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Effect of Age and Gender on the Thickness of the Corneal Epithelium Measured With Spectral Domain Anterior Segment Optical Coherence Tomography among Sample of Iraqi Population

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Abstract

Background: Corneal epithelial thickness profiles have brought increasing interest, as it can affect total corneal power and bring undesired refractive shifts and changes in a variety of corneal conditions.
Aim of Study: To measure the thickness of the corneal epithelium by using Spectral–domain anterior segment optical coherence tomography among a sample of Iraqi population and view the effects of age and gender.
Methodology: a cross-sectional observational study includes 402 eyes of 201 healthy individuals (93 men, 108 women), the corneal epithelial thickness in 25 sectors over a corneal diameter of 9 mm bilaterally via anterior segment optical coherence tomography. Patients with any ocular condition that could affect the epithelium thickness were excluded.
Results: The epithelial thickness steadily decreases with increasing age group. Corneal epithelium was significantly thicker in males in central area, as it was 50.95± 2 um in males compared to 49.81± 1.8 um in females**.** The inferior areas were thicker than superior ones; also, the temporal areas were thicker that nasal.
Conclusion: The corneal epithelial thickness became thinner with age and gender differences should be considered in the assessment of corneal epithelial thickness.
Keywords: thickness of the corneal epithelium,& Spectral Domain Anterior Segment Optical Coherence Tomography

Introduction:

The corneal epithelium (CE) plays a pivotal role in forming the eventual surface power of the cornea. It has been shown that the CE refractive power over the central 2.0-mm is 1.03 D, whereas it is a littlelower (0.85 D) over the 3.6-mm area[(1)].Tear film thickness is seven μm which covers the CE, and is has some optical role in masking imperfections of corneal anterior surface, the tear–air interface, with the underlying cornea, contribute about two thirds of the total refractive power of the eye [(2)].

With age, the eye changes related to CE, as the surface of its superficial cells becomes smoother by losingtheir microvilli, microplica, and glycocalyx [(3)], this abrasion iscaused by frequent eye blinking as well as losing the apical squamous cells [(4)].

The spectral-domain OCT (SD-OCT) was introduced in 2002, significantly increasing both scan speed and resolution, providingexcellent details for thecorneal layers,assisted by automated algorithms for generating thickness maps to be utilized in clinical practice [(5)].

Aim of the study: To measure the thickness of the corneal epithelium by using anterior segment SD-OCT (AS-OCT) map measuring 9 mm in diameter among sample of Iraqi population and view the effects of age and gender.

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Methodology:

Study Design: This cross-sectional study was conducted in Ibn Al Haitham Teaching Eye Hospital, Baghdad, in order to measure corneal epithelial thickness in normal population.

Study Population: The study included information about patients who attended LASIK Unit in Ibn Al-Haitham Teaching Eye Hospital during the period from the beginning of September 2019 until March 2020, it included 201 eyes of 402 eyes healthy individuals (93 men, 108 women).

Inclusion criteria: All candidate have to be older than 18 years old and able to give informed consent for study participation.

Exclusion Criteria: best corrected visual acuity<6/12, refraction greater than +3 diopters (D) or less than -3 D, IOP >22 mm Hg, dry eye (with a Schirmer's test 1 value of less than 10 mm), ocular surface diseases, corneal diseases, dystrophies, keratoconus and form fruste keratoconus, any previous ocular surgery or trauma, history of contact lens wear during the previous 3 weeks, cataract or vitreoretinal disease, glaucoma, systemic diseases like definite diagnosis of diabetes mellitus, autoimmune disease, and pregnancy.

Data collection: Data for the study was collected by interviewing the patient while writing down relevant information such as demographic data and history using specially designed questionnaire.

