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Correlation between Corneal Endothelial Cell Characteristics and Dry Eye Disease

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Abstract

Purpose: To correlate corneal endothelium cell density with dry eye disease compared to an age-matched control group.

Materials and Methods: In this cross-sectional study, a total of 150 eyes of 75 female students aged 19-25 years who did not have any history of eye injuries or eye disease affecting the corneal endothelium cell density, were recruited from KSU Female Campus. They were divided into groups based on their dry eye disease severity. All subjects undergone full ophthalmic examinations assessing their endothelium cell count using specular microscope and dryness level using Non-invasive Break up Time (NIBUT) using Keratograph4.

Results: The mean endothelial cell density was significantly lower in subjects with severe dryness (2620.3 ± 252.2 cell/mm^2) and moderate dryness (2801 ± 221.6 cell/mm^2) than normal subjects (3067± 196.7 cell/mm^2), p=.000.In addition, the mean cell area was lower in normal subjects (327.4± 21.5 µm^2) and increased with severity of dryness, in subjects with moderate dryness (358.9 ±27.1 µm^2) and in subjects with severe dryness (384.8 ±33.7 µm^2), p=.000.There was variation in the mean cell volume, in normal subjects was (25±3.6) and (27.2±4.3) in moderate dryness and (25.5±3.6) in severe dryness, p=.009.

Conclusion: Results succeeded to demonstrate that in moderate to severe dryness, there was a significant reduction in the corneal endothelial cell density as compared to the age- and sex-matched control group. Correlation between corneal endothelial cells Characteristics and dry eye disease Correlation between corneal endothelial cell Characteristics and dry eye disease.

Keywords: Corneal endothelium; Dryness; Specular microscope; Keratograph

Introduction

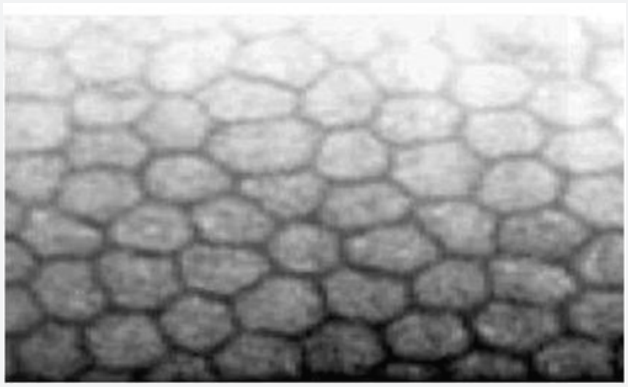

Figure 1: Specular micrograph of normal corneal endothelium cell [22].

Corneal endothelium is composed of monolayer of hexagonal cells (Figure 1), endothelium constitute the posterior corneal surface. It performs a major function in maintaining the corneal transparency, thickness and hydration [1]. The distinct arrangement of this cell layer (cell mosaic) is an eminent clinical appearance of the cornea, with images being easily captured with a specular microscope [2]. It is around 5µm thick.

The endothelium cell density reduces normally with age because of cell disintegration, ranging from 3000 to 4000cells/mm2 in children to 1000 to 2000 cells/mm2 at age of 80years [3]. The minimum cell density must be in the range of 400 to700 cells/mm2 for prompt function of the corneal endothelium. Disruptions to the endothelial mosaic can include an increase in the variation of cell shape (pleomorphism) or size (polymegathism) and endothelial cell loss [4].

Moreover to the physiological aging process, the endothelium can be negatively influenced by disease and trauma [5]. Some diseases can harm the corneal endothelium, such as Fuchs' corneal dystrophy, leading guttae (Figure 2) and corneal edema, Additional trauma during a prolonged cataract surgery especially while extracting a hard lens nucleus [2]. This may end in endothelial cell loss. A significant change in corneal endothelial cell density was found in eyes with moderate to severe dry eye disease [6].

