# Evaluation of Corneal Endothelial Changes and Corneal Tomographic Parameters in Eyes with Keratoconus

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**Running title:** Corneal endothelial changes in keratoconic eye.

**Abstract:**

**Purpose:** To evaluate changes in corneal endothelium and its correlation with tomographic parameters in different stages of keratoconus (KC).

**Methods:** This study was conducted on 95 eyes of 70 patients with KC (underwent Visian ICL V4c implantation) attending to Mansoura ophthalmic center and 40 normal controls with matching age and sex in the period from April 2018 till May 2019. All individuals were subjected to full history and ocular examination. In addition Oculus pentacam was performed to diagnose KC, grades and assessment of Keratometry, thickness at the apex, thinnest corneal thickness and Anterior and Back elevation, while Specular microscopy was performed to assess the endothelial cell counting, Coefficient of variation (C/V) and Hexagonal cell ratio.

**Results:** There were highly statistically significant differences among KC cases and the control group as regards endothelial count, C/V and hexagonal cell ratio. In addition such changes had a positive correlation with the degree of KC.

**Conclusion:** There were significant corneal endothelial changes as well as Corneal Tomographic alterations among eyes with KC compared to normal ones and these changes have a positive correlation with the severity of KC. Specular microscopic examinations in patients with KC provide important data in addition to topography.

**Keywords:** Keratoconus, endothelial count, C/V, hexagonal cell ratio tomographic parameters, endothelial changes.

## Introduction:

Keratoconus (KC) is a corneal disorder characterized by progressive localized corneal thinning and protrusion, resulting in irregular astigmatism and decreased vision [1].

Several investigators prefer to classify KC degree as regards the mean keratometry readings. The Amsler-Krumeich classification graded KC into 4 grades as regards the main K readings. Grade 1 included mean central K readings $< 48$ diopters, grade 2 included mean central K readings $\geq 48$–$< 54$ diopters, grade 3 included mean central K readings $\geq 54$–$< 55$ diopters while grade 4 included mean central K readings $\geq 55$ diopters [2].

The Scheimpflug imaging system is considered a novel corneal topography method, that takes measurements from anterior and posterior corneal surfaces [3]. This system provides more accurate, valid and 3D information about the corneal shape, such as anterior and posterior corneal surface elevation data measurement and pachymetry map [4].

Since KC is an ectatic disease which affects the anterior and posterior corneal surfaces, there may be changes in corneal endothelial cell number and shape, particularly in advanced KC stages [5].

The status of corneal endothelial cells is essential in the decision to perform crosslinking (CXL) technique and selection of CXL protocols to prevent endothelial cell toxicity in eyes with

decreased endothelial cell count and may change the selection of different techniques of keratoplasty (such as penetrating keratoplasty (PK) or Deep Anterior lamellar keratoplasty (DALK)) [6].

Corneal endothelium can be evaluated well by Specular microscopy which is a non-invasive photographic technique that allows visualization and analysis of the corneal endothelium as pachymetry, cell density, variation in size and variation in shape [7].

**Patients and methods:**

**Patient enrollment**

This was a cross-sectional and observational study conducted on 95 eyes of 70 patients with keratoconus attending to Mansoura ophthalmic center and 40 normal controls with matching age and sex in the period from April 2018 till May 2019 after approval from Institutional review board (IRB), Faculty of Medicine,

***The studied individuals were classified into two groups:***

**Keratoconus group (n=70):** underwent Visian ICL V4c implantation.

**Control group (n=40):** underwent Artiflex Lens implantation.

**All individuals were subjected to:**

Full general and ophthalmic history which include Age, Gender, Occupation and socioeconomic status and history of similar conditions were performed. Also, ocular history to exclude any previous refractive or ocular surgery and ocular injury were performed. Full ophthalmic examination including Visual acuity measurement using Landolt's broken ring chart then transformed to Log MAR was performed and Manifest refractions using the auto-refractometer were done. In addition, full slit lamp examination to assess the anterior segment was performed for cornea, sclera, anterior chamber, iris, pupil and lens. Fundus examination (ophthalmoscope) after installation of mydriatic eye drops and Intraocular pressure (IOP) assessment was done to measure Intraocular pressure is measured as part of a comprehensive eye examination after installation of anesthetic eye drops.

