ORIGINAL ARTICLE

The Distribution of Corneal Thickness in Rural Population

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Received: 02 Sep. 2017; Accepted: 19 Dec. 2017

Abstract- To determine the distribution of corneal thickness and its associated factors in the over 5-year-old population in the north and south rural areas in Iran. In this study, samples were selected using multi-stage cluster sampling. After vision and refraction tests and the slit lamp exam, the central corneal thickness (CCT), apical corneal thickness (ACT), and the thickness at four peripheral areas of the cornea were measured using Pentacam. Of the 3851 selected samples, after applying the exclusion criteria, the analysis was done on data from 2681 people. The mean age of the participants was 36.03±18.51 years, ranging from 6 to 90 years, and 58.1% of them were female. Mean CCT and ACT were 533.87 µm (95%CI: 532.05 -535.69) and 536.72 µm (95%CI: 534.9 -538.54), respectively. Mean peripheral corneal thickness was 637.46 µm (95%CI: 635.09 -639.83) in the superior quadrant, and 594.34 µm (95%CI: 592.2 -596.47), 620.81 µm (95%CI: 618.66 -622.97), and 584.55 µm (95%CI: 582.18 -586.93) in the inferior, nasal, and temporal quadrants, respectively. Linear regression analysis showed significant associations between CCT and gender (*P*=0.001), age (*P*<0.001), geographical location of residence (*P*<0.001), the radius of corneal curvature (*P*<0.001), anterior chamber depth (*P*<0.001), and corneal volume (*P*<0.001). This study is one of the few studies describing the distribution of the corneal thickness in a population of over 5-year-olds using Pentacam. Gender, anterior chamber depth, and corneal radius of curvature are some of the factors associated with CCT.

Acta Med Iran 2018;56(5):320-328.

Keywords: Corneal thickness; Cross-sectional study; Distribution

Introduction

Corneal thickness, especially the central corneal thickness (CCT), is an important parameter for evaluating corneal health, and in particular, corneal endothelial cells. In recent years, several studies have emphasized the importance of CCT assessment for accurate measurement of the intraocular pressure and better diagnosis of glaucoma (1-5), as well as for determining patient eligibility for refractive surgery (6-9). Studies in different populations have addressed corneal thickness determinants. Age, gender, refractive errors (10-12), smoking, body mass index, diabetes, and hyperglycemia (12,13) are major factors. Also, given the anatomical location of the cornea, dry weather and air pollution in industrial cities (14) were other factors considered in these studies.

Ultrasound pachymetry is the gold standard method for corneal thickness measurement; however, in light of the limitations and weaknesses of this tool, such as underestimation or overestimation of corneal thickness, as well as lower patient cooperation due to the need for topical anesthesia for using this technique, (8,15) ophthalmologists sought alternative methods in their clinical practice. One of the devices that have recently received attention is the Pentacam which, not only lacks the limitations of ultrasound pachymeters, it also provides valid and reliable information about the corneal thickness (16,17).

The increasing popularity of contact lenses and refractive surgery, ethnic, and racial differences in corneal thickness, and the variety of measurement tools

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in different studies make it necessary to obtain comprehensive information on the status of the cornea in different populations. On the other hand, studies in the country and many parts of the world have been on a particular age group, a specific sample, or clinic-based, and thus, they fail to provide a complete picture of the corneal structure in the population. Therefore, the present study, as one of the largest population-based studies, aimed to investigate the distribution of corneal thickness in people over 5 years of age in the rural north and south Iran using Pentacam.

Materials and Methods

This cross-sectional study was conducted on underprivileged rural populations in Iran in 2015. The sampling frame of the present study was based on the roster of deprived rural areas provided by the Rural Development Office of the presidential administration in the Islamic Republic of Iran. Two districts were randomly chosen: Shahyoun in the southwest (a district of Dezful County, Khuzestan Province) and Kajour in the north (a district of Noshahr County, Mazandaran Province). Then, within each district, a number of villages were randomly selected.