Examination: visual acuity, refraction via autorefraction-device (TOMEY, RC-5000, Nagoya, Japan), which contained the keratometry results. Intraocular pressure (IOP) using an air-puff tonometer (NIDEK, NT-4000, Japan). Anterior eye segment examined by tomography device (Pentacam HR; Oculus, Wetzlar, Germany).Both eyes scanned by an experienced OCT operator using the SD-OCT RTVue XR Avanti system (Optovue, Inc.) using a standard scan protocol in all eyes that were included. Lastly, the pupil was dilated by administering 1% tropicamide to observe the fundus.The corneal epithelial thickness was measured over a 9-mm diameter, the CE thickness maps were generated automatically and divided into a total of 25 sectors:

- 1 central 2-mm diameter zone,
- 8 inner zones within an annulus between the 2- and 5-mm-diameter rings,
- 8 middle zones within an annulus between the 5- and 7- mm-diameter rings,
- 8 outer zones within an annulus between the 7- and 9 mm diameter rings as described in the figure 1.

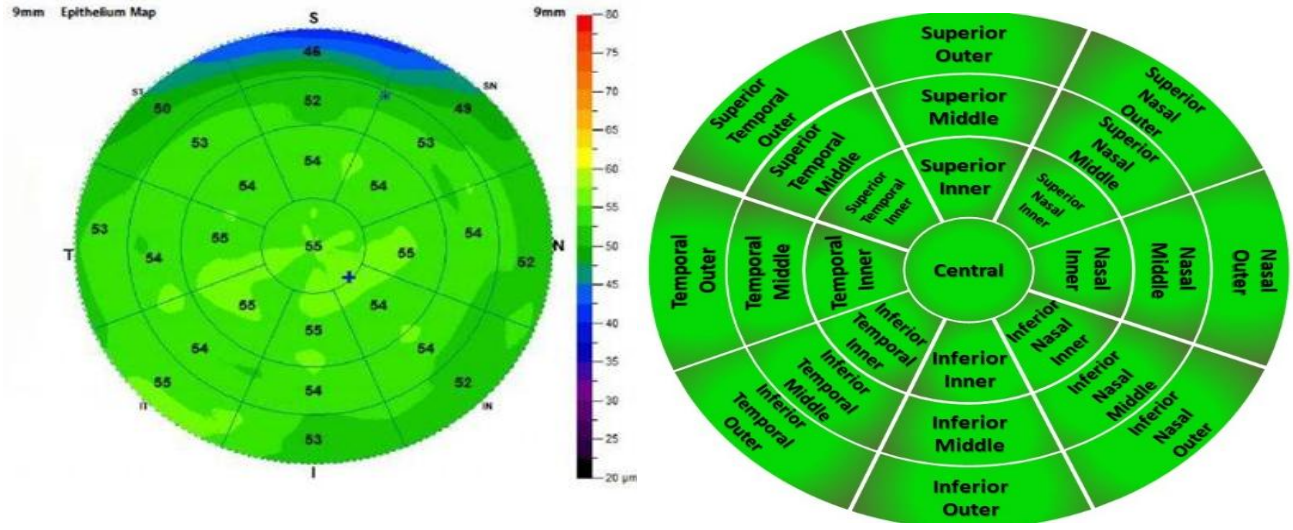

Figure 1:- (A) The CE thickness map generated automatically by AS-OCT. (B) The CE thickness map sample divided into 25 sectors

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Ethical consideration: Iraqi Board for Medical Specializations and Ibn Al-Haitham Teaching Eye Hospital approved this study. Verbal informed consent was obtained from all the participants included in the study after explaining for them the objectives of this study and clarifying the type of information required of the interview. Collected information were treated with confidentiality and autonomy throughout data collection, organization, analysis and presentation.

Statistical analysis: Data tabulation, input and coding was done by the use of IBM© SPSS© (Statistical Package for the Social Sciences) Statistics Version 23. Data normality distribution were tested using Anderson Darling test. Comparing two normally distributed variables was done using independent samples T-test, comparing between more than two variables was done by the non-parametric test; Kruskal Wallis Test as all variables did not follow normal distribution and each group had different number of cases, then multiple in-group comparisons were done using Dunn-Bonferroni post hoc method. Pearson correlation coefficient was used to investigate the correlation between age and each area; values between −0.70 to −0.90 was considered high negative, values −0.50 to −0.70 moderate, −0.30 to −0.50 low and 0.00 to −0.30 negligible. P-value less than 0.05 was considered significant throughout data analysis.