As regards, the investigations, Oculus pentacam was done for diagnosis of keratoconus, grades and assessment of Keratometry ($K_1$, $K_2$ & $K_{max}$), thickness at the apex, thinnest corneal thickness and Anterior and Back elevation and Specular microscopy was performed to assess the endothelial cell counting, Coefficient of variation (C/V) and Hexagonal cell ratio.

**Statistical Analysis of the Data:**

IBM SPSS (version 20) was utilized to assess the research data. Shapiro-Wilk test was utilized to check the data distribution normality. P value less than 0.05 was regarded to be significant. Quantitative variables were evaluated as mean and SD, median, IQR, minimum and maximum whereas categorical ones were evaluated as ratio and percent. Independent sample T and Mann Whitney tests were utilized for intergroup (among cases) comparing of continuous data without follow up readings correspondingly

**Results:**

**Patient's characteristics**

The control group included 80 persons (35 males and 45 females) with mean age of 27.53 years. The KC group included 95 patients (49 males and 46 females) with mean age of 26.16 years. No statistically significant difference existed among both groups as regards age and gender (Table 1).

Table (1): Demographic characteristics in the control and KC patients:

| | | Control group (n= 80) | KC patient (n= 95) | 95% CI | p |
|---|---|---|---|---|---|
| **Age** | | 27.53 ± 5.686 | 26.16 ± 4.684 | -0.21, 2.94 | 0.088 |
| **Gender** | **Male** | 43.8% (35) | 51.6% (49) | -0.07, 0.23 | 0.302 |
| | **Female** | 56.3% (45) | 48.4% (46) | | |

95% CI: 95% confidence interval of the mean difference among both groups. P is significant when < 0.05.
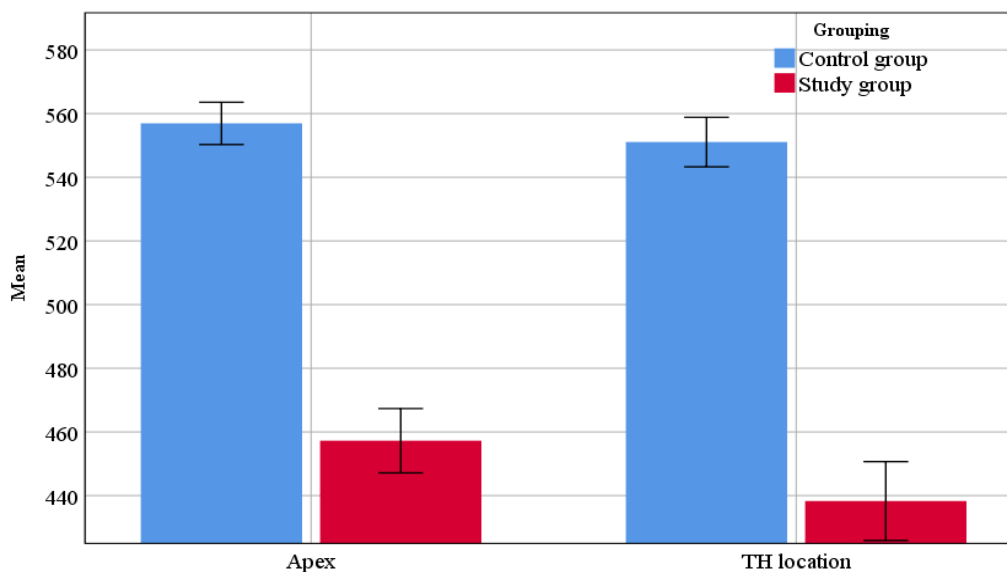
**Topographic data**

There was a statistically significant difference among both groups as regards K1, K2, Apex, Thinnest corneal thickness, Ant elevation and Post elevation where K1, K2, Ant elevation and Post elevation were significantly higher in KC group compared with controls while Apex and Thinnest corneal thickness were significantly lower in KC group compared with controls in (Table 2, figure 1).