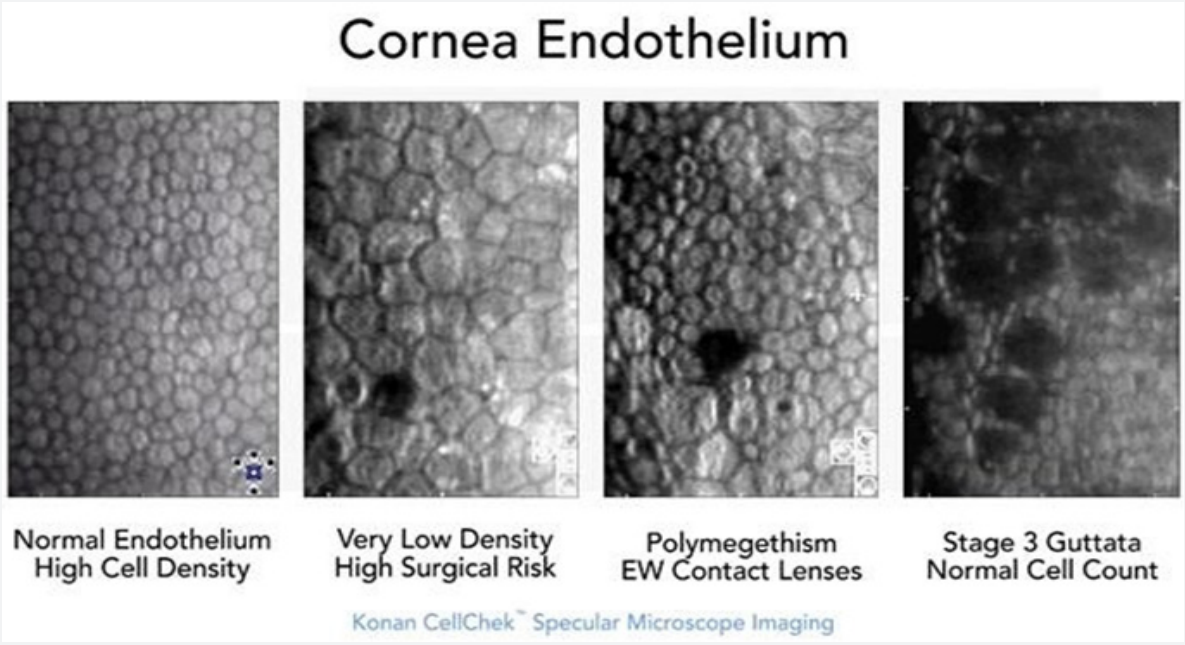

Figure 2: Specular micrograph of diseased corneal endothelium.

The tear film is a pre-ocular, thin, complex and moist structure composed of four layers (lipid layer 0.1µm, aqueous layer 7µm, mucous layer 3–30µm and glycocalyx 0.01–0.02µm from anterior to posterior) that covers the cornea, bulbar and palpebral conjunctiva [7-9]. Any abnormalities to its structure will affect ocular surface and may alter corneal clarity [10]. It has optical, mechanical, nutritional, and defensive functions [11] (Figure 3).