Results:

The mean age of the 201 patients was 40.1± 13.5 years, 64 (31.8%) were aged < 29 years, 60 (29.9%) were aged 30-44 years, 93 (46.3%) were males, as shown in table (1).

Regarding difference between superior and inferior zones in the current study, larger and more clearly defined differences were observed, as in the inner zone, highest differences were 2.96±2.7 um in 30-44 years, and 2.27±2.5um in 45-60 years, while in the middle zone highest differences were 2.12±2.4 um in < 30 years and 1.7±2.9, um in 45-60 years, and for the outer zone, highest differences were 2.79±2.1 um in <30 years and 2.29±1.7 um in >60 years (Table-2).

The difference between temporal and nasal zones according to inner, middle and outer zones' thicknesses; and it showed that highest difference in inner zone was among 30-44 years age group with 1.47±2.7 um, and lowest in >60 years with 0.57±1.6 um, while in the middle zone similar differences were observed in ages <30 and 45-60 years, with 0.66±2.3 um and 0.64±2.9 um, respectively compared to ages 30-44 and > 60 years with -0.37±1.9 um and -0.38±1.7 um, respectively, for the outer zone highest difference was observed in < 30 years with 1.53±2.2 um and > 60 years with 1.07±1.7 um. (Table-2).

Comparison in summation of central in addition to the three concentric zones; namely inner, middle and outer zones of corneal epithelium, there was a statistically significant influence of age on all the previously mentioned zones, as it was observed that the thickness steadily decreases with increasing age group, as in the central area; it was 50.96±1.5 um in <30 years, 50.3±2 um in 30-44 years, 49.67±1.7 um in 45-60 years and 48.84±1.9 in >60 years age group. (Table-2).

There was no significant difference in age between the two genders, and corneal epithelium was significantly thicker in males in central area, as it was 50.95± 2 um in males compared to 49.81± 1.8 um in females, other areas with same findings included inner and middle superior, inner and middle nasal, middle IN, however, some areas were significantly thinned in males, as in inner inferior, middle SN, and outer ST, as shown in table (3),

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Table (1): Distribution of the study group according to age and gender

Variables	Number	%
Age group in years		
<30	64	31.8
30-44	60	29.9
45-60	56	27.9
>60	21	10.4
Gender		
Male	93	46.3
Female	108	53.7
Total	201	100.0

Table (2): Distribution of epithelial thickness on the age groups in all the study group

Epithelial thickness	<30	30-44	45-60	>60	Total	P-value
Central	50.96±1.5 um	50.3±2 um	49.67±1.7 um	48.84±1.9 um	50.18±1.9 um	<.001
Inner	50.99±1.6 um	50.54±1.8 um	50.13±2 um	48.75±2 um	50.38±1.9 um	<.001
Middle	50.79±1.7 um	50.12±1.7 um	49.45±1.8 um	48.81±1.7 um	50.01±1.8 um	<.001
Outer	51.66±1.4 um	50.63±2.1 um	49.18±1.4 um	48.57±1.3 um	50.34±2 um	<.001
Temporal -Nasal						
Inner	0.75±1.9 um	1.47±2.7 um	1.11±2.5 um	0.57±1.6 um	1.04±2.3 um	.085
Middle	0.66±2.3 um [a]	-0.37±1.9 um [b]	0.64±2.9 um [a]	-0.38±1.7 um [b]	0.24±2.4 um	<.001
Outer	1.53±2.2 um [a]	0±2.1 um [b]	-0.18±1.9 um [b]	1.07±1.7 um [a]	0.55±2.2 um	<.001
Inferior-Superior						
Inner	1.81±1.9 um [a]	2.96±2.7 um [b]	2.27±2.5 um [ab]	1.74±1.6 um [a]	2.25±2.3 um	.003
Middle	2.12±2.4 um [a]	0.73±2.1 um [b]	1.7±2.9 um [a]	0.76±1.9 um [ab]	1.44±2.5 um	<.001
Outer	2.79±2.1 um [a]	1.36±2.3 um [b]	0.96±2.1 um [b]	2.29±1.7 um [a]	1.84±2.2 um	<.001
Kruskal Wallis Test followed by Multiple comparisons using Dunn-Bonferroni post hoc method **Means having different letters in the same row are differed significantly**						