Given the study sample size, the number of samples selected from each district was proportionate to their total population. Therefore, 15 villages were sampled in Shahyoun and 5 in Kajour, because the Shahyoun has smaller and less populated villages. All over-one-year old residents in each selected village were considered the target, and samples were chosen through a multistage cluster sampling approach. In each selected household, all members over 1 year of age were invited to participate in the study, and their exam date was set.

First, informed consent was obtained from all subjects. For cases under 18 years, the head of the household signed the consent form. An interview was conducted to collect demographics, and then, participants proceeded to the exam room. Examinations were conducted under normal room illumination by two optometrists. To assess inter-examiner agreement, 35 people were initially tested for visual acuity and objective refraction by both optometrists. Based on the intraclass correlation coefficients (ICC), an inter-examiner agreement was high (0.923 for uncorrected visual acuity (UCVA) and 0.897 for spherical equivalent refraction).

Examinations for each participant began with testing the UCVA using the Snellen E chart at 6 meters. For illiterate participants, instructions were provided beforehand, and for children≤ 5 years, the Lea Symbols acuity chart was used. Acuity testing was followed by objective refraction using the Nidek Ref/Keratometer ARK-510A, and results were refined through retinoscopy (Heine Beta 200 retinoscope, HEINE Optotechnik, Germany). If autorefraction was no possible for any child, objective refraction was determined by retinoscopy only. For cases with UCVA worse than 20/20, subjective refraction was done to determine best distance optical correction, and best-corrected distance visual acuity (BCVA) was recorded. Finally, all subjects had the slit lamp exam by an ophthalmologist.

All participants over the age of 5 years underwent corneal imaging with Pentacam. All images were acquired by the same technician throughout the study in accordance with the manufacturer's instructions. The latest version of the device (6.03, r=11) and Pentacam software (1.17, r=72) were used. Eye examinations (both eyes) were done under myosis between 9:00 AM and 2:00 PM. To avoid the effect of diurnal variations, examinations were done at least 3 hours after waking up. In case of error, imaging was repeated 10 minutes after instilling artificial tears. For each participant, we extracted the CCT, and the paracentral corneal thickness at 4 points (superior, inferior, temporal, and nasal) on the 3mm ring (3mm away from the apex).

Exclusion criteria

People with a history of intraocular surgery, use of contact lenses at the time of the study, corneal opacities, pterygium, strabismus, keratoconus, scissoring reflex on retinoscopy, Fleischer rings on slit lamp examination, corneal dystrophy, and ptosis was excluded. Also, Pentacam images displaying an error status were excluded from the study.

Statistical analysis

In this study, corneal thickness was described as mean and 95% confidence intervals (CI). In order to calculate standard errors, the design effect of the cluster sampling method was estimated. Simple linear and multiple regression and analysis of variance were used to investigate the relationship between corneal thickness and other studied variables.

Ethical issues

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study protocol, which was conducted in accord with the tenets of the Helsinki

Declaration. All participants signed a written informed consent.

Results

Of the 3851 people selected for this study, 3314 people participated in the study, and after applying the exclusion criteria 2681 people were eligible for inclusion. 58.1 % (1558) of the subjects of this study were female and the average age of study participants was 36.03±18.51.

The 6 to 20-year age group (25.3%) and the +70-year age group (3.7%) formed the largest and smallest age groups, respectively.

Mean CCT and apical corneal thickness (ACT) were respectively 533.87 µm (95%CI: 532.05 -535.69) and 536.72 µm (95%CI: 534.9 -538.54). Mean CCT and ACT based on gender, age, refractive status, and residence location are shown in Table 1. Mean CCT (*P*=0.034) was significantly higher in males compared to females.

