Central corneal thickness and its relationship with IOP, visual fields and optic disc parameters among glaucoma patients attending the Eye Hospital at University Teaching Hospitals in Lusaka, Zambia

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ABSTRACT

Background: Glaucoma is a heterogeneous group of optic neuropathies characterized by an acquired loss of retinal ganglion cells, optic nerve atrophy and Visual Field Defects (VFD). Raised Intraocular Pressure (IOP) is the only causal risk factor for glaucoma that can be therapeutically and surgically manipulated to change the course of the disease process. Though Goldman Applanation Tonometry (GAT) is the "gold standard" for IOP measurement, readings of IOP with GAT are believed to be influenced by Central Corneal Thickness (CCT). The study evaluated the correlation of CCT and IOP with VFD parameters like Mean Deviation (MD), Pattern Standard Deviation (PSD) and Cup-to-Disc Ratio (CDR) in Primary Open Angle Glaucoma (POAG) patients.
Objective: To determine the relationship of central corneal thickness, intraocular pressure, visual fields and optic disc parameters in Zambian primary open angle glaucoma patients.
Methods: A cross-sectional study was conducted in 2014 from January to September and all glaucoma patients visiting the University Teaching Hospitals – Eye Hospital during the study period were included if they consented to it and met the inclusion criteria. A total of 166 randomly selected newly diagnosed glaucoma patients aged 18 years and above were recruited. The CCT was measured using Kacon Ophthalmic Ultrasound system and IOP was measured by GAT. Analyses were carried out considering the level of significance at 5%.
Results: One hundred and sixty-six newly diagnosed glaucoma patients aged 18 to 88 years were included into the study. There were 85 (51.2%) males and 81 (48.8%) females with a mean age being 51.31 years. The mean IOP was 23.60 (±10.40) mmHg. The mean CCT was 531.9 (±40.59). All the participants had primary open angle glaucoma POAG. Thin CCT was significantly correlated with vertical CDR (r= - 0.023, and 0.011). Thin CCT was also significantly associated with worsened MD of visual field (r= - 0.033 and p=0.023) and PSD (r= - 0.027 and p=0.012).
Conclusions: The mean CCT of Zambian POAG patients is thinner as compared to other races. CCT was positively correlated with IOP. Patients who had thicker CCT were more likely to have low IOP compared to patients who had thinner CCT. In the POAG patients thinner CCT was associated with greater cup disc ratio and Visual Field (VF) damages than those with a thicker CCT.

Key words: Central Corneal Thickness (CCT), Cup Disc Ratio (CDR), Primary Open Angle Glaucoma (POAG), Visual Field (VF), Intraocular Pressure (IOP).

INTRODUCTION

Glaucoma is the second leading cause of global blindness and results in irreversible visual impairment[1] and the third leading cause of blindness in Zambia[2]. Primary open angle glaucoma is the most common type of glaucoma in Zambia with a prevalence of 19.0%[3]. Globally, it is predicted that by the year 2020, the number of people with open angle glaucoma and angle closure glaucoma in Africa would be over 10 million and the continent will have the highest ratio of glaucoma to adult population[1].

As IOP is the only known risk factor that can be pharmacologically manipulated in the treatment of glaucoma[3,4], accurate measurements of IOP are essential in the screening, diagnosis and management of glaucoma[5,6]. Intraocular pressure is known to be influenced by CCT measurements recorded with applanation tonometres[7,8]. Several studies[9-11] have reported that IOP is overestimated in corneas with the higher mean CCT measurement and underestimated in corneas with lower mean CCT reading. Goldmann Applanation Tonometry (GAT), the clinical gold standard for IOP measurement[12], is calibrated on a theoretical assumption of a 520 µm CCT measurement [7,13]. Thus, any variation in CCT will alter the balance between the corneal resistance to indentation and the surface tension of the tear film[14]. In an early study, Ehlers *et al*[15,16] concluded that any deviation of 70 µm on either side of 520 µm would alter the IOP by 5 mmHg. It was further noted that IOP may be incorrectly interpreted by as much as 7 mmHg for every 100 µm deviation in CCT[16]. More recently, Eballe *et al*[17] suggested that IOP would change by 2.8 mmHg per 100 µm change in mean CCT. Despite several researchers acknowledging the influence of CCT on IOP measurements, there is little agreement as to how the measured IOP should be adjusted to account for the CCT measurement[18]. This has resulted in several correction algorithms being posited[5,7] but none have been widely used or accepted[19,20].

