· Meta analysis ·

The relationship between central corneal thickness and intraocular pressure in healthy and glaucomatous eyes, a systematic review and Meta-analysis

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青光眼患者角膜中央厚度与眼压关系的 Meta 分析

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摘要

目的:系统回顾正常人群和青光眼患者中央角膜厚度与眼压的研究资料,探讨两者之间的关联与机制。

方法:在 MEDLINE 数据库和 Science Direct 数据库搜索有关角膜中央厚度与眼压关系的研究资料。另外在南方医科大学外文科部搜索 2004/2006"眼科年刊"期刊。搜索关键词包括:角膜中央厚度、眼压、青光眼、高眼压症、剥脱青光眼、压平眼压计、厚度测量法、原发性开角青光眼、Goldmann 压平眼压计。应用以下排除标准:1)非英语文献研究;2)在 2005 年以前的研究;3)案例性研究和案例点评性研究;4)与治疗方案或外科手术技术有关的研究;5)将青光眼与其他疾病,如糖尿病、高血压、心血管疾病来比,作为辅助变量;6)儿童作为研究对象的研究;7)动物作为研究对象的研究。

结果:搜索产生了 13 项研究,包括 12 个观察性研究和 1 个病例对照研究。与对照组相比,青光眼患者眼压水平明显升高(SMD:0.50,95% *CI*:0.30~0.70,$Z=4.88$,$P<0.001$);青光眼组患者角膜中央厚度水平有明显降低(SMD:-0.14,95% *CI*:-0.23~-0.05,$Z=3.14$,$P=0.002$)。Meta-回归分析结果显示年龄跟两个组之间观察到的 CCT 差异有统计学意义($P=0.025$)。

结论:与正常眼组相比,青光眼组患者表现为角膜中央厚度变薄和眼压增高。

关键词:角膜中央厚度;眼压;Goldmann 压平眼压计

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Abstract

• AIM: To evaluate the relationship between central corneal thickness and intraocular pressure in healthy and glaucomatous eyes of adults. To make up to date summary of the results of studies done on the association of central corneal thickness measurements and intraocular pressure measurements in Glaucoma patients and in healthy subject.

• METHODS: To identify relevant studies a search of MEDLINE and Science Direct databases for studies investigating the relationship between central corneal thickness (CCT) and intraocular pressure (IOP) was conducted. The Search period was from Sep. 10th to Oct. 28th of 2015. Search key words included: central corneal thickness, intraocular pressure, glaucoma, ocular hypertension, exfoliative glaucoma, applanation tonometry, pachymetry, primary open angle glaucoma, Goldmann applanation tonometry. In addition, a manual search of "*The Year Book of Ophthalmology*" Journals 2004 to 2006 Issues in the Southern Medical University Library English language section was done. The following exclusion criteria applied: 1) non-English media studies; 2) studies done before 2005; 3) case series and case reviews; 4) studies involving treatment protocols or surgical techniques; 5) studies comparing glaucomatous eyes with other conditions such as diabetes, hypertension or cardiovascular disease as secondary variables; 6) studies with children as study subjects; 7) studies with animal subjects.

• RESULTS: There were 12 observational studies and 1 case control study included. Compared to control subjects, patients had significantly increased IOP (SMD: 0.50, 95% *CI*: 0.30~0.70, $Z=4.88$, $P<0.001$). Compared to control subjects, patients had significantly decreased CCT levels (SMD: -0.14, 95% *CI*: -0.23~-0.05, $Z=3.14$, $P=0.002$). Meta-regression revealed that mean-age ($P=$

0.025) was found to have a statistically significant relation to the observed CCT difference between glaucomatous eyes and controls.

• CONCLUSION: It has been established that glaucomatous eyes tend to have thinner CCT and higher IOP compared to normal eyes.

• KEYWORDS: central corneal thickness; intraocular pressure; Goldmann applanation tonometer
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INTRODUCTION

Glaucomas are a group of ocular disorders that cause progressive excavation of the optic disc, optic atrophy and characteristic loss of the visual field, which can be arrested or moderated by adequate reduction of intraocular pressure. The level of the intraocular pressure (IOP) associated with optic nerve changes is not the same in every eye and some individuals may tolerate for long periods a pressure that would rapidly blind another[1]. The key to preventing irreversible blindness caused by Glaucoma lies in early diagnosis which can only be possible through mass screening of the population, because in this case everyone is a suspect until proven otherwise by the screening tests. Long term follow up of borderline cases to make sure they start treatment on time should they need it. Also immediate commencement of treatment for diagnosed cases with scheduled life long follow up. In recent years, basic and clinical research has had some advancements which have led to the introduction of new high tech equipment.