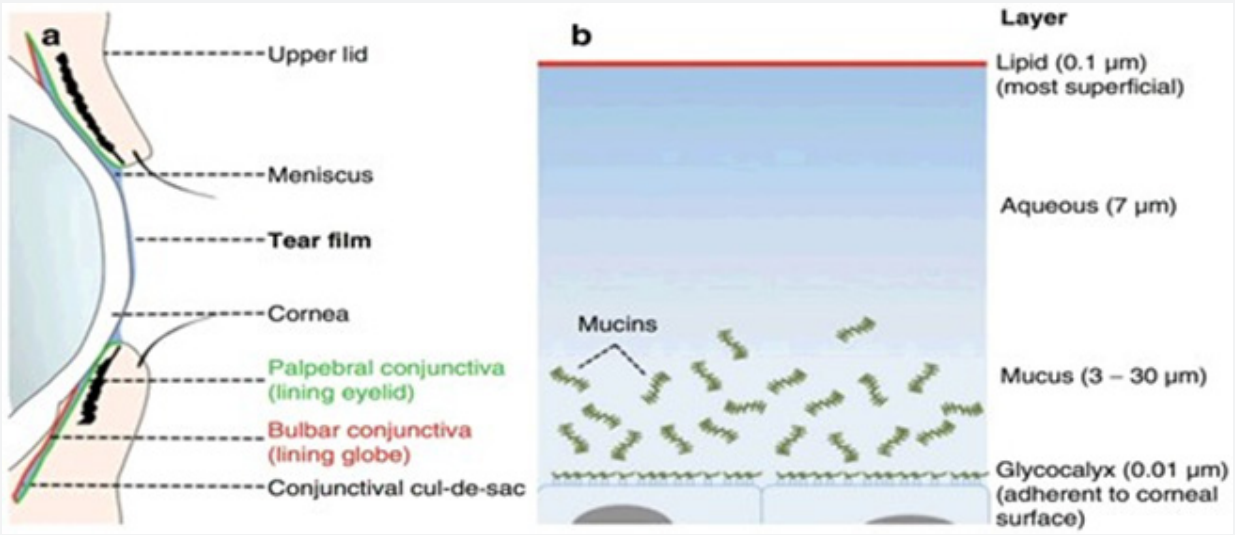

Figure 3: Theater film (a)distribution; (b) Structure [9].

Tear film total volume is 7–10µl. Normal basal tear secretion rate is 1–2 µl/min; on the other hand, the reflex tear rate is >100 µl/min [12]. Normal tear volume replacement occurs every 5-7min [9]. Tear film thickness is around 5.35 µm however the central TFT value was 5.122 ±0.034 µm [13].

International Dry Eye Workshop's (DEWS2007) provided the following definition: "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of the tear film and inflammation of the ocular surface" [14].

Any interruption to the Lacrimal Functional Unit, (a system composed of the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands), lids, and the sensory and motor nerves that supplies them [15] can destabilize the tear film leading to hyperosmolarity and eventually to ocular surface disease. These

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two considered to be the core mechanisms of the dry eye that can initiate, intensify, and alter dry eye prosperities with time [14].

Dry eye disease is classified to two major classes' aqueous deficient dry eye and Evaporative dry eye. Both lead to tear hyperosmolarity [16]. Aqueous deficient dry eye ADDE is induced by decreased lacrimal tear production and volume leading to tear hyperosmolarity followed by inflammation [17,18]. It is caused by disease in the lacrimal gland (e.g. Sjögren syndrome), obstruction to lacrimal gland outflow (e.g. cicatricial pemphigoid), homeostatic disturbance induced by blockage of the afferent pathway (e.g. topical anesthesia or trigeminal nerve section), and by blockage of efferent pathway (e.g. damage to the pterygopalatine gangli on and third order neurones) [19]. It also can becaused by systemic drugs uptake [20]. ADDE is divided to Sjögren Syndrome Dry Eye (SSDE) and non-Sjögren Syndrome Dry Eye (NSSDE) [16]. Evaporative dry eye EDE is induced by increased tear evaporation rate with normal function of the lacrimal gland. It can be caused by lid related or ocular surface related diseases, also referred to as intrinsic and extrinsic EDE, respectively [16].