Previous studies have highlighted the role of CCT as an independent risk factor for glaucoma[21,22]. Kaushik *et al*[23] suggested that thinner CCT measurements are related to greater susceptibility for glaucomatous changes. As a result, assessment of CCT has become an important part of an ocular examination since it provides information about the risk and clinical characterisation of the various glaucoma disorders[21].

The literature shows that considerable CCT data have been collected in several American, Asian and European populations[3,11]. Studies conducted in developed countries have shown that people of African descent had increased risk of developing glaucoma, and POAG is significantly more common, develops earlier, and is more severe in blacks than whites[21]. In contrast, only a few studies have investigated CCT in African populations living within the African continent. Considering the consequences of glaucoma and its prevalence in the African continent, it is important to understand the distribution of CCT measurements in African sub-populations.

The Ocular Hypertension Study (OHTS) significantly highlighted the importance of the measurement of CCT in overall diagnosis of glaucoma[21]. Other studies have highlighted the correlation of CCT with other diagnostic parameters of glaucoma [24]. The glaucomatous damage is assessed by detection of VFD, which shows the glaucomatous damage in functional terms. Humphrey Visual Field (HVF) is an automated perimetry widely used to detect VFD and monitor glaucoma progression [25]. The indices like Mean Deviation (MD) and Pattern Standard Deviation (PSD) show the damage of glaucoma in relation to normal population, and despite their limitations, are widely used in grading and staging of glaucoma[26]. Cup-to-Disc Ratio (CDR) is the clinical evaluation of optic disc using slit lamp microscope and fundus viewing lens. It indicates the diameter of the cup expressed as a fraction of the diameter of the disc and is an important clinical finding in glaucoma suspects and patients[27].

Information on CCT data on how it affects native Zambian glaucoma patients is lacking. The study endeavoured to look at the role of CCT and IOP in influencing the glaucoma disease by examining the relationship of CCT and IOP with VF and CDR with the aim of improving the management of glaucoma. This would also probably serve as a catalyst for ophthalmologists and other eye health care workers in Zambia and the region in mainstreaming the clinical decision making in glaucoma management in relation to CCT and IOP.

MATERIALS AND METHODS

Setting: The study was conducted at the University Teaching Hospitals Eye Hospital in 2014 from January to September.

Design and sampling: This was a cross-sectional hospital-based study among the 166 Zambian glaucoma patients. Newly diagnosed glaucoma patients who visited the Eye Hospital during the study period were included in the study as long as they were aged 18 years and above and consented to participation. Both eyes of each patient were examined. The diagnosis and classification of glaucoma patients were done based on IOP value, gonioscopy, optic disc evaluation and VF testing. A structured questionnaire was used to collect data from volunteering glaucoma patients with normal anterior segment. Patients not willing to participate, and those with major corneal pathology, previous intraocular and or corneal surgery were excluded from the study.

Central corneal thickness and intraocular pressure measurements: Five consecutive ultrasound pachymetry (using Kacon Ophthalmic Ultrasound System) measurements of CCT were obtained from both eyes and a mean value was then computed and recorded in micrometers (µm). The two IOP measurements were taken 15 minutes apart to rule out any tonometric effect on the pressure. The tonometer dial was set between 1 and 2 graduation marks of the prism and care was taken to avoid inaccurate readings from inappropriate fluorescein pattern resulting from excessive or insufficient fluorescein, and pressure on

the globe by the examiner or patient squeezing the eyelids. All measurements were performed under topical anaesthesia (amethocaine hydrochloride 2%). Then, two corresponding GAT measurements were obtained with the use of fluorescein staining and an average value was recorded in mmHg. The tonometer tip and the pachymeter probe tip were cleaned with dry cotton followed by swabbing the tips thoroughly with methylated spirit prep pad and allowing it to dry for 5 minutes to reduce the risk of cross-infection.