One such piece of equipment is the Goldmann applanation tonometer which has become the "gold standard" for intraocular pressure measurement in the clinical setting[2]. When Goldmann developed applanation tonometry in the 1950s, it was based on an assumed "standard" central corneal thickness of 520 micron. The principal of the Goldmann applanation tonometer is highly dependent on a constant relationship between the bending rigidity of the cornea and the surface tension between the cornea and tonometer head. Goldmann found that on average these forces were balanced at an applanation diameter of 3.06 mm which also nicely corresponded to an applanation force of 0.1 per mmHg of intraocular pressure.

Central corneal thickness(CCT) can determine the condition of the cornea and is often used to evaluate the barrier function of the cornea and pump function of the corneal endothelia. There are several sources of error in the measurement of intraocular pressure even with the Goldmann *et al*[2] applanation tonometer because it measures intraocular pressure accurately only in patients with corneas of "normal" thickness. When central corneal thickness is thicker than normal, corneal rigidity increases and intraocular pressure readings will be overestimated. In thinner corneas on the other hand, intraocular pressure readings would be underestimated. In 1975, Ehlers *et al*[3] demonstrated experimentally that the reading in applanation tonometry did depend on the CCT, to such an extent that it could have clinical implications in glaucoma diagnosis. The pressure is measured too high in non-edematous thick corneas and too low in thin corneas and edematous corneas. Several studies, including most notably the Ocular Hypertension Treatment Study, have determined a significant relationship between CCT and IOP, and the need to adjust IOP applanation tonometry readings by a factor to consider the effect of CCT in order to understand the "true" IOP[4].

A meta-analysis of possible association between CCT and IOP measures of 133 data sets, regardless of the type of eyes was assessed and revealed a statistically significant correlation; a 10% difference in CCT would result in a 3.4±0.9 mmHg difference in IOP[5]. The association was most pronounced in eyes with acute onset disease but negligibly in healthy eyes.

SUBJECTS AND METHODS

This systematic review aims to evaluate the relationship between CCT and IOP in healthy and glaucomatous eyes of adults. And to make an up to date summary of the results of studies done on the association of central corneal thickness measurements and intraocular pressure measurements in Glaucoma patients and also in healthy subjects.

Search Strategy This systematic review and Meta-analysis was conducted according to the Meta-analysis of Observational studies in Epidemiology (MOOSE) guidelines[6] and The Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) statement[7]. To identify relevant studies a search of MEDLINE and Science Direct databases for studies investigating the relationship between CCT and IOP was conducted . The search period was from Sep. 10th to Oct. 28th of 2015. Search key words included; central corneal thickness, intraocular pressure, glaucoma, ocular hypertension, exfoliative glaucoma, applanation tonometry, pachymetry, primary open angle glaucoma, Goldmann applanation tonometry. In addition a manual search of "*The Year Book of Ophthalmology*" Journals 2004 to 2006 Issues in the Southern Medical University Library English language section was done.

Study Selection The following exclusion criteria applied: 1) non-English media studies; 2) studies done before 2005; 3) case series and case reviews; 4) studies involving treatment protocols or surgical techniques; 5) studies comparing glaucomatous eyes with other conditions such as diabetes, hypertension or cardiovascular disease as secondary variables; 6) studies with children as study subjects; 7) studies with animals as study subjects.