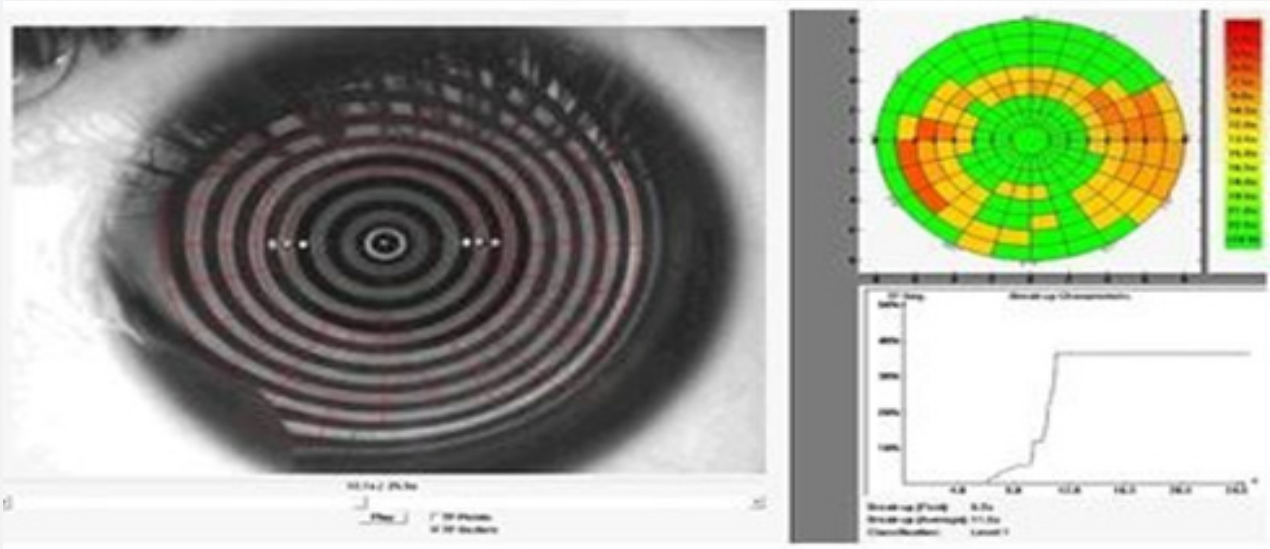

Figure 4: Non-invasive Tear Film Break Up Time (NITBUT)-Keratograph 4.

Dry eyes can be diagnosed non-invasively using Non-Invasive Tear film Breakup Time (NITBUT) and tear meniscus assessment. NITBUT is measured as the time between the last blink and the breakup of a reflected image of a target on the tear film (Figure 4). Tear meniscus assessment carries 75% to 90% of the total tear film volume. Thus, it is used to diagnose aqueous tear deficiency. Tear meniscus parameters used for tear film volume are Tear Meniscus Height TMH (the commonest) and tear meniscus radius of curvature. TMH is measured from the eye lid to the top of the meniscus, the cut-off value is <0.1mm [21] (Figure 5). Clinical examination involves the use of specular microscope and keratograph4, as non- invasive procedures, to correlate corneal endothelial cell characteristics with eye dryness.

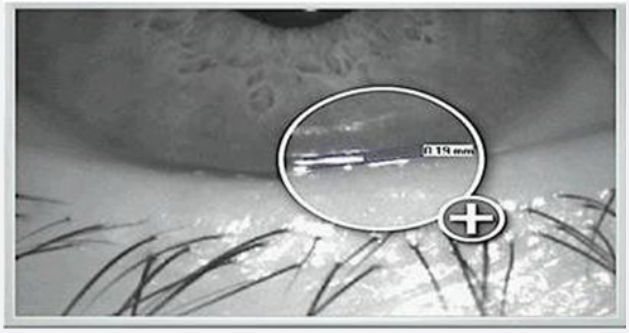

Figure 5: Tear Meniscus Height (TMH)- Keratograph 4.

Methods

Study population and Examination In this cross-sectional study, a total of 150 eyes of 75 female students aged 19-25years were recruited from King Saud University Female Campus. They were divided into groups based on their dry eye disease DED severity

a) Group 1: comprised 40 normal eyes of 20 subjects

b) Group 2: comprised 64 eyes of 32 subjects with moderate dryness

c) Group 3: comprised 46 eyes of 23 subjects with severe dryness

All subjects undergone full ophthalmic examinations including the following:

a. Measurement of refractive error using Auto Refractometer.

b. Visual acuity by Snellen chart.

c. Slitlamp examination.

d. Goldman applanation tonometry.

e. Fundoscopy.

f. Non-invasive Breakup Time (NITBUT) using Keratograph4 (to measure dryness level).

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g. Endothelium cell count using specular microscope. Subjects with break up time 10 seconds were considered to have dryness

Subjects with ocular allergic disease, keratitis, ocular surface disease, contact lens wear, glaucoma, previous ocular surgery or injury or subjects with systemic orocular treatment were excluded from this study.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0. All variables were expressed as Mean±Standard deviation. The normality of the data was first assessed using the Shapiro-Wilk test. Levene's test was used to determine homogeneous of the data. Owing to the normal distribution and homogeneous of the data, one-way ANOVA test was used to compare the means of endothelium cell characteristics between control group and DED groups. To assess the statistical significance of differences between means using a set of confidence intervals 95% multiple comparison post hocScheffe was used. The Pearson correlation analysis was used to estimate the correlations between the means of endothelium cell characteristics and the level of the NITBUT. The probability values of <0.05 were considered statically significant.