Visual field evaluation: Global indices (MD, PSD) of the VF were measured by the Humphrey field analyser (Humphrey-Zeiss, Munich, German) using the full threshold 24–2 programme. Reliable Humphrey automated perimetry was defined by having fewer than two of the following characteristics: fixation losses greater than 20%, false positive responses greater than 33%, or false negative responses greater than 33%. Glaucomatous VF loss was defined as a reliable abnormal VF with a pattern standard deviation outside 95% normal limit, or a glaucoma hemifield test outside 99% normal limit, or three or more adjacent points with P <5% on the pattern deviation probability plot of which one must have P <1% [28].

Data analysis: Data was evaluated and analyzed using Statistical Package for Social Sciences (SPSS) version 24. Mean and standard deviation was reported for continuous variables (Age, CCT, IOP, MD, PSD, CDR) while frequency and percentage for nominal/ordinal data. Shapiro Wilk's test was used to check normality of data. Post normality testing, Pearson correlation coefficient was calculated to evaluate relationship between CCT and IOP and VF parameters (MD, PSD) including CDR and thereafter correlation and regression analyses were performed. P-value of <0.05 for all the analyses was taken to be statistically significant for all the tests employed.

Ethical considerations: The University of Zambia Biomedical Research Ethics Committee (UNZABREC) approved the study (reference number 013-08-12) and was carried out in compliance with the Helsinki Declaration (2006). Further approval was obtained from Ministry of Health of Zambia through the UTH. Informed consent was obtained from each study participant and confidentiality was observed.

RESULTS

Participation and distribution: The mean age of the 166 participants was 51.31 years (SD ± 17.99 years). Among the study participants, 85 (51.2%) were males and 81 (48.8%) were females (Table 1). There was no statistical difference between the two sexes (p=0.919).

Table 1: Socio-demographic characteristics of the study participants (n = 166)

Variable	No.	(%)	Mean CCT (µm)	Mean IOP (mmHg)
Gender				
Male	85	51.2	530.47	23.35
Female	81	48.8	533.96	23.75
Age (years)				
<40	50	30.1	548.76	22.50
40-44	14	8.4	531.79	24.50
45-49	9	5.4	529.50	23.83
50-54	16	9.6	523.60	22.32
55-59	12	7.2	536.04	22.09
60-64	21	12.7	527.88	24.29
≥65	44	26.5	517.16	24.84
Ethnicity				
Tonga	22	13.3	515.34	23.21
Nyanja	36	21.7	535.64	22.99
Lozi	7	4.2	542.29	22.15
Kaonde	6	3.6	520.75	26.50
Luvale	8	4.8	535.63	26.13
Lunda	5	3	516.00	30.30
Bemba	77	46.4	535.60	22.79
Other	5	3	530.20	28.10
Total	166	100		

All the 166 (100%) patients had POAG who were all newly diagnosed. The mean duration of glaucoma disease was 41.87 months (SD ± 43.55 months). Thirty-nine (23.5%) of the patients had trabeculectomy done after being recruited in the study and the rest 127 (76.5%) did not undergo any surgical intervention. One hundred and twenty (78.4%) of the patients were commenced on timolol, 12 (7.8%) on timolol and xalatan and 21 (13.7%) of them were not on any medical treatment. Regarding other health problems 16 (9.6%) of the study subjects were diabetic, nine (5.9%) were diabetic and hypertensive while the rest did not have any other known medical illness.

Intraocular pressure and central corneal thickness: In this study it was found that the mean CCT and IOP among Zambian glaucoma patients were 532.20 µm and 23.55 mmHg respectively. The distribution of CCT observed in the study subjects resembled a Gaussian curve as shown in Figure 1.