Table 1. Distribution of central and apical corneal thickness by demographic variables and refractive status

		Central corneal thickness		Apical corneal thickness	
		Mean(95%CI)	***P***	**Mean(95%CI)**	***P***
	Total	533.87(532.05 -535.69)		536.72(534.9 -538.54)	
Gender	**Female**	532.52(530.19 -534.84)	0.034	535.37(533.05 -537.68)	0.019
	Male	535.81(532.91 -538.71)		538.64(535.73 -541.56)	
Age	**6-20**	544.45(540.66 -548.25)	<0.001	546.97(543.19 -550.75)	<0.001
	21-30	527.81(523.39 -532.22)		529.89(525.48 -534.3)	
	31-40	534.41(530.32 -538.5)		537.24(533.1 -541.37)	
	41-50	533.64(529.27 -538.01)		536.8(532.39 -541.21)	
	51-60	525.74(521.18 -530.3)		529.15(524.54 -533.76)	
	61-70	532.24(525.06 -539.42)		535.87(528.82 -542.93)	
	>70	526.84(516.08 -537.59)		530.72(520.39 -541.06)	
Refractive errors	**Emmetropia**	536.13(533.72 -538.54)	<0.001	538.76(536.34 -541.17)	<0.001
	Myopia	531.4(527.51 -535.29)		534.52(530.59 -538.45)	
	Hyperopia	530.02(525.81 -534.23)		533.19(529.02 -537.36)	
Residence location	**South**	531.26(528.62 -533.9)	<0.001	533.67(531.03 -536.3)	<0.001
	North	536.14(533.64 -538.63)		539.36(536.87 -541.86)	

The highest CCT and ACT were observed in the under 10 age group; thicknesses significantly decreased with age and the lowest CCT and ACT were observed in the 71 to 80-year age group. Findings showed that mean CCT (*P*=0.001) and ACT (*P*=0.001) significantly differed between the rural north and south of Iran.

Mean CCT (*P*=0.928) and ACT (*P*=0.738) were lower in the hyperopic group compared to the myopic group, but the difference was not significant. Mean CCT and ACT in the emmetropic group were significantly different from myopic and hyperopic groups (*P*<0.001).

Mean peripheral corneal thickness was 637.46 µm (95%CI: 635.09 -639.83) in the superior quadrant, and 594.34 µm (95%CI: 592.2 -596.47), 620.81 µm (95%CI: 618.66 -622.97), and 584.55 µm (95%CI: 582.18 -586.93) in the inferior, nasal, and temporal quadrants, respectively. Table 2 summarizes the mean peripheral corneal thickness by gender, age, refractive error, and residence location. Mean superior thickness was significantly higher in males (*P*=0.042). Residents of the northern and southern regions were significantly different in terms of peripheral thickness at all quadrants except the superior quadrant.

Linear regression analysis showed that each year of older age was associated with reduced corneal thickness by 0.51 µm (*P*=<0.001). CCT in males was on average 3.74µm higher than in females (*P*=0.016). Also, CCT in the residents of northern Iran was higher compared to residents of southern Iran. For each millimeter increase in the radius of corneal curvature, CCT decreased by 3.09 µm. For each millimeter increase in anterior chamber depth (ACD), CCT increased by 38.84 µm. Also, for each 1 mm^2 increase in corneal volume, CCT is reduced by 0.47 µm.

Table 2. Distribution of paracentral corneal thickness by demographic variables and refractive status