Ethical consideration

The protocol of the study was explained to each participant at the time of recruitment and informed consent was obtained according to the Declaration of Helsinki. The research was approved by the research ethical committee at College of applied medical sciences, King Saud University.

Results

The endothelial cell characteristics including Cell Density (CD), Cell Area (CA), Coefficient of Variations (CV), Hexagonality (HEX) and Center Cornea Thickness (CCT) of the three groups were studied and compared (Table 1-2).

Table 1: Endothelial cell characteristics of the study population in different NITBUT level groups (mean ± SD).

NITBUT level	No. of eyes	CD (cell/mm^2)	CA (µm^2)	CV (%)	HEX (%)	CCT µm)
Normal	40	3067 ± 196.7	327.4 ± 21.5	25 ± 3.6	68.1±3.5	569.8±38.22
Moderate	64	2801 ± 221.6	358.9 ±27.1	27.2±4.3	66±5.2	561±32.7
Severe	46	2620.3 ± 252.2	384.8 33.7	25.5±3.6	65.3±6.9	563±23

Table 2: One way Anova.

		Sum of Squares	df	Mean Square	F	Sig.
CD	Between Groups	4294644.280	2	2147322.140	42.279	.000**
	Within Groups	7466006.093	147	50789.157		
	Total	11760650.373	149			
	Between Groups	70407.370	2	35203.685	44.774	.000**
CA	Within Groups	115578.124	147	786.246		
	Total	185985.493	149			
CV	Between Groups	149.488	2	74.744	4.822	.009**
	Within Groups	2278.672	147	15.501		
	Total	2428.160	149			
HEX	Between Groups	191.462	2	95.731	3.177	.045*
	Within Groups	4429.932	147	30.136		
	Total	4621.393	149			
CCT	Between Groups	1803.174	2	901.587	.896	.411
	Within Groups	146985.068	146	1006.747		
	Total	148788.242	148			

*P<0.05 significant.

**P<0.01 highly significant.

The mean ECD was significantly lower in subject with severe DED (2620.3 ± 252.2 cell/mm^2) and moderate DED (2801 ± 221.6 cell/mm^2) than normal subjects (3067± 196.7 cell/mm^2) (Figure 6), p=.000. In addition, the mean cell area was lower in normal subjects (327.4±21.5 µm^2) and increased with severity of the DED, in subjects with moderate DED (358.9 ±27.1µm^2) and in subjects with severe DED (384.8 33.7µm^2) (Figure 7), p=.000.

There was variation in the mean CV, in normal subject was (25±3.6) and (27.2±4.3) in moderate DED and (25.5±3.6) in severe DED (Figure 8), p=.009. The mean HEX was lower in subjects with severe DED (65.3±6.9%) and moderate DED (66±5.2 %) than normal subjects (68.1±3.5 %) (Figure 9), p=.045. Mean CCT in normal subjects was (569.8±38.22µm), and (561±32.7 µm), (563±23 µm) in moderate and severe DED respectively (Figure 10), p=.41.

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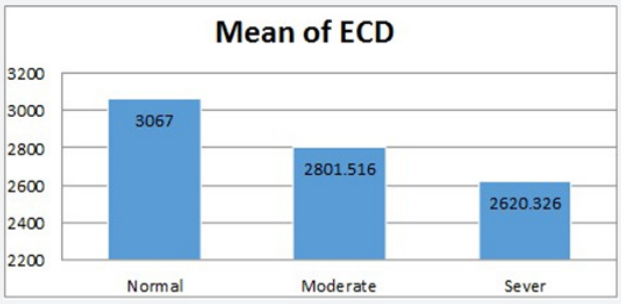

Figure 6: ECD in various groups.