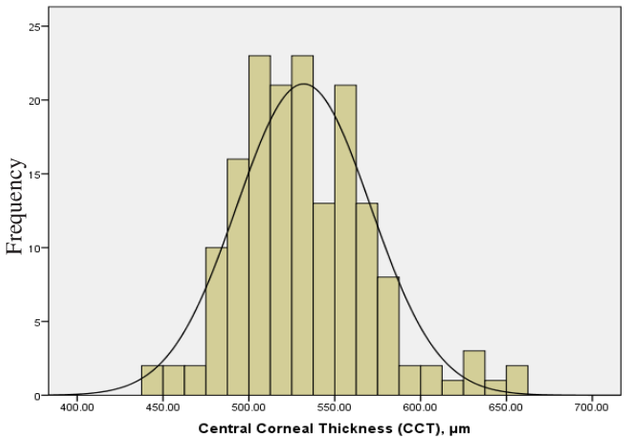

Figure 1: Distribution of CCT (µm) in the study participants

The mean IOP in males was 23.35 mmHg (SD±6.68 mmHg). In females it was 23.75 mmHg (SD±6.91 mmHg), and there was no statistically significant difference in mean IOPs between the males and females (p=0.930, and p = 0.593, 2-tailed, Independent Student T-test).

The mean CCT in females was 533.96 µm (SD±46.60 µm), which was slightly higher than the mean CCT in males where it was 530.47 µm (SD±34.05 µm) but this difference in mean CCTs was not statistically significant (p=0.563, 2-tailed, Independent Student T-test). The mean CCT was higher in the age group below 40 years of age (548.76±45.46 µm) and lower in the age group aged 65 years and above (517.16±37.86 µm) as shown in Table 1. This change in the mean CCTs was statistically significant (p=0.016, One-Way ANOVA).

Correlational analysis: There was a statistically significant decline in CCT with increase age (r=0.050, p=0.001); (Figure 2).

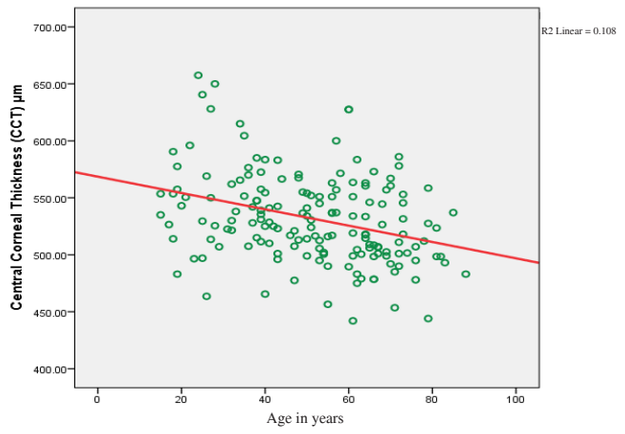

Figure 2: Relation between CCT (µm) and the age (in years) in the study participants

This study revealed a statistically significant linear relationship between CCT and IOP as per the linear regression analysis (r=0.014, p=0.010). Furthermore, in a Bivariate correlation analysis, it was found that the CCT was correlated linearly with IOP values (ρ =0.175, p<0.05) as shown in Figure 3.

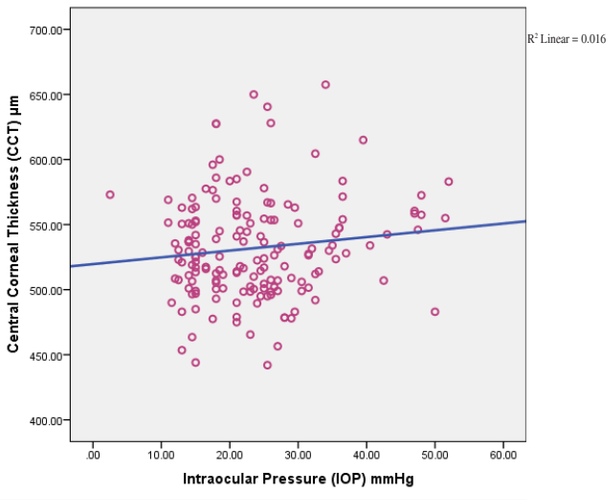

Figure 3: Relation between CCT (µm) and IOP (mmHg) in the study participants.

Ethnicity (p = 0.490) and duration of glaucoma (p = 0.666) showed no statistically significant relationship with CCT. Similarly, there was no statistically significant relationship between IOP and age, sex, and ethnicity within these study participants (p > 0.05). However, duration of glaucoma showed statistically significant relationship with IOP (p = 0.023). There was significant correlation of CCT with MD, PSD and CDR (r=-0.033, p=0.023; r=-0.027, p=0.012; r=-0.023, p=0.011 respectively), by multiple regression analysis. Correlation of CCT with MD, PSD and CDR is given in Table 2.

