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UNIVARIATE AND MULTIVARIATE REGRESSION ANALYSES OF FACTORS AFFECTING THE CENTRAL CORNEAL THICKNESS (CCT): A SINGLE TERTIARY CENTRE PERSPECTIVE

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Abstract:
Objective: *- To determine the factors influencing CCT such as age, sex, smoking habits, alcoholism, diabetes mellitus, hypertension, obesity, metabolic syndrome, corneal curvature and axial length.*
Materials and Methods: *- This prospective cross-sectional study was undertaken in Isfahan, Iran between July-2018 to Febrauary-2019. The study population consisted of 216 patients aged 18 years and older who presented to our clinic for a routine eye check-up. After a standardized interview with patients, a comprehensive ocular examination which also includes IOP and visual acuity were taken. We then measured Central Corneal Thickness (CCT) and Axial length were measured using Ultrasound Sonomed 300A+ PacScan Plus A-scan.*
Results: *- It was found that on multivariate analysis age, diabetes duration, corneal curvature and IOP were association with CCT ($p<0.05$). However, on univariate analysis, age, presence and duration of diabetes, elevated fasting blood glucose levels, alcohol abuse, corneal curvature and IOP were associated with CCT.*
Conclusion: *- The patient population in our study have corneal thickness comparable to that of Caucasians. We found that CCT was significantly associated with age, diabetes duration, corneal curvature and intraocular pressure.*

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INTRODUCTION:

The average Central Corneal Thickness (CCT) varies across different populations with mean values ranging approximately 530-550 microns in majority of the populations. It was suggested that Japanese, Central/Southern Asian, North and West Africans have thinner corneas in comparison to European, Caucasian Americans and Latin American population who tends to have thicker corneas [1-3]. The measurement of absolute value of CCT is significant in not only estimating Intra Ocular Pressure (IOP) but also to diagnose corneal and systemic pathologies [4]. The corneal endothelium maintains fluid and solute transport across the posterior corneal surface which is essential in maintaining the cornea in a modest dehydrated state to function as a transparent structure [5]. It was studies that CCT affects the measurements of IOP, with thicker CCT overestimating the IOP while thinner corneas underestimating the IOP value [6]. A thin CCT has been recently established as a predictive factor in the glaucoma progression [7]. It is therefore indicated that we study and assess the ocular, demographic and metabolic risk factors contributing to CCT.

MATERIALS AND METHODS:

Study population: - This prospective cross-sectional study was undertaken in Isfahan, Iran between July-2018 to Febrauary-2019. The study population consisted of 216 patients aged 18 years and older who presented to our clinic for a routine eye check-up. Patients with documented history of corneal refractive surgery, other corneal diseases and present (or) past contact lens use were excluded from the study.

All the patients understood the nature, methodology and risks involved in the study and consented to take part in the study. Institutional human ethics committee (IEC) approval was obtained and the provisions of the Declaration of Helsinki were followed in this study.

Study measurements: - A standardized interview was taken and a thorough ocular examination was done in the Ophthalmology unit of the study centre. Central Corneal Thickness (CCT) and Axial length were measured using Ultrasound Sonomed 300A+ PacScan Plus A-scan.

We measured IOP with Goldmann Applanation Tonometer and Corneal curvature values using automated refractor. Sleeve-down Retinoscopy technique was performed to record Refractive errors. The height was measured with wall-mounted tape (in meters) and weight with weighing scale to obtain Body Mass Index (BMI) in kg/m2.

According to WHO classification, we classified the study group based on their BMI as "Underweight" if BMI is ≤18.5 (kg/m2), "Normal" with BMI ≥18.6 and ≤25. A BMI of ≥25 but <30 was considered "Overweight" and "Obese" when BMI >30 [8]. The Blood Pressure (BP) readings were taken using Omron HEM 7120 Automatic BP monitor with Intellisense technology. According to Joint National Committee (JNC) 7, we classified participants under Hypertension if two successive BP readings measured >140/90 mm Hg. To measure serum glucose and lipid profile, fasting and postprandial blood specimens were collected. Diabetes was defined as fasting glucose of ≥126 mg/dL (7.0 mmol/l) or postprandial blood glucose levels of ≥200 mg/dL (11.1 mmol/l) as per American Diabetes Association [9].

A patient was diagnosed to have metabolic syndrome if he/she satisfied three or more of the following criteria set by WHO: (a) Hypertension with BP ≥130/85 (mm Hg); (b) BMI ≥25 (kg/m2); (c) HDL cholesterol (mg/dL) levels <40 (in males) and <50 (in females); (d) Diabetes (mg/dL) with fasting glucose ≥126 mg/dL (7.0 mmol/l) or postprandial blood glucose levels of ≥200 mg/dL (11.1 mmol/l).