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Table (3): Distribution of age and epithelial thickness on gender

Variables	Male	Female	P-value
Age	38.72±13.9 years	41.22±13.1 years	.064
Central	50.95±2 um	49.81±1.8 um	<.001
Superior inner	48.98±1.7 um	48.06±1.8 um	<.001
Superior middle	49.49±1.6 um	48.46±2.2 um	<.001
Superior outer	48.69±1.7 um	48.91±1.6 um	.178
Superior nasal inner	48.73±1.8 um	48.81±1.7 um	.639
Superior nasal middle	49.55±1.9 um	48.93±2.3 um	.003
Superior nasal outer	49±2.4 um	48.98±1.9 um	.932
Nasal inner	50.37±1.9 um	49.07±1.9 um	<.001
Nasal middle	50.67±1.9 um	49.96±2.1 um	.002
Nasal outer	49.87±2 um	49.61±2 um	.188
Inferior nasal inner	50.47±1.9 um	50.5±2.4 um	.884
Inferior nasal middle	51.12±2 um	50.3±1.3 um	<.001
Inferior nasal outer	50.14±2.1 um	49.93±1.7 um	.252
Inferior inner	50.19±2 um	50.81±1.7 um	.002
Inferior middle	50.11±1.8 um	50.24±1.8 um	.455
Inferior outer	50.23±1.8 um	50.46±1.6 um	.178
Inferior temporal inner	50.4±1.5 um	50.57±1.7 um	.265
Inferior temporal middle	50.67±1.7 um	50.89±1.9 um	.223
Inferior temporal outer	50.15±1.9 um	50.07±1.9 um	.690
Temporal inner	50.47±1.9 um	50.74±1.4 um	.111
Temporal middle	50.27±2.3 um	50.48±1.7 um	.306
Temporal outer	49.89±1.8 um	50.09±1.6 um	.234
Superior temporal inner	49.27±1.7 um	49.52±1.8 um	.163
Superior temporal middle	49.32±1.8 um	49.81±1.6 um	.004
Superior temporal outer	48.8±1.9 um	49.06±3.8 um	.005
Independent Samples T-test			

Discussion:

Advances in ophthalmic imaging have allowed the clinician to measure the CE thickness in daily practice, while the clinical implications of variations in CE thickness are increasingly being realized, there is

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still a lack of normative data for CE thickness, and only a few reports have addressed the possible factors that affect it. Many demographic, ethnic, and ophthalmologic factors have been reported to be correlated with CE thickness[6-10], and these factors could also affect CE thickness. The mean central CE thickness (50.18±1.9 um) ranging from 48.0 to 59.9 um, as reported by some previous reports[11-20].

Our study found that the epithelial layer of the cornea had a non-uniform thickness profile, as suggested in previous studies [17, 21], there seems to be debate among studies about the thickness profiles of different meridians.

Distribution of CE thickness in the current study according to location and age were not compatible to results of Haque et al. [22]as they reported thatsuperior CEthickness to be the higher compared to inferior parts. While, othersreportedthe opposite, i.e. the superior CE thickness lower compared to inferior thickness.[17, 23-25], which was comparable to our results.