Inclusion criteria applied was as follows: 1) case control studies; 2) observational studies; 3) studies involving

Table 1 Characteristics of the 13 studies included in the meta-analysis

Name/y	Type	Location	Size	n1/n2	Mean-age (SD)	M/F	Mean-CCT1 (SD)	Mean-CCT2 (SD)	Mean-IOP1 (SD)	Mean-IOP2 (SD)
Molina *et al* [10] 2010	observational	Spain	67	40/27	65.5(11.49)	unknown	533.98(37.17)	545.26(47.09)	19.23(8.58)	13.33(2.81)
De saint sardos *et al* [11] 2009	observational	Canada	264	31/233	61.5(9.2)	74/190	560(37)	557(35)	17.1(4.6)	16.0(3.3)
Lee *et al*[12] 2006	observational	Korea	567	343/224	57.2(12.6)	288/279	550.72(38.66)	553.60(39.55)	16.2(3.9)	14.4(3.0)
Yazdani *et al*[13] 2015	case-control	Iran	118	62/56	57(12)	52/66	552(34)	562(41)	18(4)	14(2)
Ozcura *et al* [14] 2015	cross sectional study	Germany	124	68/56	59.57(13.08)	45/79	527.84(42.16)	541.71(39.86)	15.88(3.82)	16.14(3.81)
Tian *et al* [15] 2015	cross sectional study	China	102	42/60	41.08(20.34)	58/44	547.69(36.95)	546.65(28.02)	15.62(2.35)	14.9(1.73)
Mangouritsas *et al*[16] 2008	prospective study	Greece	182	108/74	62.4(9.8)	83/99	526.77(35.73)	537.84(41.93)	16.38(2.73)	15.70(2.65)
Realini *et al* [17]2009	observational study	USA	85	47/38	70.0(12.8)	30/55	551(32)	562(31)	15.4(2.9)	15.0(2.3)
Abitbol *et al*[18]2009	observational study	France	133	58/75	65.68(13.9)	unknown	535.34(42.7)	560.2(36.3)	17.1(5.1)	15.9(2.6)
Barleon *et al*[19]2006	observational study	Germany	197	131/66	24-85	99/98	542(36)	544(31)	20.7(8.4)	13.3(3.1)
Rao *et al*[20] 2012	cross sectional study	India	139	62/77	51(17.7)	73/66	534(35.5)	528(30.4)	18(7.8)	15(5.4)
HirneiB *et al*[21] 2011	observational study	Germany	36	18/18	64.4(11.0)	9/9	547.8(27.0)	550.1(28.5)	15.56(2.97)	12.61(1.33)
Reznicek *et al*[22] 2013	observational study	Germany	178	142/36	61.3(4.5)	unknown	543.2(37.2)	546.6(41.4)	15.4(6.1)	14.2(2.8)

CCT: central corneal thickness ; IOP: Intraocular pressure.

primary open angle glaucoma, ocular hypertension, pseudo exfoliation glaucoma and normal tension glaucoma combined and results reported as glaucoma with means of central corneal thickness and intraocular pressure as outcomes; 4) intraocular pressure measured only by Goldmann applanation tonometry, an average of at least two measurements; 5) patients with no corneal dystrophy, edema, scar or prior history of corneal surgery.

For studies that reported primary open - angle glaucoma (POAG) separately from ocular hypertension (OHT), only results for POAG were included, other studies pooled the results for all the different types of glaucoma and were used as results for the glaucomatous eyes. Some studies had outcomes for CCT and IOP only for healthy subjects and others only for glaucoma subjects, such studies were excluded from the meta -analysis.

Data Extraction and Quality Assessment A single investigator reviewed all search results to identify eligible papers and abstracted data from selected articles onto a pre-designed data abstraction form[8]. The following information was abstracted: name of the study and year it was published (name/y), design of study (type), sample size here is the number of eyes included in the study and not necessarily the number of individual subjects. Sample size of both the case (glaucoma) group and the control (non glaucoma) group (size n), sample size for the case (glaucoma group) n1 and for the control (normal group) n2, age in the form of mean plus standard deviation (mean SD), sex: male/female with the number of participants indicated for each group. And male n =/female n =, location of the study: location, central corneal thickness was abbreviated as CCT and recorded in the form of mean plus standard deviation. Measured in micron and divided into two groups; case (CCT1) (participants with glaucoma: primary open angle glaucoma, primary angle closure glaucoma, ocular hypertension and normal tension glaucoma). The second group was the control (CCT2) (participants without glaucoma), intraocular pressure was abbreviated as IOP and recorded in the form of mean plus standard deviation. Measured in mmHg and divided into two groups; case (IOP1) (participants with glaucoma; primary open angle glaucoma, primary angle closure glaucoma, ocular hypertension and normal tension glaucoma). The second group was the control (IOP2) (participants without glaucoma) (Table 1).