		Superior	Inferior	Nasal	Temporal
		Mean(95%CI)	Mean(95%CI)	Mean(95%CI)	Mean(95%CI)
	Total	637.46(635.09 -639.83)	594.34(592.2 -596.47)	620.81(618.66 -622.97)	584.55(582.18 -586.93)
Gender	**Female**	635.66(632.61 -638.71)	593.75(590.99 -596.52)	620.71(617.96 -623.47)	582.14(579.01 -585.28)
	Male	640.01(636.26 -643.77)	595.16(591.8 -598.52)	620.96(617.5 -624.41)	587.99(584.38 -591.59)
Age	**6-20**	650.92(646.14 -655.7)	604.07(599.59 -608.54)	635.79(631.39 -640.19)	590.25(585.81 -594.69)
	21-30	633.2(627.79 -638.61)	591.65(586.74 -596.55)	619.02(614 -624.04)	581.01(575.98 -586.03)
	31-40	643.07(637.96 -648.17)	596.85(591.89 -601.82)	623.28(618.32 -628.24)	587.47(580.37 -594.57)
	41-50	639.11(633.09 -645.14)	593.29(588.04 -598.55)	620.23(615.28 -625.18)	587.9(582.21 -593.59)
	51-60	623.11(617.27 -628.95)	586.35(581.01 -591.69)	608.13(602.8 -613.46)	578.24(572.28 -584.19)
	61-70	623.77(613.2 -634.35)	587.8(578.31 -597.3)	607.06(597.69 -616.42)	580.9(571.38 -590.42)
	>70	618.19(604.22 -632.15)	580.14(568.53 -591.75)	594.67(583.95 -605.4)	567.51(554.15 -580.87)
Refractive errors	**Emmetropia**	641.18(638.08 -644.27)	596.73(593.93 -599.54)	624.05(621.29 -626.82)	586.07(582.92 -589.22)
	Myopia	634.77(629.7 -639.83)	591.52(586.9 -596.14)	618.3(613.64 -622.96)	582.17(577.11 -587.23)
	Hyperopia	629.56(623.89 -635.22)	590.44(585.4 -595.47)	613.72(608.38 -619.06)	582.99(577.4 -588.59)
Residence location	**South**	636.24(632.73 -639.75)	591.93(588.87 -595)	616.95(613.8 -620.11)	585.08(581.42 -588.74)
	North	638.51(635.3 -641.72)	596.42(593.45 -599.39)	624.16(621.23 -627.1)	584.1(581 -587.19)

Table 3. The relationship between central corneal thickness with demographic and ocular variables linear regression analysis

	Unstandardized Coefficients		Standardized Coefficients	*P*
	B	Std. Error	Beta	
Age	-0.51	0.053	25.644	<0.001
Gender	3.74	1.545	-0.255	0.016
Myopia	-0.45	1.765	0.050	0.801
Residence location	9.43	1.488	-0.005	<0.001
Radius of corneal curvature	-3.09	0.524	0.127	<0.001
Pupil diameter	0.60	1.155	-0.124	0.602
Anterior chamber depth	38.84	4.413	0.012	<0.001
Corneal volume	-0.47	0.046	0.409	<0.001

Discussion

The present study is one of the largest population-based studies in Iran, which for the first time, studies the distribution of corneal thickness and its associated factors by sampling residents of two different geographic regions in the north and south of Iran and covering a wide range of different age groups. Our findings showed that mean CCT in the studied population was 533.87 µm, which is close to the findings of some similar studies with the same mean age of our study (18-20), but as displayed in table 4, overall, there are large differences among results of different studies. In these studies, the lowest CCT was 503.3µm in the study by Tayyab *et al*., (31) in Pakistan, and the highest CCT was 593.3 µm in the study by Su *et al*., (13) in Singapore. Among the few population-based studies that have been conducted in rural areas, mean CCT was 514 µm in a sample of 4711 rural-dwellers over 30 years of age in India (25) and 505 µm in another study (33) which are lower than the averages observed in the rural population in Iran. However, differences among studied age groups in our study with the rural studies in India should be considered. Lekskul *et al*., (34) reported a mean CCT of 535.2 µm in the over 12 year age group in rural Thailand which is close to our findings. Type of design study, type of applied tools and techniques, as well as genetic and socio-economic differences can be the most important reasons for varied results in the literature. The study by Pan *et al*., in China clearly showed racial differences in mean CCT variation (35). Study of genetic differences by Aghaian *et al*., who compared Asians, African-Americans, the Chinese, and the Japanese revealed significantly thinner corneas in the black African-American race compared to other races, and among Asians, the Japanese had thinner corneas than other countries such as China and the Philippines (22). In the study by Suzuki *et al*., (36), mean CCT in more than 7,000 Japanese over 40-year-old was 517 µm, and in the study by Dohadwala *et al*., (37), mean CCT was lower in blacks than whites, which confirms the role of genetic differences in normal corneal thickness. One of the strengths of the present study is examining two different ethnicities in two different geographical regions. Our findings showed that mean CCT in northern rural-dwellers was about 5 µm higher than in southern ones. Given that no study has been done in Iranian rural populations, our ability to make any comparisons is limited. To explain the significant difference, two points should be noted. First: ethnic differences and their role in corneal thickness in different ethnicities. Second: differences in geographical location. Khuzestan is a province in the south of Iran where people are exposed to sunlight and UV radiation much more than in the north which usually has many cloudy and rainy days and less sunshine during the year. Therefore, the thinner CCT is an interesting finding in the rural south of the country which might suggest the influence of sunlight on corneal thinning.