Table 2: Correlation of CCT with various parameters (n=166)

Parameter	Univariate regression analysis		Multivariate regression analysis	
	Pearson correlation co-efficient	p-value	Pearson correlation co-efficient	p-value
MD	-0.501	<0.001	-0.033	0.023
PSD	-0.533	<0.001	-0.027	0.012
CDR	-0.422	<0.001	-0.023	0.011

There was equally a significant correlation of IOP with MD, PSD and CDR (r=-0.201, p=0.010; r=-0.171, p=0.007; r=-0.144, p=0.030 respectively) (Table 3).

Table 3: Correlation of IOP with various parameters (n=166)

Parameter	Univariate regression analysis		Multivariate regression analysis	
	Pearson correlation co-efficient	p-value	Pearson correlation co-efficient	p-value
MD	-0.405	<0.001	-0.201	0.010
PSD	-0.520	<0.001	-0.171	0.007
CDR	-0.534	<0.001	-0.144	0.030

DISCUSSION

In this study it was found that the mean CCT and IOP among Zambian glaucoma patients were 532.20 µm and 23.55 mmHg respectively. This study also showed a statistically significant association between CCT and IOP.

Though the mean CCT of this study is significantly lower than the reported mean CCT of whites, it agrees with studies done among Africans and African-Americans [4,21,24-26] which equally reported thinner mean CCT. In most of the studies performed in Nigeria the mean CCT found was higher than the Zambian CCT while those found in Cameroon, Sudan and Ghana were comparable and those from Ethiopia and South Africa were lower than the Zambian CCT[17-19]. Studies that directly compared Caucasians and African Americans found a CCT of 555.7 µm in blacks compared to 573 µm in whites[21]. This finding is what was reported in other studies conducted in other parts of Africa[17,18].

According to a meta-analysis which included 300 studies conducted over a period of 31 years, Doughty and Zaman[29] reported an expected mean CCT measurement of 535 µm. This study reported 531.96 µm which was very close to the meta-analysis figure. However, when an ultrasound device is used, the expected mean CCT is higher averaging 544 µm[29]. When compared to the mean CCT measurements reported in African studies included in this review, only studies involving the Nigerian participants[20] are comparable to the suggested normal value (544 µm). All studies involving the other African sub-populations reported considerably lower mean CCT measurements[17-19]. This includes this study which reported 531.96 µm. However, this study and others done on the continent have shown that overall, there is a broad distribution (range: 519.00 µm – 550.00 µm) of mean CCT measurements in the various African sub-populations. The highest and lowest CCT measurements were reported in the Nigerian samples[30] (547.00 – 550.00 µm) and the Ethiopian and South African samples[4] (519 µm), respectively. This difference in mean CCT of 31 µm would be significant in terms of influencing IOP.

There was difference between the lowest and the highest CCTs found in the Zambian study population compared to studies conducted elsewhere in Africa all ranging from 31 µm to 34 µm. However, the study conducted on Caucasians in USA show a difference of 40 µm[21]. The younger patients (below 40 years) had the thicker corneas compared to the older (more than 65 years). However, there was no statistical difference between the two age groups. There was no statistical difference in mean CCT between the male and female participants. This was similar with what was reported in other studies. This study also showed a statistically significant association between CCT and IOP ($p < 0.003$), (Figure 3).

The mean CCT in Caucasians[31] and Asians (predominantly Chinese)[31], when using ultrasound pachymetry, ranges between 553 µm and 563 µm, and 566 µm and 570 µm, respectively[31]. This is therefore suggestive of the fact that, on average, the Zambian POAG patients have thinner mean CCT measurements (532.20 µm) than Caucasians and Asians and like the average CCT reported in African-Americans.

Numerous studies have elaborated the positive relation of CCT and measured IOP, and the quantitative relation between them in both adults and adolescents' population has also been revealed in many reports[7,19,32]. This study demonstrated significant correlations between the CCT and IOP values. Linear regression analysis revealed a positive correlation between CCT and IOP ($r = 0.0322$, $P < 0.003$). It is worth noting that r of 0.0322 demonstrates a moderate to strong positive relationship between CCT and IOP and this was confirmed with the statistical significance of $p < 0.003$.

