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Central corneal thickness associations with systemic factors: The Colombian glaucoma study

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Abstract

Abstract Objective: To establish Central Corneal Thickness associations with systemic factors in six cities of Colombia.

Methods: A cross-sectional study was conducted in Colombia among hypertensive and diabetic patients. Two thousand sixty-seven subjects older than 50 diagnosed with SH and DM were included. Participants underwent a complete ophthalmic examination, including intraocular pressure (IOP) measurement by Goldmann tonometry, Central Corneal Thickness (CCT), and Blood pressure. The glaucoma diagnosis was confirmed by structural and functional evidence.

Results: In multiple regression analysis, a trend of thinner corneal thicknesses was observed, with increasing decades of life, 60 - 69 years (-7.14 microns (µm) p: 0.58), 70- 79 years (-2.05 µm p: 0.38), > 80 years (-7.3 p <0.056) being almost statistically significant only in patients older than 80 years. Female patients had thinner CCT (- 5.04 µm) than male patients. African- Colombian patients had thinner corneas (-9.6 µm) than mestizo patients (P= 0.002). Patients with migraine had thicker CCT (6.83 µm p <0.024) compared with no- migraine patients. Diabetic patients had thicker CCT (3.91 µm) than non-diabetic patients (P= 0.039). Finally, a 0.66 µm increase per mm hg of the systolic pressure (P=0.024) and a 0.99 µm decrease per mm hg of Systolic Perfusion Pressure (P=0.038) was observed, but no association was found between CCT and Systemic Hypertension.

Conclusion: Our study highlights the relationship between systemic factors such as age, sex, race, DM, systolic blood pressure, migraine, and systolic perfusion pressure with an ocular biomarker such as CCT.

Keywords: Open angle-glaucoma; Central Corneal Thickness; Systemic Hypertension; Diabetes Mellitus; Intraocular pressure; Migraine; Systolic pressure

1 Introduction

Corneal thickness is defined as the distance between the epithelium (anterior surface of the cornea) and the endothelium (posterior surface of the cornea); as the cornea is a prolate surface, the thickness is not the same in its central portion as in the periphery. Pachymetry can measure the thickness in microns of the central part of the cornea. This measurement varies throughout life and, in recent years, has become a critical factor in the study and diagnosis of glaucoma, taking into account that the measurement of intraocular pressure (IOP) can vary according to the central corneal thickness (CCT)[1,2].

The 2002 ocular hypertension treatment study concluded that patients with central corneal thickness measurements of less than 555 µm were three times more at risk of developing primary open-angle glaucoma (POAG) compared to a

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higher CCT (1). Since then, multiple studies have been conducted to investigate the relationship between central corneal thickness (CCT) and the likelihood of glaucoma and to identify whether systemic diseases such as systemic hypertension (SH) or diabetes mellitus (DM) influence corneal thickness.

Among these is a study conducted in Namil Meon, a central region of Korea, where patients over 40 years of age with a diagnosis of glaucoma were studied. A total of 1259 right eyes that met the inclusion criteria were evaluated. This study showed that as people aged, the CCT decreased at a rate of approximately 4 μm per decade of life, and the higher the IOP, the higher the CCT (2.73 μm /1 mmHg) and the longer the axial length, the greater the CCT. Concerning systemic diseases, it was found that patients with SH had thinner corneas (5.5 μm), and no association was found between CCT and diabetes[4].On the other hand, a study was carried out in Singapore that looked for associations between ocular and systemic diseases and central corneal thickness, in which it was found, as in the previous study, that CCT is thicker in young people and subjects with higher IOP; also patients with thicker corneas were found in patients with a history of diabetes. In conclusion, it was established that people with some metabolic component have a higher CCT, possibly secondary to alterations in the physiology of the corneal endothelium[5].

In Amsterdam, the Netherlands, the influence of chronic diabetes on the shape and thickness of the cornea was investigated in a study of both types I and II diabetes patients and healthy patients, in which the average CCT for each group was 578 μm for the control group, 586 μm for patients with DM I and 578 μm for patients with DM II. No statistical association was found between the two types of diabetes and central corneal thickness (P = 0.19)[6].