The study participants were also classified based on the smoking habits (present/past) obtained using a standardized questionnaire. We classified patients as follows: (a) Non-smoker, if smoked <100 cigarettes in their lifetime and is not an active smoker; (b) Former smoker, if smoked ≥100 cigarettes in their lifetime and current a non-smoker; (c) Current smoker, if smoked ≥100 in their lifetime and is actively smoking. Further, former smokers were classified as <1 year and >1 year, based on the information on years since smoking cessation.

Statistical analysis: - The data obtained was analysed using Statistical Package for the Social Sciences (SPSS) software version 20 (IBM Corp, Armonk, NYC, USA) and MS Excel 2019 version. A Pearson's correlation coefficient test was obtained and Mean CCT (bilaterally) across various variables were compared using ANOVA and *t*-test. Using linear regression model, the mean difference in CCT per change in parameter was derived. A p-value <0.05 was considered statistically significant.

RESULTS:

Of the total 216 eligible study subjects participating in the study, the mean age was 43.7(± 8.5) years. There were 134 (62.03%) males and 82 (37.9%) females. The mean CCT of bilateral eyes of study population was 537.5 (± 4.631) microns. We found no statistical significance in mean CCT values between male (538.2 µm) and female (536.7 µm) subjects (p=0.7). There was fall in CCT with

increasing age (p=0.003). The Pearson's correlation between bilateral mean CCT values and different variables are compared as shown in the Table-*1*.

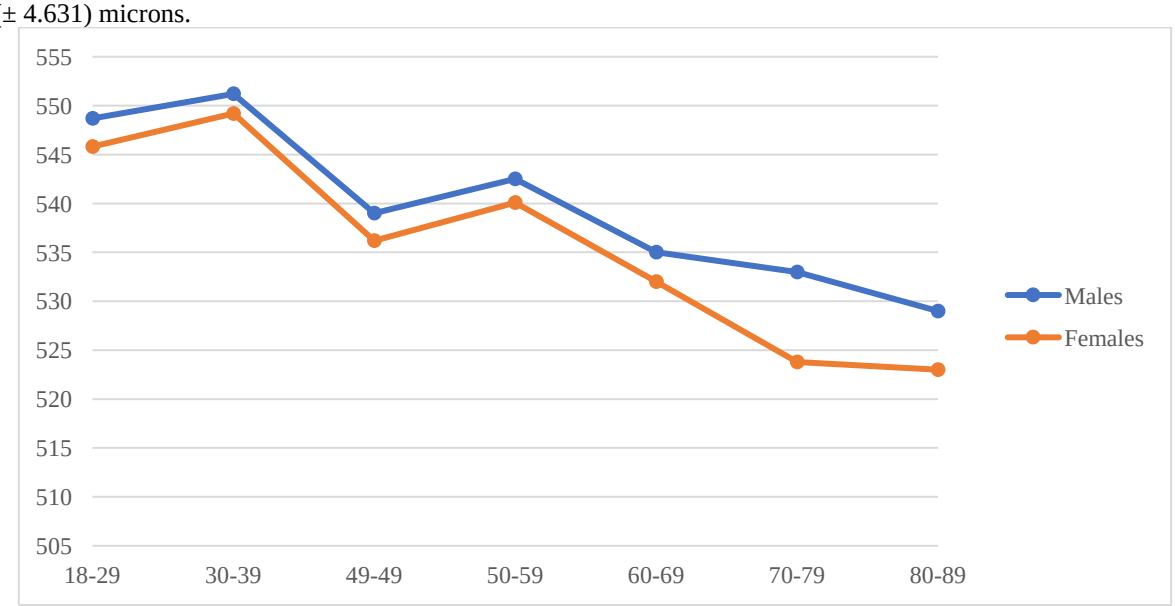
Variable (n=216)	**Pearson's correlation coefficient**	***p*-value**
BMI	0.03	0.78
Total Cholesterol	0.18	0.04*
Triglycerides	0.15	0.07
HDL	0.09	0.13
LDL	0.10	0.77
Creatinine	-0.02	0.81
Urea	-0.08	0.37
HbA1c	0.13	0.07
FBG	0.18	0.03*
Retinoscopy	0.16	0.81
Axial length	0.10	0.29
Keratometry	-0.27	0.02*
IOP	0.31	0.01*

*CCT showed statistical significance with serum cholesterol levels, FBG levels, keratometry and IOP ($p<0.05$)
LDL: Low Density Lipoprotein
HDL: High Density Lipoprotein
HbA1c: Glycosylated Haemoglobin
FBG: Fasting Blood Glucose
IOP: Intra Ocular Pressure
CCT: Central Corneal Thickness

DISCUSSION:

The present study aims to determine the mean CCT in Isfahan, Iran. There have been multiple studies among various populations throughout the world which have put forward the factors influencing the CCT, and they have shown that CCT varies across different ethnicities. In our present study the mean CCT of bilateral eyes of study population was 537.5 (± 4.631) microns.

