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