Ultimately of the relevant studies that have been conducted, a study in Nepal aimed to compare the CCT and IOP in patients with primary open-angle glaucoma (POAG) and healthy patients, where no significant difference was found between the CCT of glaucoma patients and those who did not have the diagnosis[7].

The relationship between Central Corneal Thickness and systemic factors in a Colombian population is currently unknown.

The Colombian Glaucoma study is a cross-sectional study among hypertensive and diabetic patients conducted in 6 cities in Colombia. It assessed the prevalence and relationships between these two vascular risk factors. [8]. The study aims to establish the relationship and distribution between central corneal thickness and glaucoma among patients diagnosed with systemic hypertension and diabetes mellitus in six cities in Colombia.

2 Material and methods

2.1 Study Design

A cross-sectional study of diabetic and hypertensive patients in six cities in Colombia was conducted from September 2014 to January 2019. At enrollment, individuals were ≥ 50 years old and treated with antihypertensive and anti-diabetic medications for at least one year. The diagnosis of DM and SH was verified according to the guidelines for each disease. [9], [10]. All participants were selected from SH and DM control programs. The Valle University Review Board approved this study (Approval Code 030-014), and all participants signed an informed consent form. This research was conducted according to the tenants of the Declaration of Helsinki.

2.2 Procedures

Interviews and questionnaires were used to evaluate factors related to participants' lifestyles and other health conditions, including socioeconomic status, associated comorbidities, education, and nutrition. In addition, a physical examination was performed that included measurement of height, weight, abdominal circumference, heart rate , systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.3 Ophthalmic evaluation

Each participant underwent a complete ophthalmologic examination, including visual acuity, refraction, slit-lamp examination, intraocular pressure, and pachymetry measurements. The IOP measurement was obtained from the average of three values by Goldmann tonometry. Gonioscopy was performed in a dark room using a 4-mirror goniolens (Ocular Instruments Inc., Bellevue, WA) in the primary position, with a slit beam less than 2 mm in height, followed by a dilated funduscopic examination with a 78 diopter (D) lens for evaluating the optic disc, (Ocular Instruments Inc., Bellevue, WA). Central corneal thickness (CCT) was calculated based on the average of three consecutive measurements using a PachPen handheld pachymeter (Accutome, iNC., Pennsylvania, USA).

In suspected cases of glaucoma, the diagnosis was confirmed using a visual field (VF) test with the 24-2 Swedish Interactive Threshold Algorithm (Humphrey, Carl Zeiss Meditec, Inc) and optic nerve photos with a DRS camera (digital retinography system, Centervue, Fremont, CA, USA). Trained glaucoma specialists performed the examinations using standardized protocols.

2.4 Diagnosis of Glaucoma

Suspected and confirmed cases of glaucoma were defined according to the criteria specified by Foster et al.[24] confirmed glaucoma was defined as structural and functional evidence of glaucomatous damage in at least one eye.

2.5 Statistical Analysis

Linear regression analysis was performed to assess the effect of predictive variables of systemic factors, using CCT as the dependent variable. Using a backward selection strategy, variables with p values <0.20 in bivariate analysis were included in the model selection process. A level of significance of 0.05 was used. All analyses were carried out using Stata13® (STATA Corp, College Station, TX, USA).

3 Results

Table 1 Multiple Regression Analysis. CCT as the dependent variable.