The mean CCT tends to decrease modestly as the person ages in our study (Figure-*1*) with a weak statistically significant negative correlation (R^2= 0.828), it is similar to the study conducted by Saulius Galgauskas et al., Nishiyama et al., [10-11].



Changes in the Central Corneal Thickness across different age groups

The mean CCT in patients with diabetes was 547.29 (± 4.271) µm as compared to non-diabetics 534.21 (± 3.122) µm. On multivariate regression analysis, however, we did not find any statistical significance in mean CCT among diabetic's vs non-diabetics. Similar results were obtained in the study done by Sudhir et al., and Amira El-Agamy et al., without significance (p=0.301) [12-13].

It is stipulated that impaired glucose metabolism plays a role in corneal endothelial dysfuction leading to stromal hydration and corneal swelling secondary to long standing diabetes [14].

It was also found that the CCT and HbA1c levels showed no significant correlation, the mean CCT among patient with $HbA1_c$ <6.5 g% was 532.63 (± 3.972), $HbA1_c$ of 6.5-7.9 g% was 548.23 (± 3.227) and $HbA1_c$ >8 g% was 553.95 (± 4.325) as shown in Table-*2*. This result is in concordance with Ozdamar et al., who also concluded that there was no significant correlation between CCT and $HbA1_c$ (p=0.056) [15].

Diabetes and Central Corneal Thickness

Variable	**Study sample (*n*=216)**	**Mean ± SEM**	***P*-value**
Diabetes a. Negative b. Positive	 164 52	 534.21 ± 3.122 547.29 ± 4.271	0.03*
Duration of diabetes (years) a. 0 b. <10 c. >10	 164 38 14	 529.94 ± 2.642 542.11 ± 4.884 567.85 ± 7.231	0.002**
FBG (mg/dL) a. <110 b. 110-125 c. >126	 95 69 52	 532.74 ± 3.441 538.23 ± 3.619 549.81 ± 5.326	0.008***
HbA1c a. <6.5 b. 6.5-7.9 c. >8.0	 139 48 29	 532.63 ± 3.972 548.23 ± 3.227 553.95 ± 4.325	0.2

*P=0.03 between no diabetes and >10year duration
** P=0.002 between <10 years and >10 years duration
***P=0.008 between <110 mg/dL and >126 mg/dL
HbA1c: Glycosylated Haemoglobin
FBG: Fasting Blood Glucose
SEM: Standard Error of Mean

The mean CCT among current smokers was 542.65 (±6.228) microns, which was more than that of non-smokers 532.27 (±4.219) microns without statistical significance (p=0.14). A study conducted by Nishitsuka et al., concluded that active smoking was associated with higher CCT [16]. Moreover, our study found that the mean CCT among current alcoholics was 546.82 (±3.867), whereas 535.23 (±5.744) in non-alcoholics. It was statistically significant only in univariate analysis (p=0.015), on multivariate analysis no significance was present (p=0.287) as presented in Table.

Substance abuse and Central Corneal Thickness

Category	Study sample (n=216)	Mean ± SEM	P-value
Smoking			
a. Non-smoker	159	532.27 ± 4.219	
b. Former smoker	25	539.24 ± 3.986	0.14
c. Active smoker	32	542.65 ± 6.228	
Pack years			
a. 0	159	532.85 ± 2.769	
b. 0.1-19.9	28	537.44 ± 4.613	0.71
c. 20-39.9	21	539.35 ± 5.124	
d. >40	8	552.53 ± 6.291	
Alcohol			
a. Never	169	535.23 ± 5.744	0.09
b. Current	47	546.82 ± 3.867	

It was found that CCT and keratometry values are negatively correlated with statistical significance (Pearson coeeficient= -027, p=0.02). Our findings are similar to the study carried out by Su DH et al., [17] in which they concluded that the CCT increased propotinately with radius of corneal curvature. Furthermore, Elias A et al., presented in their study that CCT and corneal curvature have negative correlation [18].

Also, the mean CCT and IOP values (bilateral) had negative correlation with higher IOP coinciding with greater mean CCT with statistical significance (Pearson coefficient= -0.31 and p=0.01). Similar results were obtained in the Godar ST el al., [19], Funagata study [20]. and Kass MA et al [21].