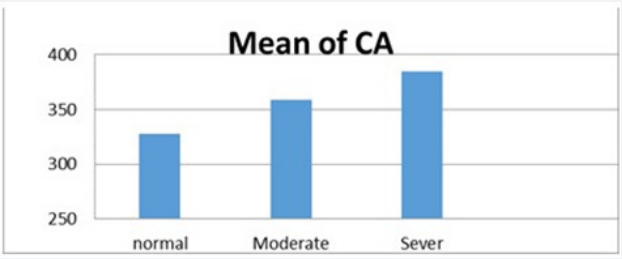

Figure 7: CA in various groups.

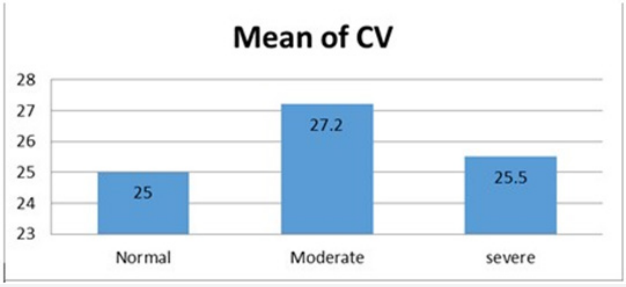

Figure 8: CV in various groups.

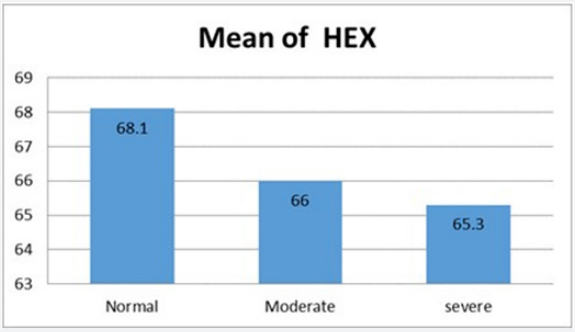

Figure 9: HEX in various groups.

CD showed higher statistically significant difference between normal to severe DED with mean difference (446.67cell/mm^2) (P=.000) than between normal to moderate DED with mean difference (265.48 cell/mm^2) (P=.000) and between moderate to severe DED with mean difference (181.18 cell/mm^2) (P=.000).

CA showed higher statistically significant difference between normal to severe DED with mean difference (-57.35µm^2) (P=.000) than between normal to moderate DED with mean difference (-31.53 µm^2) (P=.000) and between moderate to severe DED with mean difference (-25.82 µm) (P=.000).

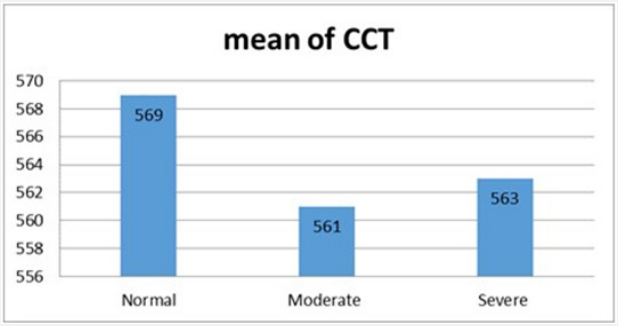

Figure 10: CCT in various groups.

Table 3: Post hoc multiple comparisons (Scheffe).

Dependent Variable	(I) NIBUT level	(J) NIBUT level	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
CD	Normal	Moderate	265.4844*	45.4237	.000**	153.156	377.813
		Severe	446.6739*	48.7221	.000**	326.189	567.159
	Moderate	Severe	181.1895*	43.5625	.000**	73.464	288.915
CA	Normal	Moderate	-31.5344*	5.6517	.000**	-45.510	-17.558
		Severe	-57.3543*	6.0620	.000**	-72.345	-42.363
	Moderate	Severe	-25.8200*	5.4201	.000**	-39.223	-12.417
CV	Normal	Moderate	-2.2469*	.7485	.013*	-4.098	-.396
		Severe	-1.9935*	.8028	.049*	-3.979	-.008
	Moderate	Severe	.2534	.7178	.940	-1.522	2.028
HEX	Normal	Moderate	2.1500	1.1065	.155	-.586	4.886
		Severe	2.8837	1.1868	.055	-.051	5.819
	Moderate	Severe	.7337	1.0611	.788	-1.890	3.358

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CCT	Normal	Moderate	8.3512	6.4147	.431	-7.513	24.215
		Severe	6.8533	6.8596	.608	-10.111	23.818
	Moderate	Severe	-1.4979	6.1535	.971	-16.716	13.720

CV showed higher statistically significant difference between normal to moderate DED with mean difference (-2.24%) (P=.013) than between normal to severe DED with mean difference (-1.99%) (P=.049) with no statistically significant between moderate to severe DED with mean difference (0.25%) (P=.94).