Table (2): Topographic data of the studied subjects:

| | Control group (n= 80) | KC patient (n= 95) | 95% CI | p |
|---|---|---|---|---|
| **K1 (D)** | $43.47 \pm 1.955$ | $47.26 \pm 5.560$ | -5.00, -2.58 | **< 0.001** |
| **K2 (D)** | $43.91 \pm 1.720$ | $50.65 \pm 6.393$ | -8.2, -5.29 | **< 0.001** |
| **Apex (µm)** | $556.92 \pm 29.906$ | $457.23 \pm 49.601$ | 87.67, 111.72 | **< 0.001** |
| **Thinnest corneal thickness(µm)** | $551.06 \pm 34.964$ | $438.28 \pm 60.770$ | 98.24, 127.32 | **< 0.001** |
| **Ant elevation(D)** | $10.86 \pm 3.149$ | $23.40 \pm 14.288$ | -15.71, -9.74 | **< 0.001** |
| **Post elevation(D)** | $8.41 \pm 3.125$ | $62.19 \pm 32.289$ | -60.39, -47.16 | **< 0.001** |

95% CI: 95% confidence interval of the mean difference among both groups. P is significant when < 0.05.



Figures (1): Topographic data of the studied subjects.

**Comparison among endothelial count, C/V and hexagonal cell ratio in the control and KC patients**

There was a statistically significant difference among both control and KC as regards endothelial count (2745.28 vs. 2623.35), C/V (28.79 vs. 29.72) and hexagonal cell ratio (69.95 vs. 62.12). The Endothelial count and hexagonal cell ratio were significantly lower in KC patients than in controls while C/V was significantly higher in KC patients than in controls (Table 3 and figure 2).

Table (3): Comparison among endothelial count, C/V and hexagonal cell ratio in the control and KC Eyes:

| | Control Eyes (n= 80) | KC Eyes (n= 95) | 95% CI | p |
|---|---|---|---|---|
| **Endothelial count** | 2745.28 ± 212.777 | 2623.35 ± 187.231 | 61.54, 182.32 | **< 0.001** |
| **Hexagonal cell ratio** | 69.95 ± 2.794 | 62.12 ± 5.063 | 6.64, 9.03 | **< 0.001** |
| **C/V** | 28.79 ± 2.433 | 29.72 ± 3.242 | -1.78, -0.08 | **0.032** |

95% CI: 95% confidence interval of the mean difference among both groups. P is significant when < 0.05.
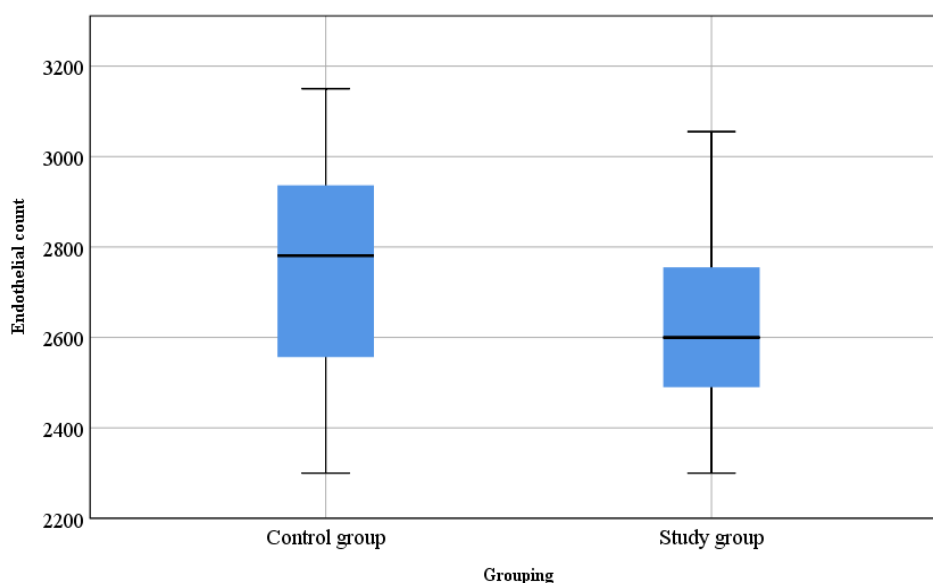


Figure (2): Endothelial count in the control and KC patients.

**Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade I group**

There was no statistically significant difference among the control group and Grade I KC patients as regards Endothelial count and C/V, while there was statistically significant difference as regards hexagonal cell ratio where, hexagonal cell ratio was significantly lower in Grade I KC patients than in controls. (Table 4, Fig. 3).

Table (4): Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade I group:

| | Control group (n= 80) | Grade I (n= 22) | 95% CI | p |
|---|---|---|---|---|
| **Endothelial count** | 2745.28 ± 212.7 | 2703.73 ± 224.6 | -61.3, 144.4 | 0.425 |
| **Hexagonal cell ratio** | 69.95 ± 2.794 | 68.40 ± 2.758 | 0.2, 2.9 | **0.023** |
| **C/V** | 28.79 ± 2.433 | 28.18 ± 2.711 | -0.6, 1.8 | 0.308 |

CI: confidence interval of the mean difference among both groups. P is significant when < 0.05.
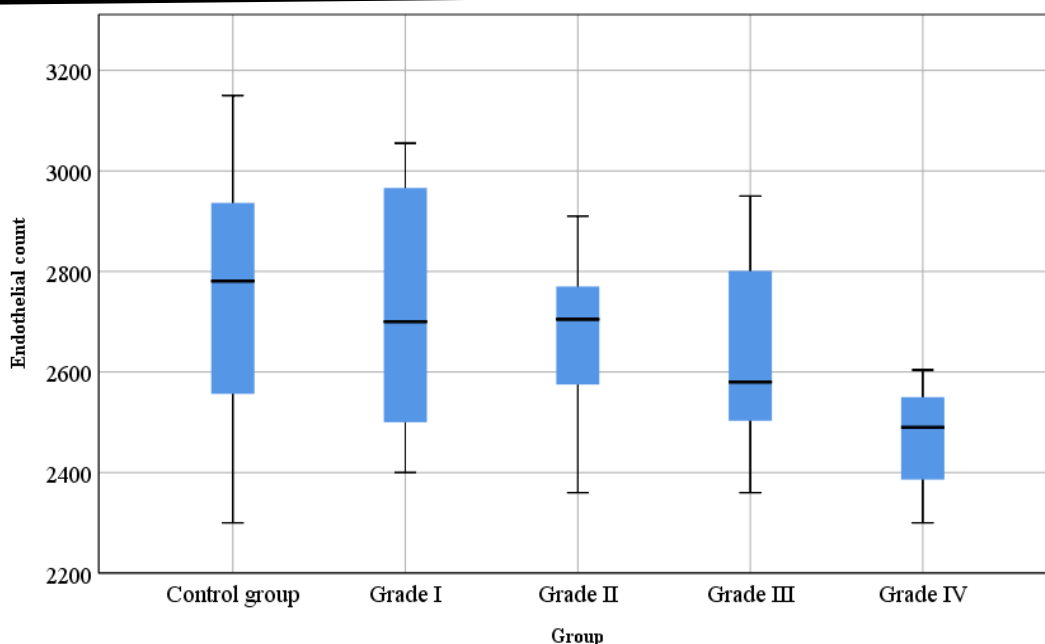
Figure (3): Endothelial count in the control and study subgroups.

**Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade II group**

Table 5 showed that there was no statistically significant difference among the control group and Grade II KC patients as regards Endothelial count and C/V, while there was statistically significant difference as regards hexagonal cell ratio where, hexagonal cell ratio was significantly lower in Grade II KC patients than in controls. (Table 5, Fig. 3).

Table (5): Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade II group:

|  | Control group (n= 80) | Grade II (n= 22) | 95% CI | p |
|---|---|---|---|---|
| **Endothelial count** | $2745.2 \pm 212.7$ | $2669.6 \pm 146.3$ | -0.2,171.4 | 0.121 |
| **Hexagonal cell ratio** | $69.95 \pm 2.794$ | $62.92 \pm 2.920$ | 5.68,8.38 | **< 0.001** |
| **C/V** | $28.79 \pm 2.433$ | $28.07 \pm 2.444$ | -0.44,1.89 | 0.220 |

CI: confidence interval of the mean difference among both groups. P is significant when < 0.05.

**Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade III group**

There was no statistically significant difference among the control group and Grade III KC patients as regards C/V, while there was statistically significant difference as regards endothelial count and Hexagonal cell ratio where, both parameters were significantly decreased in Grade III KC patients than in controls. (Table 6, Fig. 3).

Table (6): Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade III group:

|  | Control group (n= 80) | Grade III (n= 30) | 95% CI | p |
|---|---|---|---|---|
| **Endothelial count** | $2745.28 \pm 212.7$ | $2638.00 \pm 174.9$ | 21.0, 193.5 | **0.015** |
| **Hexagonal cell ratio** | $69.95 \pm 2.794$ | $60.55 \pm 2.678$ | 8.2, 10.6 | **<0.001** |
| **C/V** | $28.79 \pm 2.433$ | $29.45 \pm 2.870$ | -1.7, 0.4 | 0.232 |

CI: confidence interval of the mean difference among both groups. P is significant when < 0.05.

**Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade IV group**

There was a statistically significant difference among both control and Grade IV KC patients as regards Endothelial count, C/V and hexagonal cell ratio where Endothelial count and hexagonal cell ratio were significantly lower in Grade IV KC patients than in controls while C/V was significantly higher in Grade IV KC patients than in controls (Table 7, Fig. 3).

Table (7): Comparison among endothelial count, C/V and hexagonal cell ratio in the control and Grade IV group:

|  | Control group (n= 80) | Grade IV (n= 21) | 95% CI | p |
|---|---|---|---|---|
| **Endothelial count** | 2745.28 ± 212.7 | 2469.67 ± 101.5 | 180, 370 | **< 0.001** |
| **Hexagonal cell ratio** | 69.95 ± 2.794 | 56.92 ± 4.113 | 11.5, 14.5 | **< 0.001** |
| **C/V** | 28.79 ± 2.433 | 33.47 ± 1.723 | -5.8, -3.6 | **< 0.001** |

CI: confidence interval of the mean difference among both groups. P is significant when < 0.05.

**Discussion:**

Keratoconus (KC) is a disease that develops in the puberty period, which affects both sexes and is frequently bilateral. Although its pathogenesis has not been clarified yet, it has been shown that environmental and genetic factors play a role in the onset of the disease [8, 9].

The disease leads to progressive thinning of the corneal stroma, ectasia and irregular astigmatism associated with it and decreases visual acuity. It is characterized by changes in the structures of corneal epithelium and stroma and stromal thinning associated. In addition, specular microscopy also revealed some differences in terms of cell number and morphology in the endothelium compared to healthy individuals [10, 11].

Thus, the aim of the current study was to assess changes in corneal endothelium and its correlation with tomographic parameters in different stages of KC.

The current study was conducted on 95 eyes of 70 patients with KC attending to Mansoura ophthalmic center and 40 normal controls with matching age and sex in the period from April 2018 till May 2019 after approval from Institutional review board (IRB), Faculty of Medicine, Mansoura University.

As regards demographic characteristics among the control and KC, the control group included 80 persons (35 males and 45 females) with mean age of 27.53 yrs. The KC group included 95 patients (49 males and 46 females) with mean age of 26.16 yrs. No statistically significant difference existed among both groups as regards age and gender.

In the same line, Orucoglu and Toker conducted a study on KC versus normal eye. Regarding the control group, the research included 513 eyes of 268 subjects with an average age of 32 yrs, ranging from 8 to 74 yrs old. Regarding sex, 48.1% of patients were male while 51.9% were female. In the KC group, the study included 656 eyes of 338 cases with an average age of 31.18 yrs, ranging from 13 to 64 yrs old. Two hundred fourteen patients were male and 124 were female. The average spherical refraction of normal eyes was −0.88D. The two groups didn't vary significantly as regards the age and sex [12].