Body Mass Index and Central Corneal Thickness

Categories	Study sample (*n=216*)	Mean ± SEM
BMI (kg/m2)		
a. <25	106	529.44 ± 3.421
b. 25-30	72	538.71 ± 3.959
c. >30	38	540.66 ± 6.527

BMI: Body Mass Index

SEM: Standard Error of Mean

Intraocular pressure and Central Corneal Thickness

Category	Study sample (*n*=216)	Mean ± SEM	*P*-value
IOP (mm Hg)			
a. <12	88	525.73 ±4.594	
b. 12-15	71	532.58 ±3.881	0.002*
c. >15	57	546.12 ±4.625	

*p<0.05 Indicates statistical Significance
IOP: Intra Ocular Pressure
SEM: Standard Error of Mean

Keratometry and Central Corneal Thickness

Category	Study sample (*n*=216)	Mean ± SEM	*P*-value
Keratometry (dioptre)			
a. <42	59	548.36 ± 6.231	
b. 42-48	147	534.51 ± 5.214	0.06
c. >48	10	419.42 ± 9.441	

SEM: Standard Error of Mean

Age-wise distribution of Central Corneal Thickness

Category	Frequency	Mean ± SEM
Age (years)		
a. 28-30	40	547.88 ± 4.742
b. 30-40	52	542.29 ± 4.237
c. 40-50	38	537.77 ± 5.201
d. 50-60	47	531.59 ± 4.774
e. >60	39	528.32 ± 5.238

SEM: Standard Error of Mean

Univariate regression analysis for association of central corneal thickness

Variable	Mean difference in CCT (*β* coefficient)	C.I (95%)	*P*- value[a]
Age (years)	-0.58	-1.42-0.72	0.027*
Sex (male to female)	-1.39	-11.97-9.23	0.82
Diabetes (absent to present)	13.75	2.38-26.45	0.01*
Diabetes duration (years)	14.24	5.76-23.91	0.008*
FBG (per 1mg/dL)	0.13	0.02-0.23	0.014*
HbA1c (per g%)	3.55	-0.16-6.88	0.07
Hypertension (absent to present)	-4.96	-15.59-7.72	0.4
Hypertension duration	-6.42	-17.20-3.82	0.18
BMI (kg/m^2)	0.18	-1.18-1.70	0.7
Smoking (absent to present)	4.59	-2.82-10.45	0.24
Smoking (pack per year)	2.65	-4.50-8.94	0.49
Alcohol (absent to present)	12.53	2.36-23.48	0.015*
Metabolic syndrome	-3.28	-14.28-6.91	0.6
Total cholesterol (per 1 mg/dL)	0.14	-0.002-0.28	0.059
LDL	0.15	-0.05-0.29	0.18
HDL	0.35	-0.19-0.28	0.15
TG	0.10	-0.02-0.25	0.08
Urea	-0.47	-1.18-0.32	0.27
Creatinine	-2.18	-32.27-28.65	0.8
Retinoscopy	2.63	-1.72-9.76	0.66
Axial length	3.74	-2.67-10.32	0.29
IOP	3.59	2.14-4.92	0.001*
Keratometry	1.76	-8.47-1.32	0.02*

a:Wald *p* value
FBG: Fasting Blood Glucose
HbA1c: Glycosylated Haemoglobin
BMI: Body Mass Index
LDL: Low Density Lipoprotein
HDL: High Density Lipoprotein
TG: Triglycerides
IOP: Intraocular Pressure

Multivariate regression analysis for association of central corneal thickness

Variable	*β* coefficient	95% C.I for *β*		*P*-value[a]
		Upper limit	Lower limit	
Age	-0.83	-1.3	-0.2	0.003
Diabetes	-18.27	-57.2	18.4	0.321
Diabetes duration	37.42	7.6	67.4	0.013
FBG	-0.004	-0.3	0.2	0.842
HbA1c	-0.59	-7.4	5.6	0.876
Hypertension duration	2.37	-9.2	15.3	0.741
Height (in cm)	0.03	-0.5	0.6	0.955
Alcohol consumption	6.78	-4.5	17.8	0.287
Total Cholesterol	0.17	-0.4	0.7	0.324
LDL	-0.17	-0.7	0.5	0.522
HDL	0.28	-0.4	0.8	0.419
TG	0.09	-0.3	0.5	0.744
IOP (bilateral)	2.71	1.4	4.8	0.002
Keratometry (bilateral)	-3.65	-7.4	-0.2	0.028

a: Wald *p* value
FBG: Fasting Blood Glucose
HbA1c: Glycosylated Haemoglobin
BMI: Body Mass Index
LDL: Low Density Lipoprotein
HDL: High Density Lipoprotein
TG: Triglycerides
IOP: Intraocular Pressure

CONCLUSION:

The patient population in our study have corneal thickness comparable to that of Caucasians. We found that CCT was significantly associated with age, diabetes duration, corneal curvature and intraocular pressure.

In univariate analysis, it was concluded that age, diabetes and its duration, high FBG levels, alcohol abuse, keratometry and intraocular pressure were associated with CCT. In multivariate regression analysis, however, only age, presence of diabetes and its duration, keratometry and intraocular pressure only appeared to influence the CCT.

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