HEX showed no statistically significant difference between normal to moderate DED with mean difference (2.15%) (P=.15) and between normal to severe DED with mean difference (2.88%) (P=.05) and between moderate to severe DED with mean difference (0.73%) (P=.78).

CCT showed no statistically significant difference between normal to moderate DED with mean difference (8.35 µm) (P=.43) and between normal to severe DED with mean difference (6.85µm) (P=.60) and between moderate to severe DED with mean difference (-1.49 µm) (P=.97) (Table 3).

The ECD showed statistically significant negative correlation with the NITBUT level (rs=-.6, P=0.000), CA showed statistically significant positive correlation with the NITBUT level (rs=.61, P=0.000), CV showed weak positive correlation with the NITBUT level (rs=.191 P=0.19), HEX showed weak negative correlations with the NITBUT level (rs=-.194P=0. 18), and CCT showed irrelevant (very weak) negative correlations with the NITBUT level (Table 4).

Table 4: Comparison between NITBUT and Endothelial cell characteristics.

Parameter (mean)	r (personcorrelation)	p-value
CD (cell/mm^2)	-.600*	0.000**
CA (µm^2)	.614*	0.000**
CV (%)	.191*	.019*
HEX (%)	-.194	.018
CCT(µm)	-.079	.340

Discussion

Author	No. of subjects	Instrument used	Result
Current Study 2017	Group1:40 normal eyes of 20 subjects Group2:64eyes of32subjects with moderate dryness Group3:44 eyes of 22subjects with severe dryness	Specular microscopy CEM-530 NITBUT Keratograph4	This cross-sectional study showed That in moderate to severe DED, there was a significant reduction in the corneal endothelial cell density (ECD) as compared to the age-and sex-matched control group. ECD showed significant correlation with clinical severity of the disease, as judged by the level of non-invasive tear breakup time test. In addition, in DED there is a significant reduction in percentage of hexagonal cells (Polymegathism) and an increase in endothelial cell area and coefficient of variation (pleomorphism) that correlates With clinical severity of the disease.
Kheirkh et al. 2015	15 normal subjects 45patientswith DED.	IVCM using a Heidelberg Retina Tomography3 With the Rostock Cornea Module.	Eyes with DED displayed a Significant reduction in corneal ECD indeed that correlates with clinical severity of the disease and Significant lower sub basal nerve density than did those in the control group.
RohitShettyetal. 2015	43 healthy control 52DEDpatients	IVCM imaging using Rostock Corneal Module/Heidelberg Retina Tomograph ll	A significant decrease in SBNP features (corneal nerve fiber length, fiber density, fiber width, total branch density, nerve branch density, and fiber area) was observed in DED patients with
Ceyhun Arıcı, et al. 2014	252 eyes of 126 healthy volunteers	Specular microscopy	It has been reported that there is a negative correlation between CA and CD.
Bernardo Bercht, et al.,2014	Group 1 (2-4- month-old) Group 2 (48- month-old) Group 3 (10years of age).	Specular microscopy	It has been reported that there is a negative correlation between endothelial cell density and an endothelial cell area and pleomorphism. Pleomorphism.

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Conclusion

In conclusion, results succeeded to demonstrate that in moderate to severe DED, there was a significant reduction in the corneal Endothelial Cell Density (ECD) as compared to the age- and sex-matched control group. ECD showed significant correlation with clinical severity of the disease, as judged by the level of non-invasive tear breakup time test. In addition, in DED there is a significant reduction in percentage of hexagonal cells (Polymegethism) (-ve) and an increase in endothelial cell area and coefficient of variation (pleomorphism) (+ve) that correlates with clinical everity of the disease.

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Declaration of Interest

The author declares no potential conflicts of interest with respect to the authorship, and/or publication of this article.

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