Literature has highlighted CCT's impact on glaucoma related factors with controversies. Some literature shows that thin cornea is not associated with POAG or Primary Angle Closure Glaucoma (PACG)[32]. Other studies revealed population with thin CCT to be at increased risk of glaucoma development, and thicker corneas having less glaucoma[33]. This study established that there was a significant association between CCT and glaucoma disease progression with

the participants having thinner corneas presenting with severe disease as demonstrated by significant MD, PSD and CDR. This confirms the suggestion by Kaushik *et al*[24] that thinner CCT measurements are related to greater susceptibility for glaucomatous changes. CCT should therefore be an important part of an ocular examination since it provides information about the risk and clinical characterisation of the various glaucoma disorders[21].

However, some studies found out that patients with ocular hypertension had thicker corneas, and those with normal tension glaucoma had thin corneas[34]. Nevertheless, the widely acceptable results are from multicentre OHTS which revealed that the risk for development of glaucoma is greater in eyes with low CCT and lower in eyes with higher CCT[35]. This is probably attributed to under- and over-estimation of IOP due to variations in CCT.

MD and PSD give the estimation of VF defects, and are widely used to interpret, classify and document progression in glaucoma patients. This study found negative and significant correlation between CCT and VF parameters like MD and PSD. Studies utilizing multivariate regression models have found negative and significant relation between CCT and VF parameters like MD and PSD[37]. In another study to find correlation between CCT and severity of glaucoma using Advanced Glaucoma Intervention Study VF scoring criteria, it was found that score was significantly higher in the thinner CCT eyes, as compared to the thicker CCT eyes. This confirmed CCT as an independent risk factor for glaucomatous VF defects[37]. This study seems to agree with these findings by Mansouri *et al*[38] and Sullivan-Mee *et al*[39]. Other studies also highlighted significant negative correlation between CCT and VF parameters[38,39]. Whether CCT is an independent factor for glaucomatous damage or progression remains controversial.

CDR estimation remains an important clinical finding in glaucoma patients. OHTS shows increased risk of glaucomatous damage in patients having high CDR[36]. We found negative and statistically significant correlation between CCT and CDR, demonstrating thicker corneas to be having less CDR. This is consistent with findings by Kim *et al*[28]. Who found negative and significant correlation between CCT and CDR, though after multiple regression analysis the correlation appeared to be not statistically significant. Wangsupadilok *et al*[41] also found negative and significant relation between CCT and CDR[42]. In one study, a significant negative correlation was detected between CDR and CCT ($r = 0.102$, $P < 0.001$). However, there are studies showing no correlation between CCT and vertical CDR[43]. One study found significant correlation between CCT and CDR in one eye, and not significant relation in another eye[18]. Wu and co-workers[43] found negative correlation between these two variables, which was not statistically significant. Thus, it is implied from our study and literature that thinner corneas have high CDR, and vice-versa.

The IOP level correlates with topographic changes in the optic disc in eyes of patients suspected of having high-tension glaucoma[43]. The findings of this study agree with this postulation by Tanito *et al*[45], in the sense that IOP was found to have a significant association with severe disease manifestation. This effect IOP was noted to affect disease severity in all age groups. From this study it can be postulated that IOP as an important part of an ocular examination must be done in all adult patients for quick and early diagnosis of glaucoma. The same study has suggested that IOP of between 18 and 21 mmHg, and <18 mmHg is a safe target level in the treatment of patients suspected of having high-tension glaucoma to delay topographic optic disc changes[44]. This study agrees with this suggestion and further wishes to recommend that IOP of between 10 mmHg and 15 mmHg would even be a better target as determined in the study.

CONCLUSIONS

The findings in this study agree with previous reports that there are racial differences in CCT values. The mean CCT of Black Zambian participants were lower than those of Caucasians and other races. Also, in general, findings agree with previous studies that there is an association between CCT and IOP. Patients who had higher mean CCT were more likely to have high IOP compared to patients who had thinner CCT although this was not statistically significant. Thinner CCT and IOP were associated with greater cup disc ratio and Visual Field (VF) damages than those with a thicker CCT.

Competing interests: The authors declare that there is no competing interest.

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