Topographic data of the studied subjects demonstrated that there were significant differences among both groups as regards K1, K2, Apex, Thinnest corneal thickness, Ant elevation and Post elevation where K1, K2, Ant elevation and Post elevation were significantly higher in KC group compared with controls while Apex and Thinnest corneal thickness were significantly lower in KC group in comparison with the control group.

In agreement, Orucoglu and Toker, E. demonstrated that, all Pentacam parameters (K1, K2, Astigmatism, Apex, Asphericity Ant elevation and Post elevation) showed highly statistically significant change among keratoconic eyes in comparison with the normal ones (P < 0.001) except the distance from corneal apex to thinnest location parameter (P=0.349) [12].

Similarly, Ambrósio et al., revealed that there were statistically significant variations were among normal and keratoconic eyes as regards whole Pentacam parameters (P<.001), with the exception of horizontal position of TP

(P=.79). The best parameters were ART-Ave (TP/PPI Ave) and ART-Max (TP/PPI Max) with AUR of 0.987 and 0.983, correspondingly [13].

In the same line, Huseynli and Abdulaliyeva conducted a study which compares the topographic map among normal, subclinical KC and KC. They found no significant changes as regards mean and maximum keratometry or astigmatism among the subclinical KC and control cases (p≥0.07). On the other hand, the remaining values were significantly different among the analyzed groups. Comparison of bilateral subclinical KC eyes to the fellow eyes of clinical KC eyes demonstrated significant changes in corneal thickness variables (CCT, ThCT) (p<0.01). The CV (CV 3-7) values demonstrated lower distribution in the bilateral subclinical KC group in comparison with the unilateral KC group (p<0.01). On the contrary, the remaining diagnostic variables demonstrated no significant variations among the groups [14].

In addition, Pairwise comparisons among the clinical KC and other groups of eyes demonstrated the next significant changes: keratoconic Vs normal eyes, all variables (p<0.01); keratoconic Vs fellow eyes, entire variables with the exclusion of Thin L.Dist Abs, CV7; and KC Vs bilateral subclinical KC eyes, all variables except flat keratometry, astigmatism and volume values [14].

As regards, comparison between endothelial count, C/V and hexagonal cell ratio in the control and KC patients, there was a significant difference among both control and KC as regards endothelial count (2745.28 vs. 2623.35), C/V (28.79 vs. 29.72) and hexagonal cell ratio (69.95 vs. 62.12). The Endothelial count and hexagonal cell ratio were significantly lower in KC patients than in controls while C/V was significantly higher in KC patients than in controls.

In agreement, Bozkurt et al. assessed the endothelial count in mild, moderate and severe KC and revealed that, there was a significant variation in endothelial count values as regards stage of KC, with the lowest value being in severe KC (2628±262 cells/mm2, 2541.9±260.4 cells/mm2 and 2414.6±384.3 cells/mm2 in mild, moderate, and severe stages,

correspondingly) (p<0.001). In addition, they revealed that, the correlations among ECD and keratometric values, anterior and posterior elevation parameters, and thickness parameters were statistically significant (p<0.05) [15]. Moreover, Hollingsworth and his colleagues conducted their study on 29 KC eyes and 29 control eyes and revealed increased ECC in eyes with KC (3250±352cells/mm2) in comparison with healthy eyes (3056±365cells/mm2). The degree of polymegathism didn't vary between cases with KC (0.35±0.05) and matched controls (0.38±0.07) [16].

On the other hand, Ghosh and his colleagues demonstrated that, the corneal cell morphology of cases with KC varied significantly from the healthy ones except in ECD (P=0.072) [17]. Moreover, Timucin et al. demonstrated that, the mean ECC was 2731.6 ± 303.2cells/mm2 in patients with KC and 2664.9 ± 319.5cells/mm2 in controls. There was no difference among the densities (P=0.4). In addition, no significant correlations were found among the ECD data and CCT [18].

The alterations between the present study and Ghosh et al. (2017) Timucin et al. (2013) studies may be owing to insufficient sample size within the various KC stages, alterations in exclusion criteria (present or prior contact lens use), measurement equipment, Procedures for image acquisition and cell density measurement (image size and location, method of cell counting either manually or automatically), and classification of KC severity [17, 18].