The question of investigator bias at data collection and abstraction was minimized by the use of a pre-designed data abstraction form[9]. The principal summary measure obtained was difference in means.

Figure 1 shows a Flow Chart illustrating the process followed during the Selection of Articles included in the meta - analysis.

Statistical Analysis Statistical data analysis was done with the use of STATA software Version 12.0. Since the principal summary measure was difference in means the effect size was standard mean difference. The Meta-analysis was done in two parts: 1) meta-analysis of the difference in means of IOP of the patients and controls; 2) meta-analysis of the difference in means of the CCT of the patients and that of controls. For both meta - analyses, a test of heterogeneity was done with weighting of individual studies and a sum of weights for all the 13 studies included by way of a forest plot. Meta regression was carried out to explore the sources of heterogeneity. Evaluation of publication bias was done using a funnel plot, in addition the Egger's and Begg's tests were employed. Sensitivity analysis was also done to assess the agreement of the summary results.

RESULTS

The literature search yielded 13 studies which included 1152 eyes of glaucoma patients and 1040 eyes of control subjects. The studies included were published between the years 2006 and 2015. There were 12 observational studies and 1 case control study included. There were seven European studies, four Asian studies and two North American studies.

Meta - analysis for IOP In the heterogeneity test, the results showed that heterogeneity was present ($Q=51.61$, $I^2=76.8\%$, $P<0.001$). Therefore, the random effects model was used to conduct the overall mean IOP difference between patients and controls. Compared to control subjects, patients had significantly increased IOP levels (SMD: 0.50, 95% *CI*: 0.30 ~ 0.70, $Z=4.88$, $P<0.001$. The forest plot is shown in Figure 2.

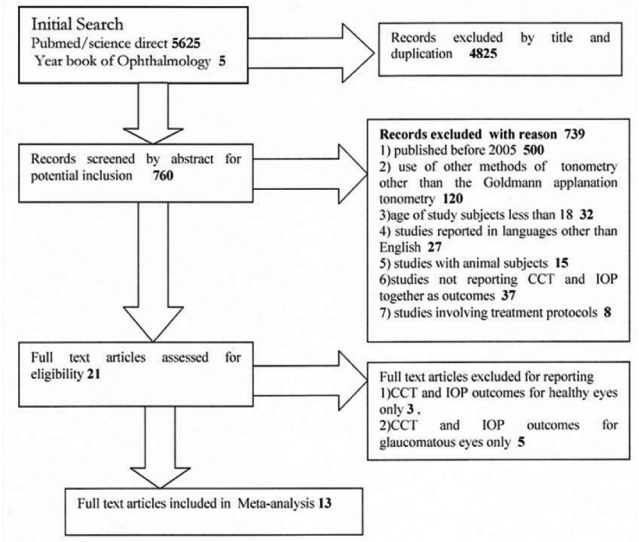

Figure 1 Flow chart for selection of articles.

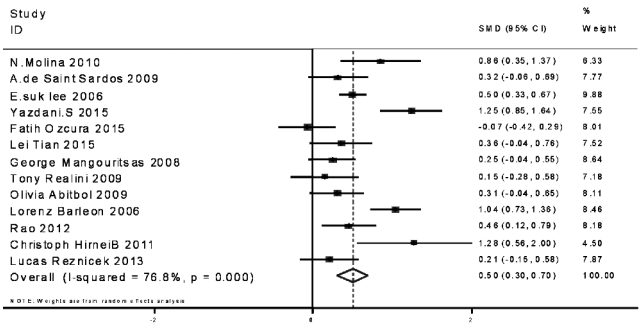

Figure 2 Test of heterogeneity for 13 studies reporting IOP difference between patients and controls.

Meta-Regression To explore the sources of heterogeneity, meta-regression analysis was conducted in this meta-analysis. Table 2 shows the effects of covariates on IOP difference between patients and controls. Meta-regression revealed that none of the covariates were found to have a statistically significant relationship to the observed IOP difference between patients and controls.

Evaluation of Publication Bias The funnel plot did not show a skewed or asymmetrical shape. Also, the results of Egger's test ($t=0.44$, $P=0.670$) and Begg's test ($Z=0.61$, $P=0.542$) both showed $P>0.05$. Therefore, it can be assumed that publication bias was absent. The funnel plot is shown in Figure 3.