Central Corneal Thickness	**B - coefic**	**P. value**	**[95% Conf.**	
			inferior	**superior**
Age(years)				
60-69	-1.15	0.58	-5.23	2.93
70 -79	-2.05	0.386	-6.68	2.58
>80	-7.3	0.059	-14.89	0.28
sex				
female	-5.04	0.005	-8.57	-1.5
Ethnicity base: mestizo				
African - Colombian	-9.66	0.002	-15.66	-3.65
White	0.24	0.926	-4.86	5.34
Body Mass Index				
Overweight	-1.65	0.42	-5.66	2.36
Obesity	3.94	0.079	-0.46	8.35
Intraocular Pressure	0.52	0.299	-0.46	1,49
Family History of Glaucoma	-1.22	0.555	-5.26	2.83
Dyslipidemia	1.84	0.276	-1.47	5.15
Migraine	6.33	0.024	0.85	11.81
Ocular Perfusion Pressure	-0.08	0.725	-0.53	0.37
Systolic Perfusion Pressure	-0.99	0.038	-1.93	-0.06
Diastolic Perfusion Pressure	0			
Systemic Hypertension	-5.07	0.094	-10.99	0.86
Diabetes Mellitus	3.91	0.039	0.2	7.61
Systolic Pressure	0.66	0.024	0.09	1.23

A total of 2085 subjects completed the interview and ophthalmologic examination, of which 18 were excluded because they met one or more exclusion criteria. One thousand nine hundred seventy-four patients had Central Corneal

Thickness measurement. The average age of the 2067 participants was 65.6±8.8 years; 65.93% (1324) were female, 11.0% (227) had only DM, 59.6% (1231) had only SH, and 29.4% (608) had both diseases. Of 2067 SH and DM patients, 142 were identified with confirmed glaucoma and 226 subjects with suspected glaucoma. [8].

In multiple regression analysis, CCT as a dependent variable, a trend of thinner corneal thicknesses was observed, with increasing decades of life, 60 - 69 years (-7.14 µm p:0.58), 70- 79 years (-2.05 µm p: 0.38), > 80 years (-7.3 p <0.056) being almost statistically significant only in patients older than 80 years. Female patients had thinner CCT (- 5.04 µm p= 0.005)) than male patients. African- Colombian patients had thinner corneas (-9.6 µm) than mestizo patients (P= 0.002). Patients with migraine had thicker CCT (6.83 µm p <0.024) compared with no- migraine patients. Diabetic patients had thicker CCT (3.91 µm) than non-diabetic patients (P= 0.039). Finally, a 0.66 µm increase per mm hg of the systolic pressure (P=0.024) and a 0.99 µm decrease per mm hg of Systolic Perfusion Pressure (P=0.038) were observed. However, no association was found between CCT and Systemic Hypertension. (Table 1)

4 Discussion

It is increasingly important to know the associations between central corneal thickness (CCT) with systemic and ocular factors, allowing more accurate and timely diagnoses.

4.1 Age and CCT

In our study, a trend of thinner corneal thicknesses was observed with increasing decades of life, being almost statistically significant only in patients older than 80. (p <0.056)

Contrary to our results, in a population-based glaucoma prevalence study of residents aged > 40 years in Korea, In univariate analysis, a thicker CCT was correlated significantly with younger age (P < 0.001), CCT decreased by 4.0 µm for every decade of life (95% confidence intervals [CI] 2.4-5.5 m) [4]. These findings also correlate with the Singapore study, which also found an association of decreased CCT with older age (P < 0.001) with an average of 5.1 microns/decade [5].

4.2 Gender and CCT

Our study evidenced female patients with thinner CCT (- 5.04 microns) than male patients.

In this study item, we found multiple discrepancies between various studies because there is no agreement on whether there is an association between any specific sex. The Singapore study, a population-based cross-sectional study of 3,280 Malay subjects, found no statistical difference in CCT between the sexes (P = .16) [5].

On the other hand, the Nepalese study carried out with patients diagnosed with glaucoma and healthy patients found that in the group of patients with glaucoma, women had significantly thicker corneas than men with a difference of 10.9 µm (P = 0.003), while in the group of healthy patients there was no statistical difference [7].

Finally, concerning the results of the Korean study, it was found that males had higher average CCT (5.8 µm more, (P = 0.001)) than females [4].

4.3 Ethnicity and CCT

In our study, African- Colombian patients had thinner corneas (-9.6 µm) than mestizo patients (P= 0.002). Similar results were found in a South African Eye Study. The mean CCT readings in the African, mixed ethnicity and Caucasian participants were 514.77±31.86, 531.77±35.17, and 549.97±30.51 µm (P<0.001) [11].). Similar to what was reported, Wang et al. in a multiethnic population study where blacks had thinner CCT (537.3 µm, SD 39.9), and the thickest corneas were reported in Whites (558.5 µm, SD 40.3) [12].