Table 4. Comparison of mean central corneal thickness (CCT) values in different studies

Author	Country and Date	Age Group (years)	CCT Mean±SD (µm)	Measurement Tool
Nishitsuka *et al.*[12]	Japan 2005- 2007	≥35	544.7±34.6	Automated specular-type pachymeter
Tomidokoro *et al.*[21]	Japan 2007	≥40	0.521±0.032	Specular-type pachymeter
Hashemi *et al.*[1]	Iran 2009	≥14	555.6±39.9	Orbscan II
Hashemi *et al.*[10]	Iran 2011	40-64	528.5±35.8	Pentacam
Su DH *et al.*[13]	Singapore 2008	40-80	593.3±0.70	Ultrasound pachymeter
Aghaian *et al.*[22]	USA 2004	≥30	542.9	Ultrasound pachymeter
Gao *et al.*[23]	USA 2013	≥40	551.6±33.4	Ultrasound pachymeter
Zhang *et al.*[24]	China 2008	≥40	556.2±33.1	slit lamp-based optical
Nangia *et al*[25]	India 2010	≥30	514±33	ultrasound pachymeter
Nemesure *et al*[26]	USA 2003	50- 79	533.3±37.2	Ultrasound pachymeter
Rashid *et al.*[27]	Iraq 2016	25 – 60	551.02±36.28	Pentacam
Rufer *et al.*[19]	--	18- 83	534±36	Pentacam
Landers *et al.*[28]	Australia 2007	14- 51	511±34	Pentacam
Altinok *et al*[29]	Turkey 2007	6-88	552.2±35.9	not mentioned
Doughty *et al.*[30]	UK 2002	32-60	0.533+/-0.033 mm	Ultrasound pachymeter
Sng *et al.*[18]	2016	≥40	533.9±34.0	Ultrasound pachymeter
Tayyab *et al.*[31]	2016	47.31 ±11.78	503.96±12.47	TopCon non-contact specular microscope
Kivanc *et al.*[32]	2016	5- 8	526.8±37.9	Ultrasound pachymeter
Current Study	2015	6-90	533.87 (95%CI: 532.05-535.69)	Pentacam

It seems that there is an interaction among residence location, environmental exposure, and race and ethnicity which can be responsible for CCT differences in different locations and different races. The comparison of mean CCT in urban and rural areas of Iran also shows a higher CCT in urban-dwellers compared to people living in rural areas. In the population-based study in Tehran, mean CCT was 26 µm thicker than our rural-dwellers of the south and 21 µm thicker than rural-dwellers of northern Iran (1). A similar difference was also observed in the 40 to 64-year-old population-based study in Shahroud, and mean CCT was higher in urban-dwellers in Shahroud compared to the corresponding age group of the rural sample in our study (10). The difference in diet and lifestyle, and perhaps access to eye care can be some of the important reasons for these differences in mean CCT. Understanding the exact cause and effect in mean CCT difference in urban versus rural regions requires conducting analytical studies with different methodologies.