Sensitivity Analysis The result of sensitivity analysis showed that the fourth[13] and the tenth[19] study had greater influence than other studies. After omitting these two studies, the combined effect size of meta-analysis became 0.437 (0.253, 0.620) and 0.447 (0.256, 0.638) respectively. It indicated that the results of meta-analysis in this paper were robust and stable.

Meta-analysis for CCT In the heterogeneity test, the results showed that mild heterogeneity was present ($Q=18.06$, $I^2=33.5\%$, $P=0.114$) though statistically insignificant. And the fixed effects model was used to conduct

Table 2 Effects of covariates on IOP difference between patients and controls

Covariates	Coefficients	S.E.	T	P
Study type	−0.3745	0.2288	−1.64	0.130
Sample size	−0.0003	0.0009	−0.34	0.743
Mean-age	−0.0020	0.0164	−0.12	0.908
Female proportion	−0.0192	0.0162	−1.19	0.269

IOP: Intraocular pressure.

Table 3 Effects of covariates on CCT difference between patients and controls

Covariates	Coefficients	S.E.	t	P
Study type	0.0698	0.1384	0.50	0.624
Sample size	0.0003	0.0004	0.86	0.407
Age mean	−0.0210	0.0080	−2.62	0.025
Female proportion	−0.0077	0.0068	−1.13	0.292

CCT: Central corneal thickness.

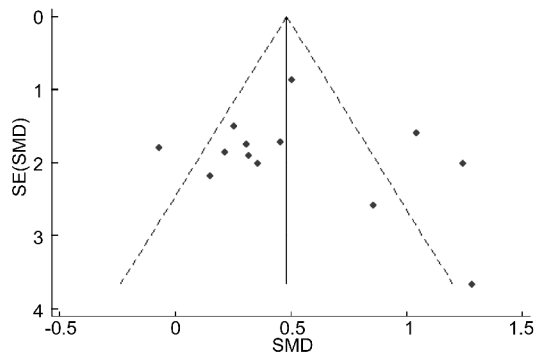

Figure 3 Funnel plot with pseudo 95% confidence interval.

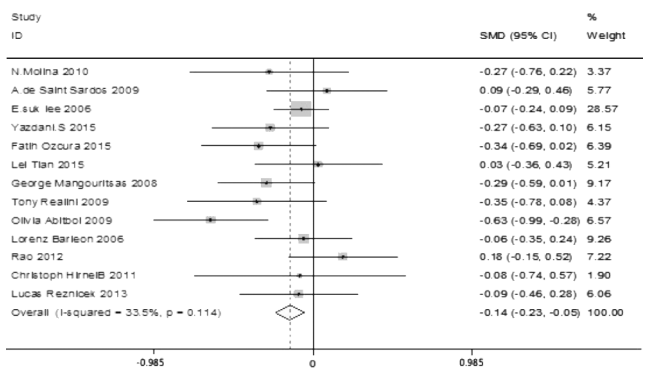

Figure 4 Assessment of heterogeneity.

the overall mean CCT difference between patients and controls. Compared to control subjects, patients had significantly decreased CCT (SMD: −0.14, 95% *CI*: −0.23 ~ −0.05, $Z=3.14$, $P=0.002$). The forest plot is shown in Figure 4.

The Forest plot shows Assessment of heterogeneity of 13 studies reporting CCT difference between patients and controls.

Meta-Regression To explore the sources of heterogeneity, meta-regression analysis was conducted in this meta-analysis. Table 3 shows the effects of covariates on CCT difference between patients and controls. Meta-regression

revealed that age mean ($P=0.025$) was found to have a statistically significant relation to the observed CCT difference between the two groups.

Evaluation of Publication Bias The funnel plot did not show a skewed or asymmetrical shape. Also, the results of Egger's test ($t=-0.68$, $P=0.509$) and Begg's test ($Z=-0.12$, $P=0.903$) both showed $P>0.05$. Therefore, it can be assumed that publication bias was absent. The funnel plot is shown in Figure 5.

Sensitivity Analysis The result of sensitivity analysis showed that the third (Lee *et al*[12] 2006) and the ninth (Abitbol *et al*[18] 2009) study had greater influence than other studies. After omitting these two studies, the combined effect size of meta-analysis became -0.172 (-0.279, -0.067) and -0.110 (-0.203, -0.017) respectively. It indicated that the results of meta-analysis in this paper were robust and stable.