4.4 Migraine and CCT

Our results showed that patients with migraine had thicker CCT (6.83 µm p <0.024) compared with no- migraine patients.

Contrary to our results, Doyle and co-authors, in a retrospective analysis, studied 108 eyes of 54 patients with Normal Tension Glaucoma (NTG) and 54 patients with primary open-angle glaucoma (POAG). Mean CCT was 512 ± 31 µm in the group of patients with NTG with vascular risk factors such as migraine (n = 13) and 533 ± 31 µm in patients with

NTG without vascular risk factors (n = 41) (p = 0.034). Central corneal thickness in NTG was significantly lower than in POAG, and corneas were thinner in NTG patients with vascular risk factors as migraine.

4.5 Diabetes Mellitus and CCT

In our study, diabetic patients, had thicker CCT (3.91 µm) than non-diabetic patients (P= 0.039). Similar results were found in The Singapore Malay Eye Study, a population-based cross-sectional study of three thousand two hundred eighty Malay adults ages 40–80. After controlling for gender and age, central corneas were significantly thicker in persons with diabetes than those without diabetes (547.2 µm vs. 539.3 µm, P<0.001) [13].

Opposed to our results, Wiemer et al.; compared diabetes (type I and II) with healthy patients, where no significant variation was found between the CCT of the three groups [6]. It also coincides with the results obtained by Hwang et al., where no significant association was found between these two variables. (P=0.892) [4].

4.6 Systemic Hypertension, Systolic blood pressure, Systolic Perfusion pressure, and CCT

The associations found are related statistically significantly to Arterial Pressure and Systolic Perfusion Pressure but not directly to Systemic Hypertension.

In multiple regression analysis, we could establish a 0.66 µm increase per mm hg of the systolic pressure (P=0.024) and a 0.99 µm decrease per mm hg of Systolic Perfusion Pressure (P=0.038), but no association was found between CCT and Systemic Hypertension.

Wong and co-authors conducted a Chinese population-based cross-sectional study similar to our results. In multiple regression models, CCT increased with greater Radial Corneal Curvature (P < .001) and Diabetes Mellitus (P <0.03), diminished with age (P < .001), but no relationship was found with Systemic Hypertension. [14] Also, Nishituzs studied a population of Japanese adults. After multivariate adjustment, characteristics associated with increased CCT were HbA1c concentrations, body mass index, impaired glucose tolerance, diabetes, and current smoking, but no association was found with Systemic Hypertension [15]. Contrary to our results, a Korean study concluded that Subjects with Systemic Hypertension had 4.1 µm thinner CCT than those without hypertension (age, sex-adjusted, P < 0.027)(6). We did not find scientific literature regarding the association of systolic pressure and systolic blood pressure with CCT, so we considered these novel findings.

This study, to our knowledge, is the first program-based study to report associations between CCT and systemic factors in a Colombian population.

A strength of our study is the recruitment of patients with two essential vascular risk factors for glaucoma. The implementation of standardized protocols for conducting the study makes the information collected from the six participating cities comparable, increasing the quality of the information. One potential weakness of our research is that people were directly enrolled in the SH and DM programs, which likely represents a modified cohort due to changes in their lifestyles and habits, probably not reflective of a real-world scenario. Due to the study's cross-sectional design, it is impossible to establish causal associations conclusively. However, these findings represent a starting point for further studies that evaluate the biological association between CCT and systemic factors.

5 Conclusion

Our study highlights the relationship between systemic factors such as age, sex, race, DM, systolic blood pressure, migraine, and systolic perfusion pressure with an ocular biomarker such as CCT.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of ethical approval

The Universidad del Valle Review Board approved this study (Approval Code 030-014), and all participants signed informed consent. This research was conducted according to the Declaration of Helsinki.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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