Reinstein et al [26]proposed that each blink causes a friction with some degree of abrasion affecting the CE of the superiorly. While Du et al, proposed thatcontinuouspressure applied by the upper eyelid superiorly,leads tochronic thinning [27]. King-Smith et al, [21]proposed that pooled tear inferiorlymake false-higher thickness readings[28]. Hashmani et al in 2018 proposed that contact duration of the upper cornea is shorted compared to inferior parts, leading to a more rapid desquamation of the CE, and subsequently thins with time, with less lubricant and nourishmentfactors superiorly[23].

Kim et al. [29] demonstrated the nasal–temporal differences were not always significant among healthy Korean, while other studies [25, 30-32] demonstrated that the nasal areas are thicker than temporal areas. Interestingly, our study demonstrated that the temporal areas are thicker than nasal areas; this may be related to demographic and ethnic factors. The causemay be associated with external factors, possibly resultingfrom peripheral sun rays focusing, where they pass laterally toward the cornea, and undergo refraction to be focused on the limbic region,and the unhinderedrays, cross from lateral to medial limbus, however, the shadow of the nose at medial side decrease the intensity of rays heading to lateral part[33-36].

Reinstein et al. [25],Rush et al.[37]Francoz et al. [13] reported no identified significant associations between CE thickness and age. Kanellopoulos et al.[24], similarly, didn't report age-related differences in CE thickness, this was contradictory toresults of Yang et al. [38] who reported thinning of paracentral and midperiphery with aging, but not forthe central 2-mm region. Kim et al.[29]and Samy et al. [32] reported that there were significant thinning in the central 2mm zone with aging regardless of gender, which wasconsistent with our results.

A number of reports regardingthe transitional zone between corneal and scleral epithelium in normal subjectsproposed that the cellular density and diameter alters with advancing age, in a picture of increasing mean diameter accompanied by decrementin cellular density[39, 40]. Zheng and Xu[41]discovered Vogt palisades, which was thought to containlimbal epithelial stem cells (LESCs), and these cells decrease in number with age; while basal cells of CE increase in size and decrease in number.This could be interpreted as with aging the ability of LESCs to compensate CE decrease, and thus the thickness of the epithelium decrease as a consequence.

Hashmani et al. [23] demonstrated that the males had a 1.9-um thicker epithelium in the center,also Kanellopoulos et al. [24] and Wu et al. [42] agreed with our findings; however, their results show that the central corneal epithelium have slightly smaller differences with 1.52 um and 1.34 um, respectively. Some authorsproposed that endocrinediscrepancies may affect ocular tissues growing rates[43, 44].

A potential explanation for contradictory results of the aforementioned reports could be the uncontrolled factors influencingCE thicknessvalues such as race, ethnicity, sex, refractive status, tear film thickness, climate status and the temperature in each country and using different equipment and/ or technology. It is possible with further advances in OCT technology; may enable to entirely exclude the tear

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film effectsinCE thickness measurements, providingbetter precision and accuracy in the assessments of the epithelium.

Limitations

1. The corneal diameter is larger than 9 mm measured by the device.
2. Differences between the intrpalpebral height between subjects.
3. CE thickness data of the OCT system include the precorneal tear film, the thickness of which has been reported to be between 2 and 7 um [87-89], which can overestimate the thickness, especially in the inferior areas.

Conclusions:-

1. We have measured corneal epithelial thickness among healthy Iraqi subjects over a larger corneal area than in previous reports using a new SD-OCT.
2. We demonstrated that The CE thickness became thinner with age, these findings could be valuable in refractive surgeries especially in age over 45, and gender differences should be considered in the assessment of CE thickness, especially in the central area.
3. Our observations of the peripheral corneal epithelium may be of value in disorders that specifically affect these regions, such as peripheral corneal degenerations

Recommendations:

1. Measurement with AS-OCT of the CE thickness could aid in clinical assessment and planning treatments of the cornea.
2. We should measure CE thickness in cases of topography or tomography is not sufficient, to give us a diagnostic decision regarding ectatic corneal disorders.
3. Further and larger studies are also recommended to further validation of the results.

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