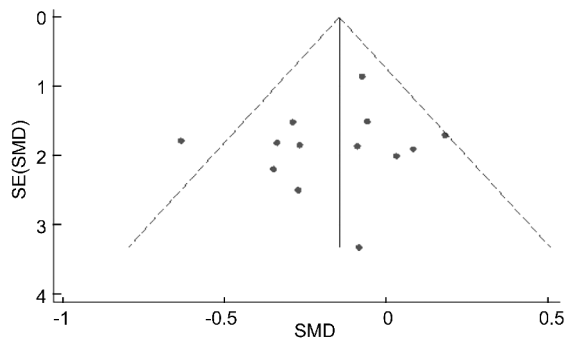

Figure 5 Funnel plot with pseudo 95% confidence interval.

DISCUSSION

Ever since the results of the Ocular Hypertension Treatment Study of 2002 resounded the relationship between CCT and IOP the next question for most researchers has been on quantifying this relationship[4]. The opportunity for a meta-analysis with the review of results from studies done in the last decade was the motivation for designing this study. In this study it is clear that the mean IOP for glaucomatous eyes was found to be higher than that of the control eyes (SMD: 0.50, 95% *CI*: 0.30 ~ 0.70, $Z=4.88$, $P<0.001$). Significant heterogeniety was present among the studies included which shows that studies were picked at random irrespective of their results. On meta regression, none of the covariates were found to have a statistically significant association to the observed difference in IOP between patients and controls.

The mean CCT of glaucomatous eyes was smaller compared to the control eyes, meaning that the glaucomatous eyes had thinner central corneal thickness compared to the control eyes (SMD: -0.14, 95% *CI*: -0.23 ~ -0.05, $Z=3.14$, $P=0.002$). Here heterogeniety was present but insignificant, also showing some randomness in the results of the included studies. On meta regression, mean-age ($P=0.025$) was found to have a statistically significant association to the observed CCT difference between glaucomatous eyes and control eyes. This association might in a small way be due to the degeneration of the corneal endothelium where it undergoes loss of cells with increasing age, the normal density reducing from 2300 cells/mm^2 at birth to 2000 cells/mm^2 in old age. Endothelial repair is limited to enlargement and sliding of existing cells, with little capacity for cell division[23]. This suggests that corneal thinning is inevitable with increasing age, however further research is necessary to explore the evidence of the entire mechanism which causes thinning of the cornea with age.

Perhaps the fact that this study used only the Goldmann applanation tonometer as the method of tonometry eliminated the challenge of comparing IOP readings taken by different methods and also the unavoidable question of how different methods of tonometry are affected by CCT. Francis *et al*[24] in the comparison of Goldmann applanation tonometry (GAT) and Dynamic contour tonometer found that mean IOP for the entire population by GAT was significantly lower compared with dynamic contour. Both GAT and Dynamic contour IOP levels were lowest for thin CCT and increased stepwise with increasing CCT but this difference was more pronounced with GAT than with Dynamic contour. The difference between GAT and Dynamic contour IOP measurements was largest for thin CCT and decreased for thicker CCT. Thus thinner CCT produced larger differences in IOP measurements by GAT compared to those by Dynamic contour, thicker CCT produced smaller differences in IOP measurements by GAT compared to those by Dynamic contour.

Molina *et al*[10] found that a positive correlation existed between IOP by GAT and CCT; it was such that each 10 micron decrease of CCT produces an increase of 0.47 mmHg in IOP. And then Iyamu *et al*[25] found that the association between measured IOP and CCT in normotensive subjects was not significant, however they found that the difference in mean CCT across age groups was statistically significant, CCT seemed to decrease with age. De Saint Sardos *et al*[11] concluded that glaucoma patients had higher IOP than those without glaucoma but the difference was not significant. They also found that there was no significant difference in CCT between the glaucoma patients and normal subjects. It has been established that glaucomatous eyes tend to have thinner CCT and higher IOP compared to normal eyes. In the fight against glaucoma being able to accurately predict risk and prognosis of the disease is very important and pachymetry is clearly a vital piece of the puzzle.

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