Our findings showed that mean CCT was approximately 3.5 µm higher in males than female. This result is consistent with the findings of other studies (24-226,36,38). However, Brandt *et al*., (39) reported that mean CCT was higher in females, and Hashemi *et al*., (1) found no significant inter-gender difference in this regard. Since most studies agree that males have thicker corneas, researchers attribute it to physiological and hormonal differences such as estrogen levels in females (40). Goldich *et al*., (41) reported corneas to be thinner at the beginning of the menstrual cycle and thicker at the end of the cycle; attention to this issue is of particular importance during screening programs and drawing conclusions about inter-gender thickness differences.

The most important strength of this study is including a large age range. One important question that has remained unanswered concerns the possible role of age in CCT changes and some researchers believe that age-related corneal thickness changes cannot be predicted. Lack of a clear relationship between age and CCT has been more common in studies of white populations rather than non-white ones. (42) Most studies (18,35, 43,44) agree that mean CCT is thinner in older people than younger people, and this study also showed that for every one-year increase in age, the corneal thickness reduces by about 0.50 µm. Our findings showed that mean CCT difference between the youngest and oldest age groups is more than 30.0 µm. Some studies also suggest that for each decade increase in age, the cornea thins by about 2 to 6.5 µm (45, 46). In a study of 485 people, Eballe *et al*., (47) reported a 4.2 µm reduction in corneal thickness per decade of aging. In a population-based study of more than 1,600 Lithuanian adults aged 18 to 90 years, corneal thickness decreased by 2 to 8 µm per decade of aging (45). Due to methodological limitations of a cross-sectional study effect, prospective longitudinal studies are more powerful for identifying cohort effects or age effects. In the 40 to 64 year old Iranian population of the five-year cohort study by Hashemi *et al*., mean CCT was 529.3 µm at baseline which significantly reduced by 1.5 µm to 527.8 µm after 5 years; the proper methodology of the study confirms the role of age on corneal thinning, or in other words, the age-effect (48).

In describing the effect of age on corneal thinning, Battle *et al*., (49) state that when corneal endothelial cells are lined up next to each other, older age is associated with reduced endothelial cell density, and thus, reduced CCT. The reason behind the gradual loss of endothelial cells is still unclear, and the most likely hypothesis, as proposed by Green, is the dysfunction in hydrogen peroxide metabolizing enzymes and other free radicals in the process of aging (50). On the other hand, contrary to these findings, Ruffer *et al*., reported a positive relationship between aging and increased corneal thickness in a study of 777 healthy eyes (51). There are also a few studies that reject any correlation between age and CCT, and state that there is no significant increase or decrease in CCT in relation to age (29,52-54).

Our findings showed that mean CCT is significantly lower by 11 µm in hyperopics and 6.5 µm in myopic cases compared to emmetropic individuals. On the contrary, we found no significant CCT difference between hyperopic and myopic cases, but the literature suggests that the cornea is thinner in myopic people than hyperopics, and the thickness decreases linearly at higher levels of myopia (55). In the study by Pedersen *et al*., (56), mean CCT was about 11 µm lower in myopics than emmetropic individuals, but the difference was not significant possibly due to low sample size. In the study by Ucakhan *et al*., (57), there was a significant difference between emmetropes and high myopic cases but not low myopics. In contrast to these findings, mean CCT in myopics was about 13 µm thicker than normal eyes in the study by Wang *et al*., (58). Given the importance of CCT in performing refractive surgery and the belief that a CCT less than 500 µm will result in serious complications, CCT measurement in various stages of myopia can have a significant impact on decision making about interventions.

In conclusion, the present study is the first to describe the corneal thickness in a sample of over 5-year-old-Iranians and the first to study the distribution of this parameter in the rural population in Iran. Results point to the effect of age, gender, geographic region, as well as the biometric parameters of the cornea and anterior chamber on CCT.

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