As regards comparison between endothelial count, C/V and hexagonal cell ratio among the control and the four studied KC groups there were statistically significant differences as regards endothelial count, C/V and hexagonal cell ratio where these three parameters were significantly lower in KC groups than in controls. Similarly, Taşlı et al., demonstrated that, ECC and hexagonal cell ratio were significantly lower in severe KC compared to mild and moderate KC and the coefficient of variation was higher in severe KC compared to the other groups (p <0.001). When the patients were compared according to the pachymetry value at the thinnest point of the cornea, the endothelial cell number and the hexagonal cell ratio were found

to be lower in the group with pachymetry less than 400 μm (p <0.001). The coefficient of variation was higher in the same group compared to the others (p <0.001) [8].

In the same line, Mocan et al. reported that there was significant reduction in endothelial cell density in cases with KC in comparison with normal ones. In addition, such decrease correlated with the degree of KC [19]. In addition, Uçakhan et al. demonstrated that the mean endothelial cell hexagonality percent was significantly lower in KC group compared to the control group (P<0.05). When broken down, although the mean hexagonality percent in eyes with severe KC seemed to below (39.9% and 61.5% by automatic and manual counts respectively) in comparison with those with mild (53.7% and 88.3% by automatic and manual counts respectively) or moderate (48.1% and 80.0% automatic and manual counts respectively) KC, this difference didn't reach clinical significance, probably owing to the limitation of numbers of mild KC eyes [20].

On the other hand, Timucin et al. revealed that, the mean endothelial count was 2759 + 267.8cells/mm2 in mild KC cases. There was no difference among the outcomes of the mean ECC in the mild KC group and the normal subjects (P=0.2). Regarding mild KC group, there was no significant association between the ECD and the CCT (P = 0.7). In addition, non-significant weak and +ve correlation was detected between the steepest keratometric data and the ECD (P=0.3) in eyes with KC. The mean ECD was 2747±368.2cells/mm2 in cases with moderate KC. There was no difference among the moderate KC and the normal individuals in the mean ECD (P=0.2). Regarding mild KC group, there was no significant correlation among the ECD and CCT (P>0.05). The mean ECD was 2698.5±278.2 cells/mm2 in patients with severe KC [18].

In addition, the mean ECD in severe KC had no significant variation in comparison with the control ones (P=0.86). As regards severe KC cases, no significant association was detected among the ECD and CCT (P > 0.05) [18]. Furthermore, El-Agha et al. conducted a study on 40 eyes of 29 patients with KC in which corneal endothelium was assessed by SM and corneal topography and thickness data were acquired from Scheimpflug-based corneal tomography. They demonstrated that, there was no significant correlation between KC stage and the ECD (P = 0.91), CV (P = 0.94), or percent of hexagonality (6A) (P = 0.51). When mild-to-moderate KC (stages 1 and 2) was compared with severe KC (stage 3), the change wasn't significant as regards ECD (P=0.1), CV (P=0.3), or 6A (P=0.4). However, there was a trend toward lower ECD and percent of hexagonality, and a greater CV with KC advancement [10].

The discrepancies among the current result and both Timucin et al. and El-Agha et al. studies may be owing to insufficient number of eyes within the various KC stages, alterations in exclusion criteria (present or prior contact lens usage), measurement equipment, procedures for image acquisition and cell density measurement (image size and location) and classification of KC severity [10, 18].

**Conclusion:**

The current study concluded that, there were significant Corneal Endothelial Changes as well as Corneal Tomographic alterations among eyes with KC in comparison with normal ones. In addition such changes have a positive correlation with the severity of KC. Specular microscopic examinations in patients with KC provide important data in addition to topography.

**Conflict of Interest**

Authors declare no conflicts of interest.

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**Ethics declarations.**

**Conflict of interest**

Azza M. Abdelrahman, Rania K. Farag, Sherief E. ElKhouly, Hesham I. ElSerogy, all authors have no conflicts of interest that are directly relevant to the content of this review.

**Funding:** No sources of funding were used to conduct this review.

**Reviewer disclosures:** No relevant financial or other relationships to disclose.

**Declaration of interest:** No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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